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February 5 - 8, 2002: Organophosphate Pesticides: Preliminary OP Cumulative Risk Assessment

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You will need the free Microsoft PowerPoint (PPT) Viewer EXIT Disclaimer to view some of the files on this page. If you need help accessing these documents, please contact Donald Wood at (202) 564-8378 or wood.donald@epa.gov for assistance.

Federal Register Notice

Federal Register Notice announcing this meeting.

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Meeting Materials

- Comparison of Acute NOAELS and Benchmark Doses for Female Brain Cholinterase Inhibition

(PDF) (6 pp, 103K)
- Summary Changes to Dose - Response Monitoring (PDF) (1 pg, 17K)
- Revision to SAP Question #1 For Food Session and Revision to SAP Question #1 For Food Session "Preliminary Cumulative Risk Assessment for Organophosphorous Pesticides: Review of Methodology" (PDF) (4 pp, 48K)
- Rolling Time Frame Approach (PDF) (4 pp, 30K)
- Organophosphate Pesticides: Preliminary OP Cumulative Risk Assessment Table of Contents
- Organophosphate Pesticides Preliminary Cumulative Risk Assessment: Health Effects Input Files
  Water Data
- Session Results:
  - Session 1 (MS PowerPoint) (67 pp, 382K) -- Preliminary Cumulative Risk Assessment: Organophosphorous Pesticides
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  - Session 3 (PDF) (12 pp, 604K) -- Drinking Water Exposure Assessment
  - Session 4 (MS PowerPoint) (58 pp, 4MB) -- Residential Non-Occupational Exposure Assessment
  - Session 5 (MS PowerPoint) (24 pp, 181K) -- Session on Risk Characterization
  - February 5, 2002 Proceedings (PDF) (182 pp, 499K)
  - February 5, 2002 Proceedings - Part 2 (PDF) (50 pp, 149K)
  - February 6, 2002 Proceedings (PDF) (66 pp, 199K)
  - February 6, 2002 Proceedings - Part 2 (PDF) (192 pp, 516K)
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  - February 7, 2002 Proceedings - Part 2 (PDF) (136 pp, 390K)

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Meeting Minutes

- Final Meeting Minutes (PDF) (94 pp, 431K)
- Final Meeting Minutes Addendum (XLS) (4MB)

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ENVIRONMENTAL PROTECTION AGENCY

[OPPTS–00329; FRL–6814–9]

National Advisory Committee for Acute Exposure Guideline Levels for Hazardous Substances; Notice of Charter Renewal

AGENCY: Environmental Protection Agency (EPA).

ACTION: Notice.

SUMMARY: The charter for EPA's National Advisory Committee for Acute Exposure Guideline Levels for Hazardous Substances (NAC/AEGL Committee) is renewed for an additional 2-year period. EPA has determined that the NAC/AEGL Committee is necessary and finds that it is in the public's interest that the NAC/AEGL Committee be continued.

FOR FURTHER INFORMATION CONTACT: *For general information contact*: Barbara Cunningham, Acting Director, Environmental Assistance Division (7401), Office of Pollution Prevention and Toxics, Environmental Protection Agency, 1200 Pennsylvania Ave., NW., Washington, DC 20460; telephone number: (202) 554–1404; e-mail address: TSCA-Hotline@epa.gov.

For technical information contact: Paul S. Tobin, Economics, Exposure, and Technology Division (7406M), Office of Pollution Prevention and Toxics, Environmental Protection Agency, 1200 Pennsylvania Ave., NW., Washington, DC 20460; telephone number: (202) 564–8557; e-mail address: tobin.paul@epa.gov.

SUPPLEMENTARY INFORMATION:

I. General Information

A. Does this Action Apply to Me?

This action is directed to the public in general. This action may be of particular interest to anyone who may be affected if AEGL values are adopted by government agencies for emergency planning, prevention, or response programs, such as EPA's Risk Management Program under the Clean Air Act and Amendments Section 112r. It is possible that other Federal agencies besides EPA, as well as State agencies and private organizations, may adopt AEGL values for their programs. As such, the Agency has not attempted to describe all the specific entities that may be affected by this action. If you have any questions regarding the applicability of this action to a particular entity, consult the technical person listed under **FOR FURTHER INFORMATION CONTACT**.

B. How Can I Get Additional Information, Including Copies of this Document or Other Related Documents?

1. *Electronically*. You may obtain electronic copies of this document, and certain other related documents that might be available electronically, from the EPA Internet Home Page at http://www.epa.gov/. To access this document, on the Home Page select ''Laws and Regulations,'' ''Regulations and Proposed Rules,'' and then look up the entry for this document under the ''**Federal Register**—Environmental Documents.'' You can also go directly to the **Federal Register** listings at http://www.epa.gov/fedrgstr/.

2. *In person*. The Agency has established an official record for this action under docket control number OPPTS–00329. The official record consists of the documents specifically referenced in this action, any public comments received during an applicable comment period, and other information related to this action, including any information claimed as Confidential Business Information (CBI). This official record includes the documents that are physically located in the docket, as well as the documents that are referenced in those documents. The public version of the official record does not include any information claimed as CBI. The public version of the official record, which includes printed, paper versions of any electronic comments submitted during an applicable comment period, is available for inspection in the TSCA Nonconfidential Information Center, North East Mall Rm. B–607, Waterside Mall, 401 M St., SW., Washington, DC. The Center is open from noon to 4 p.m., Monday through Friday, excluding legal holidays. The telephone number for the Center is (202) 260–7099.

II. Background

A. What Action is the Agency Taking?

EPA is renewing the charter for the NAC/AEGL Committee for an additional 2-year period.

The NAC/AEGL Committee provides advice and recommendations to the Administrator of EPA on issues associated with the development of acute exposure guideline levels for hazardous substances. Acute exposure guideline levels for hazardous substances are used by other Federal agencies, State and local governments, and private organizations for exposure limits in chemical emergency programs.

It is determined that the NAC/AEGL Committee is in the public's interest and is related to the performance of duties imposed on the Agency by law.

B. What is the Agency's Authority for Taking this Action?

The charter for the NAC/AEGL Committee is in accordance with the provisions of FACA, 5 U.S.C. App., section 9(c).

List of Subjects

Environmental protection, Acute exposure guideline levels, Hazardous substances, Public health, Safety, Worker protection.

Dated: January 3, 2002.

Stephen L. Johnson,

Assistant Administrator for the Office of Prevention, Pesticides, and Toxic Substances.

[FR Doc. 02–961 Filed 1–14–02; 8:45 am]

BILLING CODE 6560–50–S

ENVIRONMENTAL PROTECTION AGENCY

[OPP;–00756;FRL–6820–1]

FIFRA Scientific Advisory Panel; Notice of Public Meeting

AGENCY: Environmental Protection Agency (EPA).

ACTION: Notice.

SUMMARY: There will be a 4–day meeting of the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) and Food Quality Protection Act (FQPA) Scientific Advisory Panel (SAP) to review a set of issues being considered by the Agency pertaining to methods used to conduct a preliminary cumulative risk assessment for organophosphorous pesticides. Seating at the meeting will be on a first-come basis. Individuals requiring special accommodations at this meeting, including wheelchair access, should contact Paul Lewis at the address listed under **FOR FURTHER INFORMATION CONTACT** at least 5 business days prior to the meeting so that appropriate arrangements can be made.

DATES: The meeting will be held on February 5th–8th, 2002 from 8:30 a.m. to 5 p.m.

ADDRESSES: The meeting will be held at the Sheraton Crystal City Hotel, 1800 Jefferson Davis Highway, Arlington, VA 22202. The telephone number for the Sheraton Crystal City Hotel is (703) 486–1111.

Requests to participate may be submitted by mail, electronically, or in person. Please follow the detailed instructions for each method as provided in Unit I. of the

SUPPLEMENTARY INFORMATION: To ensure proper receipt by EPA, your request must identify docket control number

OPP–00756 in the subject line on the first page of your response.

FOR FURTHER INFORMATION CONTACT: Paul Lewis, Designated Federal Official, Office of Science Coordination and Policy, (7201M), Environmental Protection Agency, Ariel Rios Bldg., 1200 Pennsylvania Ave., NW., Washington, DC 20460; telephone number: (202) 564–8450; fax number: (202) 564–8382; e-mail address: lewis.paul@epa.gov.

SUPPLEMENTARY INFORMATION:

I. General Information

A. Does this Action Apply to Me?

This action is directed to the public in general. This action may, however, be of interest to persons who are or may be required to conduct testing of chemical substances under the Federal Food, Drug, and Cosmetic Act (FFDCA), FIFRA and FQPA. Since other entities may also be interested, the Agency has not attempted to describe all the specific entities that may be affected by this action. If you have any questions regarding the applicability of this action to a particular entity, consult the person listed under **FOR FURTHER INFORMATION CONTACT.**

B. How Can I Get Additional Information, Including Copies of this Document and Other Related Documents?

1. *Electronically*. A meeting agenda and background documents relevant to this meeting are now available. The EPA's position paper and questions to the FIFRA SAP, and Panel composition (i.e. SAP members and consultants) will be available as soon as possible, but no later than mid January. In addition, the Agency may provide additional background documents as the material becomes available. You may obtain electronic copies of these documents, and certain other related documents that might be available electronically, from the FIFRA SAP Internet Home Page at http://www.epa.gov/scipoly/sap. To access this document on the Home Page select **Federal Register** notice announcing this meeting. You can also go directly to the **Federal Register** listings at http://www.epa.gov/fedrgstr/.

2. *In person*. The Agency has established an administrative record for this meeting under docket control number OPP–00756. The administrative record consists of the documents specifically referenced in this notice, any public comments received during an applicable comment period, and other material information, including any information claimed as Confidential Business Information (CBI). This administrative record includes the documents that are physically located in the docket, as well as the documents that are referenced in those documents. In addition, the Agency may provide additional background documents as the material becomes available. The public version of the administrative record, which includes printed, paper versions of any electronic comments that may be submitted during an applicable comment period, is available for inspection in the Public Information and Records Integrity Branch (PIRIB), Rm. 119, Crystal Mall #2, 1921 Jefferson Davis Hwy., Arlington, VA, from 8:30 a.m. to 4 p.m., Monday through Friday, excluding legal holidays. The PIRIB telephone number is (703) 305–5805.

C. How Can I Request to Participate in this Meeting?

You may submit a request to participate in this meeting through the mail, in person, or electronically. Do not submit any information in your request that is considered CBI. To ensure proper receipt by EPA, it is imperative that you identify docket control number OPP–00756 in the subject line on the first page of your request. Public statements presented at the meetings should not be repetitive of previously submitted oral or written statements.

Oral comments: Although requests for oral comments are accepted until the date of the meeting (unless otherwise stated), to the extent that time permits, interested persons may be permitted by the Chair of the FIFRA SAP to present oral statements at the meeting. Each individual or group wishing to make a brief oral presentation to the SAP is strongly advised to submit their request to the person listed under **FOR FURTHER INFORMATION CONTACT** no later than noon Eastern Standard Time, Thursday, January 31, 2002 in order to be included on the meeting agenda. The request should identify the name of the individual making the presentation, the organization (if any) the individual will represent, and any requirements for audiovisual equipment (e.g., overhead projector, 35 mm projector, chalkboard). Oral statements before the Panel are limited to approximately 5 minutes unless prior arrangements have been made. In addition, the speaker should bring to the meeting 30 copies of their comments and presentation slides for distribution to the Panel at the meeting.

Written comments: Although requests for written comment are accepted until the date of the meeting (unless otherwise stated), the Agency encourages that written statements be submitted no later than noon Eastern Standard Time, Thursday, January 31, 2002 to provide Panel members the time necessary to consider and review the comments. There is no limit on the extent of written comments for consideration by the Panel. Persons wishing to submit written comments at the meeting should contact the person listed under **FOR FURTHER INFORMATION CONTACT** and submit 30 copies.

1. *By mail*. You may submit a request to: Public Information and Records Integrity Branch (PIRIB), Information Resources and Services Division (7502C), Office of Pesticide Programs (OPP), Environmental Protection Agency, Ariel Rios Bldg., 1200 Pennsylvania Ave., NW., Washington, DC 20460.

2. *In person or by courier*. Public Information and Records Integrity Branch (PIRIB), Information Resources and Services Division (7502C), Office of Pesticide Programs (OPP), Environmental Protection Agency, Rm. 119, Crystal Mall #2, 1921 Jefferson Davis Hwy., Arlington, VA. The PIRIB is open from 8:30 a.m. to 4 p.m., Monday through Friday, excluding legal holidays. The PIRIB telephone number is (703) 305–5805.

3. *Electronically*. You may submit your request electronically by e-mail to: opp-docket@epa.gov. Do not submit any information electronically that you consider to be CBI. Use WordPerfect 6.1/8.0 or ASCII file format and avoid the use of special characters and any form of encryption. Be sure to identify by docket control number OPP–00756. You may also file a request online at many Federal Depository Libraries.

II. Background

A. Purpose of the Meeting

The Food Quality Protection Act of 1996 amended the FIFRA and the FFDCA. One of the major changes is the requirement that EPA consider risk posed by pesticides acting by common mechanism of toxicity. For such groups of pesticides, EPA's Office of Pesticide Programs (OPP) has treated cumulative risk, under FQPA, as the risk of a common toxic effect associated with concurrent exposure by all relevant pathways and routes.

Organophosphorous pesticides were assigned priority for tolerance reassessment early during the process of FQPA implementation. OPP considered whether this group of pesticides caused common toxic effects by a common mechanism of toxicity using EPA's ''guidance for identifying pesticide chemicals and other substances that have a common mechanism of toxicity.'' The inhibition of acetylcholinesterase was a focal point given that most

organophosphorous pesticides cause this response as their critical and common effect. When acetylcholinesterase is inhibited, acetylcholine accumulates and cholinergic toxicity results due to continuous stimulation of cholinergic receptors throughout the central and peripheral nervous systems which innervate virtually every organ in the body. Cholinergic effects associated with exposures to OP pesticides have been found in both humans and animals.

OPP proceeded with the methodology and risk assessment development in a step by step process. The approach to the risk assessment was evaluated using a case study of 3 organophosphorous pesticides. That assessment was reviewed by the SAP (September and December, 1999), who recommended that OPP proceed with a more comprehensive case study. OPP developed the hazard, dose-response and exposure assessment for twenty four OP pesticides and brought it to the SAP for comment in September and December of 2000. Based on the comments, the hazard and dose-response assessment was revised and again reviewed by the SAP in September, 2001.

The exposure assessment of the OP pesticides presented here incorporates probabilistic approaches in all pathways considered: Food, drinking water, and residential/non-occupational. The methodology for conducting a preliminary cumulative risk assessment for the organophosphorous pesticides presented here is a first time that the Agency has assessed risk combining multiple sources of exposure for multiple chemicals acting via a common mechanism of toxicity. The general methodology and the specific approach have been under development for 5 years and have been subject to extensive peer review and public comment.

B. Panel Report

The Panel will prepare a report of its recommendations to the Agency in approximately 60 days. The report will be posted on the FIFRA SAP web site or may be obtained by contacting the Public Information and Records Integrity Branch at the address or telephone number listed in Unit I. of this document.

List of Subjects

Environmental protection.

Dated: January 8, 2002.

Vanessa Vu,

Director, Office of Science Coordination and Policy

[FR Doc. 02–960 Filed 1–14–02; 8:45 am]

BILLING CODE 6560–50–S

ENVIRONMENTAL PROTECTION AGENCY

[FRL–7128–9]

Notice of the Eighth Meeting of the Mississippi River/Gulf of Mexico Watershed Nutrient Task Force

AGENCY: Environmental Protection Agency (EPA).

ACTION: Notice; announcement meeting.

SUMMARY: This notice announces the Eighth Meeting of the Mississippi River/Gulf of Mexico Watershed Nutrient Task Force. The purpose of this Task Force, consisting of federal, state, and tribal members, is to lead efforts to coordinate and support nutrient management and hypoxia-related activities in the Mississippi River and Gulf of Mexico watersheds. The major matter to be discussed at the meeting is the implementation of the Action Plan for Reducing, Mitigating, and Controlling Hypoxia in the Northern Gulf of Mexico. The Plan was developed in fulfillment of a requirement of section 604(b) of the Harmful Algal Blooms and Hypoxia Research Control Act (Pub. L. 105–383—Coast Guard Authorization Act of 1998) and was submitted as a Report to Congress on January 18, 2001. The public will be afforded an opportunity to provide input to the Task Force during open discussion periods. The meeting coincides with a meeting of the Ohio River Valley Water Sanitation Commission in the vicinity, and will afford opportunities for exchange between the participants of both meetings. The meeting room accommodates approximately 125 people.

DATES: The two-day meeting will be held from 2 p.m.–5:30 p.m., February 7, 2002 and from 8 a.m.–3:30 p.m., February 8, 2002.

ADDRESSES: The meeting will be held at the Radisson Hotel and Suites Downtown, 200 North Fourth Street, St. Louis, MO 63102. A block of rooms has been reserved at the hotel. For reservations, call (314) 621–8200 or 1–800–925–1395. When making room reservations, use the group name ''EPA Mississippi River/Gulf of Mexico Meeting.'' (Internet: *http://www.radisson.com/stlouismo*)

FOR FURTHER INFORMATION CONTACT: Dr. Mary Belefski, U.S. EPA, Assessment and Watershed Protection Division (AWPD), Mail Code 4503F, 1200 Pennsylvania Avenue, NW., Washington, DC 20460; Phone (202)–260–7061; E-mail: *belefski.mary@epa.gov.* For additional information on logistics and accommodations, contact Ansu John, Tetra Tech, Inc., 10306 Eaton Place, Suite 340, Fairfax, VA 22030; Phone: (703) 385–6000; E-mail: *ansu.john@tetratech-ffx.com.*

Dated: January 8, 2002.

Robert Wayland III,

Director, Office of Wetlands, Oceans, and Watersheds.

[FR Doc. 02–956 Filed 1–14–02; 8:45 am]

BILLING CODE 6560–50–P

ENVIRONMENT PROTECTION AGENCY

[FRL–7129–1]

Notice of Public Meeting of the National Environmental Education Advisory Council

Notice is hereby given that the National Environmental Education Advisory Council, established under section 9 of the National Environmental Education Act of 1990 (the Act), will hold a public meeting on January 31 and February 01, 2002. The meeting will take place at the Four Seasons Hotel, 411 University Street, Seattle, WA, 98101 from 9 am to 5 pm on Thursday, January 31st and Friday, February 1st. The purpose of this meeting is to provide the Council with an opportunity to advise EPA's Office of Communications, Education and Media Relations (OCEMR) and the Office of Environmental Education (OEE) on its implementation of the Act. Members of the public are invited to attend and to submit written comments to EPA following the meeting.

For additional information regarding the Council's upcoming meeting, please contact Ginger Keho, Office of Environmental Education (1704), Office of Communications, Education and Media Relations, U.S. Environmental Protection Agency, 1200 Pennsylvania Avenue, NW., Washington, DC 20460 or call (202) 564–0453.

Dated: January 8, 2002.

Ginger Keho,

Designated Federal Official, National Environmental Education Advisory Council.

[FR Doc. 02–957 Filed 1–14–02; 8:45 am]

BILLING CODE 6560–50–N

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FIFRA Scientific Advisory Panel (SAP) February Meeting Agenda

January 31, 2002

OPEN MEETING
FEBRUARY 5-8, 2002
FIFRA SAP WEB SITE https://www.epa.gov/oscpmont/sap/
OPP Docket Telephone: (703)305-5805

TUESDAY, FEBRUARY 5, 2002
SHERATON CRYSTAL CITY HOTEL
1800 JEFFERSON DAVIS HIGHWAY
ARLINGTON, VIRGINIA 22202
703-486-1111

METHODS USED TO CONDUCT A PRELIMINARY CUMULATIVE RISK ASSESSMENT FOR ORGANOPHOSPHATE PESTICIDES

- **8:30 AM Introduction and identification of Panel members** - Ronald J. Kendall, Ph.D. (FIFRA SAP Session Chair)
- **8:45 AM Administrative procedures by Designated Federal Official** - Mr. Paul Lewis
- **8:50 AM Welcome** - Mr. Stephen L. Johnson, Assistant Administrator, Office of Prevention, Pesticides and Toxic Substances, EPA
- **9:00 AM Opening Remarks** - Ms. Marcia E. Mulkey Director (Office of Prevention, Pesticides and Toxic Substances, Office of Pesticide Programs, EPA)
- **9:10 AM Introduction, goals and objectives** - Ms. Margaret Stasikowski (Office of Pesticide Programs, EPA)
- **9:45 AM Public Comments** Jennifer Sass, Ph.D., on behalf of the Natural Resources Defense Council
  Mr. Daniel Botts, Florida Fruit & Vegetable Association, on behalf of the FQPA Implementation Working Group
  Mr. Jeffrey Driver, Infoscientific.com, Inc., on behalf of the FQPA Implementation Working Group
  Mr. Jack Zabik, Dow AgroSciences, on behalf of the FQPA Implementation Working Group
  Mr. Adam Goldberg, on behalf of Consumers Union

- **10:30 AM BREAK**
- **10:45 AM Public Comments (continued)**
- **12:30 PM LUNCH**

SESSION 1: HAZARD AND DOSE RESPONSE ANALYSIS

- **1:30 PM Hazard/relative potency factor** - Anna B. Lowit, Ph.D (Office of Pesticide Programs, EPA), R. Woodrow Setzer, Ph.D. (Office of Research and Development, EPA) and Vicki Dellarco, Ph.D. (Office of Pesticide Programs, EPA)
- **3:00 PM BREAK**
- **3:15 PM Public Comments** Mr. Tim Pastoor, Syngenta Corporation, on behalf of the FQPA Implementation Working Group
- **4:00 PM Panel discussion**

1. A) In September 2001, the FIFRA SAP made some specific recommendations to EPA

concerning refinements of its dose response analysis of cholinesterase data on OPs such as:

- the derivation of the adjustment factor "B" and modification of the decision tree for use of "B";
- a formal analysis of residuals;
- minor revision to the agency's OPCumRisk program (i.e., revision of the calculation as of the goodness of fit statistic and deletion on p- and t-values);
- consideration of the appropriate measure of relative potency;
- expression of inhalation exposure in the same units as the oral doses and adjustment for actual treatment durations;
- consideration of the impact of individual animal data instead of summary information;
- and derivation of oral doses from the actual dietary intake rates.

Please comment on how the Agency addressed the recommendations listed above (I.B and III.B.3). **Lead Discussant: Stephen Brimijoin, Ph.D. Associate Discussants: Patrick Durkin, Ph.D., Rory Conolly, Ph.D. and Eugene McConnell, D.V.M.**

B) Several of these issues were addressed by the application of the nonlinear mixed effect model for combining cholinesterase data. In addition, EPA utilized the profile likelihood method for estimating horizontal asymptotes when they could not be estimated jointly with the other parameters. Please comment on the use of these statistical procedures in the dose-response assessment of the organophosphate pesticides.

Lead Discussant: Steven Heeringa, Ph.D. Associate Discussants: Christopher Portier, Ph.D., Peter Macdonald, D. Phil, and Lauren Zeise, Ph.D.

- **5:30 PM ADJOURNMENT**

WEDNESDAY, FEBRUARY 6, 2002
SHERATON CRYSTAL CITY HOTEL
1800 JEFFERSON DAVIS HIGHWAY
ARLINGTON, VIRGINIA 22202
703-486-1111

METHODS USED TO CONDUCT A PRELIMINARY CUMULATIVE RISK ASSESSMENT FOR ORGANOPHOSPHATE PESTICIDES (CONTINUED)

SESSION 1: HAZARD AND DOSE RESPONSE ANALYSIS (continued)

- **8:30 AM Introduction and identification of new Panel members** - Ronald J. Kendall, Ph.D. (FIFRA SAP Session Chair)
- **8:45 AM Administrative procedures by Designated Federal Official** - Mr. Paul Lewis
- **8:50 AM Follow-up from previous day's discussion** - Randolph Perfetti, Ph.D. (Office of Pesticide Programs, EPA)
- **9:00 AM Panel discussion (continued)**

2. An exponential model was utilized by EPA in the July, 2001 Preliminary Hazard and Dose-Response Assessment of the Organophosphate Pesticides. Based on the equation used in the July 2001 document, cholinesterase activity decreases linearly in the low dose region of the dose response curve. Stakeholders present at the Technical Briefing (August 2001) and also a few members of the SAP (September 2001) suggested that a flat low dose region may be a more appropriate modeling approach. In response to this issue, EPA has further investigated the shape of the low dose region of the dose-response curve. Two versions of the exponential model were used in the December 2001 hazard and dose-response assessment. One version, called the basic model, describes a linear low dose region and is similar to the approach used in the July 2001 document. All 29 OPs were fit to the basic model. The second version, called the expanded model, incorporates two additional variables, shape and displacement, which describe a flat low dose region of the dose-response curve. The female brain ChE data supported a flat low dose region for eight OPs (azinphos methyl, bensulide, disulfoton, malathion, methyl parathion, phorate, phosmet, and terbufos).

Please comment on the mathematical derivation of the expanded model in addition to the profile likelihood method for estimating the shape and displacement parameters when they could not be estimated jointly with the other parameters (I.B and III.B.1).

Lead Discussant: Peter Macdonald, D. Phil Associate Discussants: Jean Harry, Ph.D., Lorenz Rhomberg, Ph.D. Rory Conolly, Ph.D. and Patrick Durkin, Ph.D.

- **10:00 AM BREAK SESSION 2: ASSESSMENT OF FOOD EXPOSURE**

- **10:15 AM Assessment of food exposure** - William O. Smith, Ph.D. and Mr. David Miller (Office of Pesticide Programs, EPA)
- **11:45 AM LUNCH**
- **12:45 PM Public Comments** Ms. Ingrid Kelley, Bayer Corporation, on behalf of the FQPA Implementation Working Group
- **1:30 PM Panel discussion**

1. In the Preliminary OP Cumulative Risk Assessment, OPP used all available PDP monitoring data generated since 1994 as the basis for the residue distributions of pesticides in treated foods. As a result, some foods have multiple years of data (as many as 5), while others have only a single year of data. All years of data were included to provide the most robust residue data set possible. These data were extended to cover foods and processed forms of foods for which data are not directly available. Additionally, some foods were included in the analysis based on less robust data from FDA.

OPP is conducting a sensitivity analysis in which the residue contributions from specific foods (either one at a time or in combination with other foods) are removed from the analysis. This analysis is being conducted as part of an effort to determine the contributions of specific food commodities and chemicals to the upper tail of the exposure distribution. Some preliminary results are shown in Table 1 of the addendum to this document.

Partly as a result of this exercise, OPP has observed that the more variables (e.g., commodities, chemicals, years of data) that are included in the exposure distribution, the more difficult it becomes to affect the tail of the distribution by removing commodity/pesticide combinations from the calculations. While removal of most exposure contributors results in a demonstrable change in the lower portion of the distribution, the exposures at the upper end of the tail (for example the 99.9^{th} percentile) are relatively unaffected by removal of a single commodity, even if it is identified by DEEM as a frequent contributor to the high end of the exposure distribution.

Please discuss the significance of this observation and its potential impact on interpretation of the output distributions and results from highly complex distributional analyses such as the Preliminary OP Cumulative Risk Assessment.

Lead Discussant: Steven Heeringa, Ph.D., Associate Discussants: Ruby Reed, Ph.D. , Rory Conolly, Ph.D. and Lauren Zeise, Ph.D.

2. A) The Calendex model can be used in a number of modes to develop a profile of exposure estimates. In the current assessment, OPP conducted a series of single-day assessments arrayed chronologically to develop a response surface of exposures. A constant percentile of exposure was selected to represent the potential exposure to a given percentile of the population. For example, the 99^{th} percentile for each day would be arrayed for 365 days to reflect the population estimate across the calendar year. Calendex can also be used in a multi-day sequential series analysis, also referred to as a "rolling time frame mode." A rolling time frame provides an estimate of the average of daily exposures for an individual calculated over multiple (7, 14, 21, or 28) days, for each multiple day period over the course of a year, (e.g., days 1 - 7, then days 2 - 8, then days 3 - 9, etc.). In this mode, an individual's food exposure is tracked across the calendar year by randomly selecting day one or day two of that individual's reported consumption from the CSFII and combining each commodity which comprises that consumption with randomly selected residue values for each day of the calendar year. These rolling averages for each individual are assembled to develop a distribution of rolling average exposures.

During previous SAP meetings, the Panel has expressed concern about the use of CSFII records to represent longitudinal consumption patterns for individuals. Concern arose as a result of the design of the CSFII study, in which two **nonconsecutive** days of data (separated by 3 to 10 days) were collected for each individual.

Please comment on the use of CSFII data to support each of these two modes of Calendex as they pertain to the cumulative risk assessment of pesticides in foods.

Lead Discussant: Peter Macdonald, D. Phil Associate Discussants: Natalie Freeman, Ph.D. Ruby Reed, Ph.D. and Steven Heeringa, Ph.D.

B) The random selection of PDP residue values assumes that the residues in foods consumed across a series of days are independent of each other. In other words, foods consumed are from unrelated sources and there is no carryover from one day to another. This assumption may be inappropriate given that many consumers obtain food in bulk (i.e., multi-day)

quantities that may have similar treatment history and would typically consume this food over a short multi-day period (e.g., leftovers). In such a case the residues contained in the foods would violate the assumption of independence.

Please comment on the use of PDP data to support each of these two modes of Calendex as they pertain to the cumulative risk assessment of pesticides in foods. What issues are likely to accrue from the assumption of independence in residue data?

Lead Discussant: Ruby Reed, Ph.D. Associate Discussants: Steven Heeringa, Ph.D., Peter Macdonald, D. Phil and Lauren Zeise, Ph.D.

- **3:15 PM BREAK**

SESSION 3: ASSESSMENT OF DRINKING WATER EXPOSURE

- **3:30 PM Assessment of drinking water exposure** - Mr. Kevin Costello (Office of Pesticide Programs, EPA) and Mr. Nelson Thurman (Office of Pesticide Programs, EPA)
- **4:30 PM Public Comments** Mr. Ray Layton, Du Pont, on behalf of the FQPA Implementation Working Group
- **5:15 PM ADJOURNMENT**

THURSDAY, FEBRUARY 7, 2002
SHERATON CRYSTAL CITY HOTEL
1800 JEFFERSON DAVIS HIGHWAY
ARLINGTON, VIRGINIA 22202
703-486-1111

METHODS USED TO CONDUCT A PRELIMINARY CUMULATIVE RISK ASSESSMENT FOR ORGANOPHOSPHATE PESTICIDES (CONTINUED)

SESSION 3: ASSESSMENT OF DRINKING WATER EXPOSURE (continued)

- **8:30 AM Introduction and identification of new Panel members** - Ronald J. Kendall, Ph.D. (FIFRA SAP Session Chair)
- **8:45 AM Administrative procedures by Designated Federal Official** - Ms. Olga Odiott
- **8:50 AM Follow-up from previous day's discussion** - Randolph Perfetti, Ph.D. (Office of Pesticide Programs, EPA)
- **9:00 AM Panel discussion**

1. After evaluation of available monitoring data and consideration of the available tools for estimating pesticide exposure in drinking water, the agency adapted available tools to provide watershed-level estimates of residues in drinking water sources. These tools have been presented to the SAP in the past in relation to individual chemical assessments and have been improved as a result of panel feedback. Because of differences between individual and cumulative assessments, this assessment reflects novel uses for some of these tools. The approach used in the Preliminary OP Cumulative Risk Assessment:

  - Used PRZM/EXAMS with the Index Reservoir, along with local site characteristics to estimate concentrations in the drinking water reservoir
  - Simulated multiple OP uses on multiple fields within that watershed
  - Adjusted for area within the watershed that potentially contributed OP loads to the reservoir using a cumulative adjustment factor
  - Provided a qualitative, rather than quantitative, assessment of treatment effects on residues

Are there significant flaws in this approach and its assumptions that would be likely to lead to consistent significant underestimation of daily levels of residues in surface water across the calendar year (for instance, an order of magnitude)? If such flaws exist, what can be done to correct them? What additional information and/or tools might be available that will meet the goals/needs of the cumulative OP assessment?

Lead Discussant: Paul Capel, Ph.D. Associate Discussants: Bernard Engel, Ph.D., Peter Richards, Ph.D. and Richard Bull, Ph.D.

2. It is not feasible to conduct drinking water assessments for every watershed in which OP pesticides are used. Therefore, regional water exposure assessments were used to represent exposures from typical OP usage conditions at one of the more vulnerable surface watersheds in the region. Each regional assessment focuses on areas where combined OP exposure is

likely to be among the highest within the region as a result of total OP usage and vulnerability of the drinking water sources. In this manner, OPP is confident that if the regional cumulative risk assessment finds that exposure in water is not a significant contributor to the overall OP exposure in that area, it will not be a significant contributor in other areas in the region.

Does the SAP see anything that would call this assumption into question? If the regional approach, with its assumptions is inadequate, what can be done to improve the approach?

Lead Discussant: Peter Richards, Ph.D. Associate Discussants: Richard Bull, Ph.D., Bernard Engel, Ph.D. and Paul Capel, Ph.D.

- **10:30 AM BREAK SESSION 4: ASSESSMENT OF RESIDENTIAL/NON-OCCUPATIONAL EXPOSURE**
- **10:45 AM Assessment of residential/non-occupational exposure** - Mr. Jeff Evans (Office of Pesticide Programs, EPA)
- **11:30 AM Public Comments** Jeffrey Driver, Infoscientific.com, on behalf of the FQPA Implementation Working Group
- **12:15 PM LUNCH**
- **1:15 PM Panel discussion**

1. Historically, the Agency has relied on means (primarily arithmetic or geometric) from residue and exposure studies for key input variables in exposure assessments. The recent development of calendar based models and others having features to incorporate distributions of exposure values has presented the Agency an opportunity to consider using all available data points from existing exposure and residue studies. In the Cumulative Risk Assessment Case study presented to the FIFRA Scientific Advisory Panel in September, 2000, most of the exposure variables were presented as uniform distributions. The exceptions were for variables that are reasonably well established , such as exposure durations taken from the Agency's Exposure Factors Handbook. The data used in the Case Study and in the preliminary CRA, are believed to be from well conducted studies of generally high quality. However, these data sets tend to be small (e.g., n = 10 - 30) and are being used to address wide variety of exposure situations. The uniform distribution appears to be most appropriate for these relatively small data sets because it relies on easily established values such as the minimum and maximum and provides the most conservative estimate of the standard deviation (riskanalal@lyris.pnl.gov).

Does the Panel have any additional comments or thoughts on OPP's use of the uniform distribution in general or on OPP's selection of the uniform distribution for the specific parameters chosen? What criteria, if any, would the SAP recommend for developing parametric input distributions from available data? Under what circumstances, if any, would it be appropriate to use available data empirically? Does the Panel have any recommendations on how sensitivity analyses could be performed to determine if the assumption of a uniform distribution is responsible for a majority of the risk at the tails of the exposure distribution.

Lead Discussant: John Adgate, Ph.D. Associate Discussants: Natalie Freeman, Ph.D., Dale Hattis, Ph.D., and Richard Bull, Ph.D.

2. The use of calendar based models also allows exposure assessors to consider exposure from a variety of sources from the same or from different chemicals. Longitudinal survey data such as the National Human Activity Pattern Survey (NHAPS) are available for consideration by HED for use in future assessments. In addition, from a practical standpoint, the use of such survey data ensures combinations of exposure do not come from unrealistic random combinations that current models may produce (e.g., activities adding up more than 24 hours in a day).

The use of calendar based models provides an opportunity to explore the potential for the co-occurrence of multiple sources of exposures from residential pathways. In the cumulative assessment, OPP used summary statistics from sources such as the Exposure Factors Handbook (EFH) regarding the time spent indoors, time spent on lawns and time spent at other outdoor locations. In the preliminary assessment, we assumed these activities were stochastically independent. OPP is currently evaluating data in the EFH such as data from the National Human Activity Pattern Survey (NHAPS) to determine if it can directly incorporate (i.e., empirically) information on an individual's activity patterns over a full day from this database to account for the likelihood and duration that an individual might be exposed to a pesticide through various activities over the course of a day. Please comment on whether and how OPP might directly incorporate NHAPS (or similar time use data) into the software to better account for variation in activities across individuals?

Lead Discussant: Natalie Freeman, Ph.D. Associate Discussants: John Adgate, Ph.D. , Dale Hattis, Ph.D., Ruby Reed, Ph.D. and Patrick Durkin, Ph.D.

- **2:45 PM BREAK**

SESSION 5: RISK CHARACTERIZATION

- **3:00 PM Risk characterization** - Mr. David Miller and Elizabeth Doyle, Ph.D. (Office of Pesticide Programs, EPA)
- **4:00 PM Public Comments** Mr. Jack Zabik, Dow AgroSciences, on behalf of the FQPA Implementation Working Group
- **5:00 PM ADJOURNMENT**

FRIDAY, FEBRUARY 8, 2002 SHERATON CRYSTAL CITY HOTEL 1800 JEFFERSON DAVIS HIGHWAY ARLINGTON, VIRGINIA 22202 703-486-1111

METHODS USED TO CONDUCT A PRELIMINARY CUMULATIVE RISK ASSESSMENT FOR ORGANOPHOSPHATE PESTICIDES (CONTINUED)

SESSION 5: RISK CHARACTERIZATION (continued)

- **8:30 AM Introduction** - Stephen Roberts, Ph.D. (FIFRA SAP Session Chair)
- **8:45 AM Administrative procedures by Designated Federal Official** - Ms. Olga Odiott
- **8:50 AM Follow-up from previous day's discussion** - Randolph Perfetti, Ph.D. (Office of Pesticide Programs, EPA)
- **9:00 AM Panel discussion**

1. There are several key principles for conducting a cumulative risk assessment. One such principle concerns the time frame of both the exposure (e.g., What is the exposure duration?) and of the toxic effect (e.g., What are the time to peak effects and the time to recovery?). Both must be adequately characterized prior to performing a cumulative risk assessment so that an individual's exposure is matched with relevant toxicological values in terms of duration. There are several important considerations with respect to the temporal characteristics of the exposures and of the cholinesterase inhibitory effects of organophosphorus pesticides in estimating their cumulative risk.

- There may be single day (spike) or short-term exposures to organophosphorus pesticides via food, nonoccupational/residential uses, and drinking water, as well as more or less continuous exposure via the diet (food).
- In the Preliminary OP Cumulative Risk Assessment, OPP used relative potency factors and points of departure developed from cholinesterase inhibition in rats exposed to pesticides for 21 days or more. This practice was adopted to reflect cholinesterase inhibition at a point in the treatment schedule at which a steady state had been achieved. OPP elected to use data reflecting a steady state in the interest of producing relative potency factors (RPFs) that are reproducible and reflect less uncertainty due to rapidly changing time-sensitive measures of cholinesterase. In addition, when the compounds are at steady state, the differences in toxicokinetics among the OPs are less likely to impact the assessment.
- OPP has information that indicates that the American population, in general, has some continuous level of exposure to OPs. Biomonitoring data from NHANES suggests that more than 80% of the American public have urinary metabolites indicating possible exposure to OPs.
- Most animal data available to OPP are developed using laboratory animals that were not previously exposed to OPs. In other words, the laboratory animals used in the toxicology studies were naive in their exposure to OPs. These studies show that OP's can produce cholinesterase inhibition after a single exposure. A rough comparison of the BMD_{10}s derived from female brain rat cholinesterase data from 21 days or longer duration with NOAELs based on cholinesterase data from single-dose studies reveals good similarity of values, with differences rarely exceeding two- to three-fold.
- Animal data suggest that recovery from a single exposure may take days to weeks.

In light of all these factors, OPP wants to evaluate exposure across the most appropriate time frame(s). In the Preliminary OP Cumulative Risk Assessment, OPP developed a distribution of single consecutive day exposures, considering the pattern of MOEs occurring at a particular percentile of exposure across the calendar year. This approach focuses on exposure to the population of interest as a whole rather than attempting to track the variation in an individual's exposure from various sources of pesticide exposure. As an example, at the 95^{th} percentile of exposure, each day of the year will reflect a 95th percentile exposure for the entire population and not reflect what may be lower, multi-day average exposures for any given individual.

Calendex allows calculation of multi-day, rolling averages of exposure estimates for the individuals within the population. While this may allow for a match between selected exposure

time frames (e.g., 7 day or longer) and the hazard endpoint, OPP is concerned that this may not adequately permit estimates of risk associated with shorter duration exposures.

Please comment on how best to evaluate risk, taking into account the temporal characteristics of the hazard endpoint (i.e., cholinesterase inhibition) and the temporal characteristics of the exposure patterns for the food, drinking water, and residential/nonoccupational pathways, with specific reference to:

- the pros and cons of various approaches of combining the exposure and hazard time frames to estimate cumulative risk, and
- methods to bound or estimate the biases in each approach. **Lead Discussant: Lorenz Rhomberg, Ph.D. Associate Discussants: Stephen Brimijoin, Ph.D., Peter Richards, Ph.D. Ruby Reed, Ph.D. Dale Hattis, Ph.D. Natalie Freeman, Ph.D. and Steven Heeringa, Ph.D. and Patrick Durkin, Ph.D.**

2. In the Preliminary OP Cumulative Risk Assessment, Section I.H lists a number of potential follow-up activities proposed by OPP. This list is not exhaustive. Does the Panel recommend any additional follow-up activities or sensitivity analyses beyond those listed? Does the Panel have any thoughts or recommendations about how these additional analyses should be conducted? Which activities should receive the greatest priority?

Lead Discussant: Dale Hattis, Ph.D. Associate Discussants: Lorenz Rhomberg, Ph.D., Rory Conolly, Ph.D., Eugene McConnell, D.V.M., Patrick Durkin, Ph.D., Peter Macdonald, D. Phil, Jean Harry, Ph.D. and John Adgate, Ph.D.

- **12:00 PM ADJOURNMENT**

Please be advised that agenda times are approximate. For further information, please contact the Designated Federal Official for this meeting, Mr. Paul Lewis, via telephone: (202) 564-8450; fax: (202) 564-8382; or email:lewis.paul@epa.gov.

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Methods to Conduct a Preliminary Cumulative Risk Assessment for Organophosphorous Pesticides - Panel Members

January 17, 2002

FIFRA SCIENTIFIC ADVISORY PANEL (SAP)
OPEN MEETING
FEBRUARY 5-8, 2002
FIFRA SAP WEB SITE https://www.epa.gov/scipoly/sap/ OPP Docket Telephone: (703)305-5805

TUESDAY, FEBRUARY 5, 2002
SHERATON CRYSTAL CITY HOTEL
1800 JEFFERSON DAVIS HIGHWAY
ARLINGTON, VIRGINIA 22202
703-486-1111

Introduction Hazard and Dose Response Analysis
FIFRA SAP Session Chair
Ronald Kendall, Ph.D.
Professor and Chairman, Department of Environmental Toxicology
Director, The Institute of Environmental and Human Health, Texas Tech University
Texas Tech University Health Sciences Center
Box 41163, 1207 Gilbert Drive, Reese Center
Lubbock, TX 79416

Designated Federal Official
Mr. Paul Lewis
FIFRA Scientific Advisory Panel
USEPA
Office of Science Coordination and Policy
1200 Pennsylvania Avenue, N.W.
7201M
Washington, DC 20460
(202) 564 8450; FAX: (202) 564-8382
lewis.paul@epa.gov

FIFRA Scientific Advisory Panel Members
Herb Needleman, M.D.
Professor of Psychiatry and Pediatrics
School of Medicine
University of Pittsburgh
310 Keystone Building
3529 Fifth Avenue
Pittsburgh, PA 15213

Christopher J. Portier, Ph.D.
Director, Environmental Toxicology Program

National Institute of Environmental Health Sciences
111 T.W. Alexander Drive, Bldg. 101, Room A330
Research Triangle Park, NC 27709-12233

Stephen M. Roberts, Ph.D.
Professor and Program Director
University of Florida
Center for Environmental & Human Toxicology
Building 471 Mowry Road
Gainesville, Florida 32611

Mary Anna Thrall, D.V.M.
Professor, Department of Pathology
College of Veterinary and Biomedical Sciences
Colorado State University
Fort Collins, CO 80523

FQPA Science Review Board Members

John Adgate, Ph.D.
University of Minnesota
School of Public Health
420 Delaware St. S.E.
Minneapolis, MN 55455

William Brimijoin, Ph.D.
Department of Pharmacology
Mayo Clinic and Medical School
200 1st st SW
Rochester, MN 55905

Richard Bull, Ph.D,
MoBull Consulting
8382 Gage Boulevard
Suite O, Box 511
Kennewick, WA 99336

Rory Conolly, Sc.D.
Senior Scientist
Chemical Industry Institute of Toxicology Center for Health Research
6 Davis Drive
Research Triangle Park, North Carolina 27709

Patrick Durkin, Ph.D., Vice President
Syracuse Environmental Research Associates, Inc.
5100 Highbridge Street
Building 42C
Fayetteville, NY 13066

Natalie Freeman, Ph.D.
Robert Wood Johnson School of Medicine
Department of Environmental and Community Medicine
170 Frelinghuysen Road
Piscataway, NJ 08854

Jeanne Harry, Ph.D.
National Institute of Environmental Health Science
111 Alexander Drive

Research Triangle Park, NC 27709

Steven Heeringa, Ph.D.
Institute for Social Research
University of Michigan
PO Box 1248
Ann Arbor, MI 48106

Ernest McConnell, DVM
President
Toxpath Inc.
3028 Ethan Lane
Raleigh, NC 27613

Peter MacDonald, D. Phil.
Professor of Mathematics and Statistics,
Department of Mathematics and Statistics,
McMaster University
1208 Main Street West
Hamilton, Ontario, Canada L8S4K1

Nu-May Ruby Reed, Ph.D.
Staff Toxicologist
California Environmental Protection Agency
Department of Pesticide Regulation
1001 "I" Street
Sacramento, California 95814-2828

Lorenz Rhomberg, Ph.D.
Gradient Corporation
238 Main Street
Cambridge, MA 02142

Lauren Zeise, Ph.D., Chief
Reproductive and Cancer Hazard Assessment
Office of Environmental Health Hazard Assessment
1515 Clay Street, 16th Floor, Oakland, CA 94612

WEDNESDAY, FEBRUARY 6, 2002
SHERATON CRYSTAL CITY HOTEL
1800 JEFFERSON DAVIS HIGHWAY
ARLINGTON, VIRGINIA 22202
703-486-1111

Methods Used to Conduct a Preliminary Cumulative Risk Assessment for Organophosphorous Pesticides

Hazard and Dose Response Analysis

FIFRA SAP Session Chair
Ronald Kendall, Ph.D.
Professor and Chairman, Department of Environmental Toxicology
Director, The Institute of Environmental and Human Health, Texas Tech University
Texas Tech University Health Sciences Center
Box 41163, 1207 Gilbert Drive, Reese Center
Lubbock, TX 79416

Designated Federal Official
Mr. Paul Lewis
FIFRA Scientific Advisory Panel
Office of Science Coordination and Policy

Environmental Protection Agency
1200 Pennsylvania Avenue, N.W.
(7201M)
Washington, DC 20460
(202) 564 8450; FAX: (202) 564-8382
lewis.paul@epa.gov

FIFRA Scientific Advisory Panel Members

Herb Needleman, M.D.
Professor of Psychiatry and Pediatrics
School of Medicine
University of Pittsburgh
310 Keystone Building
3529 Fifth Avenue
Pittsburgh, PA 15213

Christopher J. Portier, Ph.D.
Director, Environmental Toxicology Program
National Institute of Environmental Health Sciences
111 T.W. Alexander Drive, Bldg. 101, Room A330
Research Triangle Park, NC 27709-12233

Stephen M. Roberts, Ph.D.
Professor and Program Director
University of Florida
Center for Environmental & Human Toxicology
Building 471 Mowry Road
Gainesville, Florida 32611

Mary Anna Thrall, D.V.M.
Professor, Department of Pathology
College of Veterinary and Biomedical Sciences
Colorado State University
Fort Collins, CO 80523

FQPA Science Review Board Members

John Adgate, Ph.D.
University of Minnesota
School of Public Health
420 Delaware St. S.E.
Minneapolis, MN 55455

William Brimijoin, Ph.D.
Department of Pharmacology
Mayo Clinic and Medical School
200 1st st SW
Rochester, MN 55905

Richard Bull, Ph.D,
MoBull Consulting
8382 Gage Boulevard
Suite O, Box 511
Kennewick, WA 99336

Rory Conolly, Sc.D.
Senior Scientist
Chemical Industry Institute of Toxicology Center for Health Research
6 Davis Drive

Research Triangle Park, North Carolina 27709

Patrick Durkin, Ph.D., Vice President
Syracuse Environmental Research Associates, Inc.
5100 Highbridge Street
Building 42C
Fayetteville, NY 13066

Natalie Freeman, Ph.D.
Robert Wood Johnson School of Medicine
Department of Environmental and Community Medicine
170 Frelinghuysen Road
Piscataway, NJ 08854

Jeanne Harry, Ph.D.
National Institute of Environmental Health Science
111 Alexander Drive
Research Triangle Park, NC 27709

Steven Heeringa, Ph.D.
Institute for Social Research
University of Michigan
PO Box 1248
Ann Arbor, MI 48106

Ernest McConnell, DVM
President
Toxpath Inc.
3028 Ethan Lane
Raleigh, NC 27613

Peter MacDonald, D. Phil.
Professor of Mathematics and Statistics,
Department of Mathematics and Statistics,
McMaster University
1208 Main Street West
Hamilton, Ontario, Canada L8S4K1

Nu-May Ruby Reed, Ph.D.
Staff Toxicologist
California Environmental Protection Agency
Department of Pesticide Regulation
1001 "I" Street
Sacramento, California 95814-2828

Lorenz Rhomberg, Ph.D.
Gradient Corporation
238 Main Street
Cambridge, MA 02142

Lauren Zeise, Ph.D., Chief
Reproductive and Cancer Hazard Assessment
Office of Environmental Health Hazard Assessment
1515 Clay Street, 16th Floor, Oakland, CA 94612

Assessment of Food Exposure

FIFRA SAP Session Chair

Ronald Kendall, Ph.D.
Professor and Chairman, Department of Environmental Toxicology
Director, The Institute of Environmental and Human Health, Texas Tech University
Texas Tech University Health Sciences Center
Box 41163, 1207 Gilbert Drive, Reese Center
Lubbock, TX 79416

Designated Federal Official

Mr. Paul Lewis
FIFRA Scientific Advisory Panel
Office of Science Coordination and Policy
Environmental Protection Agency
1200 Pennsylvania Avenue, N.W.
(7201M)
Washington, DC 20460
(202) 564 8450; FAX: (202) 564-8382
LEWIS.PAUL@EPA.GOV

FIFRA Scientific Advisory Panel Members

Herb Needleman, M.D.
Professor of Psychiatry and Pediatrics
School of Medicine
University of Pittsburgh
310 Keystone Building
3529 Fifth Avenue
Pittsburgh, PA 15213

Christopher J. Portier, Ph.D.
Director, Environmental Toxicology Program
National Institute of Environmental Health Sciences
111 T.W. Alexander Drive, Bldg. 101, Room A330
Research Triangle Park, NC 27709-12233

Stephen M. Roberts, Ph.D.
Professor and Program Director
University of Florida
Center for Environmental & Human Toxicology
Building 471 Mowry Road
Gainesville, Florida 32611

Mary Anna Thrall, D.V.M.
Professor, Department of Pathology
College of Veterinary and Biomedical Sciences
Colorado State University
Fort Collins, CO 80523

FQPA Science Review Board Members

John Adgate, Ph.D.
University of Minnesota
School of Public Health
420 Delaware St. S.E.
Minneapolis, MN 55455

William Brimijoin, Ph.D.
Department of Pharmacology
Mayo Clinic and Medical School
200 1st st SW
Rochester, MN 55905

Richard Bull, Ph.D,
MoBull Consulting
8382 Gage Boulevard
Suite O, Box 511
Kennewick, WA 99336

Rory Conolly, Sc.D.
Senior Scientist
Chemical Industry Institute of Toxicology Center for Health Research
6 Davis Drive
Research Triangle Park, North Carolina 27709

Patrick Durkin, Ph.D., Vice President
Syracuse Environmental Research Associates, Inc.
5100 Highbridge Street
Building 42C
Fayetteville, NY 13066

Natalie Freeman, Ph.D.
Robert Wood Johnson School of Medicine
Department of Environmental and Community Medicine
170 Frelinghuysen Road
Piscataway, NJ 08854

Jeanne Harry, Ph.D.
National Institute of Environmental Health Science
111 Alexander Drive
Research Triangle Park, NC 27709

Steven Heeringa, Ph.D.
Institute for Social Research
University of Michigan
PO Box 1248
Ann Arbor, MI 48106

Ernest McConnell, DVM
President
Toxpath Inc.
3028 Ethan Lane
Raleigh, NC 27613

Peter MacDonald, D. Phil.
Professor of Mathematics and Statistics,
Department of Mathematics and Statistics,
McMaster University
1208 Main Street West
Hamilton, Ontario, Canada L8S4K1

Nu-May Ruby Reed, Ph.D.
Staff Toxicologist
California Environmental Protection Agency
Department of Pesticide Regulation
1001 "I" Street
Sacramento, California 95814-2828

Lorenz Rhomberg, Ph.D.
Gradient Corporation
238 Main Street
Cambridge, MA 02142

Lauren Zeise, Ph.D., Chief
Reproductive and Cancer Hazard Assessment
Office of Environmental Health Hazard Assessment
1515 Clay Street, 16th Floor, Oakland, CA 94612

Assessment of Drinking Water Exposure

FIFRA SAP Session Chair
Ronald Kendall, Ph.D.
Professor and Chairman, Department of Environmental Toxicology
Director, The Institute of Environmental and Human Health, Texas Tech University
Texas Tech University Health Sciences Center
Box 41163, 1207 Gilbert Drive, Reese Center
Lubbock, TX 79416

Designated Federal Official
Mr. Paul Lewis
FIFRA Scientific Advisory Panel
Office of Science Coordination and Policy
Environmental Protection Agency
1200 Pennsylvania Avenue, N.W.
(7201M)
Washington, DC 20460

FIFRA Scientific Advisory Panel Members
Herb Needleman, M.D.
Professor of Psychiatry and Pediatrics
School of Medicine
University of Pittsburgh
310 Keystone Building
3529 Fifth Avenue
Pittsburgh, PA 15213

Christopher J. Portier, Ph.D.
Director, Environmental Toxicology Program
National Institute of Environmental Health Sciences
111 T.W. Alexander Drive, Bldg. 101, Room A330
Research Triangle Park, NC 27709-12233

Stephen M. Roberts, Ph.D.
Professor and Program Director
University of Florida
Center for Environmental & Human Toxicology
Building 471 Mowry Road
Gainesville, Florida 32611

Mary Anna Thrall, D.V.M.
Professor, Department of Pathology
College of Veterinary and Biomedical Sciences
Colorado State University
Fort Collins, CO 80523

FQPA Science Review Board Members

John Adgate, Ph.D.
University of Minnesota
School of Public Health

420 Delaware St. S.E.
Minneapolis, MN 55455

William Brimijoin, Ph.D.
Department of Pharmacology
Mayo Clinic and Medical School
200 1st st SW
Rochester, MN 55905

Richard Bull, Ph.D,
MoBull Consulting
8382 Gage Boulevard
Suite O, Box 511
Kennewick, WA 99336

Paul Capel, Ph.D.
University of Minnesota
122 Cive Building
Minneapolis, MN 55455

Rory Conolly, Sc.D.
Senior Scientist
Chemical Industry Institute of Toxicology Center for Health Research
6 Davis Drive
Research Triangle Park, North Carolina 27709

Patrick Durkin, Ph.D., Vice President
Syracuse Environmental Research Associates, Inc.
5100 Highbridge Street
Building 42C
Fayetteville, NY 13066

Bernard Engel, Ph.D.
Purdue University
1146 ABE
West Lafayette, IN 47907-1146

Natalie Freeman, Ph.D.
Robert Wood Johnson School of Medicine
Department of Environmental and Community Medicine
170 Frelinghuysen Road
Piscataway, NJ 08854

Jeanne Harry, Ph.D.
National Institute of Environmental Health Science
111 Alexander Drive
Research Triangle Park, NC 27709

Steven Heeringa, Ph.D.
Institute for Social Research
University of Michigan
PO Box 1248
Ann Arbor, MI 48106

Ernest McConnell, DVM
President
Toxpath Inc.
3028 Ethan Lane
Raleigh, NC 27613

Peter MacDonald, D. Phil.
Professor of Mathematics and Statistics,
Department of Mathematics and Statistics,
McMaster University
1208 Main Street West
Hamilton, Ontario, Canada L8S4K1

Lorenz Rhomberg, Ph.D.
Gradient Corporation
238 Main Street
Cambridge, MA 02142

R. Peter Richards, Ph.D.
Director, Water Quality Laboratory
Heidelberg College
310 E. Market Street
Tiffin, OH 44883

Lauren Zeise, Ph.D., Chief
Reproductive and Cancer Hazard Assessment
Office of Environmental Health Hazard Assessment
1515 Clay Street, 16th Floor, Oakland, CA 94612

THURSDAY, FEBRUARY 7, 2002
SHERATON CRYSTAL CITY HOTEL
1800 JEFFERSON DAVIS HIGHWAY
ARLINGTON, VIRGINIA 22202
703-486-1111

Methods Used to Conduct a Preliminary Cumulative Risk Assessment for Organophosphorous Pesticides Assessment of Residential/Non-occupational Exposure

FIFRA SAP Session Chair
Ronald Kendall, Ph.D.
Professor and Chairman, Department of Environmental Toxicology
Director, The Institute of Environmental and Human Health, Texas Tech University
Texas Tech University Health Sciences Center
Box 41163, 1207 Gilbert Drive, Reese Center
Lubbock, TX 79416

Designated Federal Official
Ms. Olga Odiott
FIFRA Scientific Advisory Panel
Office of Science Coordination and Policy
Environmental Protection Agency
1200 Pennsylvania Avenue, N.W. (7201)
Washington, DC 20460
(202) 564-8450; FAX: (202) 564-8382
odiott.olga@epa.gov

FIFRA Scientific Advisory Panel Members
Herb Needleman, M.D.
Professor of Psychiatry and Pediatrics
School of Medicine
University of Pittsburgh
310 Keystone Building
3529 Fifth Avenue
Pittsburgh, PA 15213

Christopher J. Portier, Ph.D.
Director, Environmental Toxicology Program
National Institute of Environmental Health Sciences
111 T.W. Alexander Drive, Bldg. 101, Room A330
Research Triangle Park, NC 27709-12233

Stephen M. Roberts, Ph.D.
Professor and Program Director
University of Florida
Center for Environmental & Human Toxicology
Building 471 Mowry Road
Gainesville, Florida 32611

Mary Anna Thrall, D.V.M.
Professor, Department of Pathology
College of Veterinary and Biomedical Sciences
Colorado State University
Fort Collins, CO 80523

FQPA Science Review Board Members
John Adgate, Ph.D.
University of Minnesota
School of Public Health
420 Delaware St. S.E.
Minneapolis, MN 55455

William Brimijoin, Ph.D.
Department of Pharmacology
Mayo Clinic and Medical School
200 1st st SW
Rochester, MN 55905

Richard Bull, Ph.D,
MoBull Consulting
8382 Gage Boulevard
Suite O, Box 511
Kennewick, WA 99336

Rory Conolly, Sc.D.
Senior Scientist
Chemical Industry Institute of Toxicology Center for Health Research
6 Davis Drive
Research Triangle Park, North Carolina 27709

Patrick Durkin, Ph.D., Vice President
Syracuse Environmental Research Associates, Inc.
5100 Highbridge Street
Building 42C
Fayetteville, NY 13066

Natalie Freeman, Ph.D.
Robert Wood Johnson School of Medicine
Department of Environmental and Community Medicine
170 Frelinghuysen Road
Piscataway, NJ 08854

Dale Hattis, Ph.D.
George Perkins Marsh Institute
Clark University

Worchester, MA 01610

Jeanne Harry, Ph.D.
National Institute of Environmental Health Science
111 Alexander Drive
Research Triangle Park, NC 27709

Steven Heeringa, Ph.D.
Institute for Social Research
University of Michigan
PO Box 1248
Ann Arbor, MI 48106

Ernest McConnell, DVM
President
Toxpath Inc.
3028 Ethan Lane
Raleigh, NC 27613

Peter MacDonald, D. Phil.
Professor of Mathematics and Statistics,
Department of Mathematics and Statistics,
McMaster University
1208 Main Street West
Hamilton, Ontario, Canada L8S4K1

Nu-May Ruby Reed, Ph.D.
Staff Toxicologist
California Environmental Protection Agency
Department of Pesticide Regulation
1001 "I" Street
Sacramento, California 95814-2828

Lorenz Rhomberg, Ph.D.
Gradient Corporation
238 Main Street
Cambridge, MA 02142

Risk Characterization

FIFRA SAP Session Chair
Stephen M. Roberts, Ph.D.
Professor and Program Director
University of Florida
Center for Environmental & Human Toxicology
Building 471 Mowry Road
Gainesville, Florida 32611

Designated Federal Official
Ms. Olga Odiott
FIFRA Scientific Advisory Panel
Office of Science Coordination and Policy
Environmental Protection Agency
1200 Pennsylvania Avenue, N.W. (7201)
Washington, DC 20460
(202) 564-8450; FAX: (202) 564-8382
odiott.olga@epa.gov

FIFRA Scientific Advisory Panel Members

Herb Needleman, M.D.
Professor of Psychiatry and Pediatrics
School of Medicine
University of Pittsburgh
310 Keystone Building
3529 Fifth Avenue
Pittsburgh, PA 15213

Christopher J. Portier, Ph.D.
Director, Environmental Toxicology Program
National Institute of Environmental Health Sciences
111 T.W. Alexander Drive, Bldg. 101, Room A330
Research Triangle Park, NC 27709-12233

Stephen M. Roberts, Ph.D.
Professor and Program Director
University of Florida
Center for Environmental & Human Toxicology
Building 471 Mowry Road
Gainesville, Florida 32611

Mary Anna Thrall, D.V.M.
Professor, Department of Pathology
College of Veterinary and Biomedical Sciences
Colorado State University
Fort Collins, CO 80523

FQPA Science Review Board Members
John Adgate, Ph.D.
University of Minnesota
School of Public Health
420 Delaware St. S.E.
Minneapolis, MN 55455

William Brimijoin, Ph.D.
Department of Pharmacology
Mayo Clinic and Medical School
200 1st st SW
Rochester, MN 55905

Richard Bull, Ph.D,
MoBull Consulting
8382 Gage Boulevard
Suite O, Box 511
Kennewick, WA 99336

Rory Conolly, Sc.D.
Senior Scientist
Chemical Industry Institute of Toxicology Center for Health Research
6 Davis Drive
Research Triangle Park, North Carolina 27709

Patrick Durkin, Ph.D., Vice President
Syracuse Environmental Research Associates, Inc.
5100 Highbridge Street
Building 42C
Fayetteville, NY 13066

Natalie Freeman, Ph.D.

Robert Wood Johnson School of Medicine
Department of Environmental and Community Medicine
170 Frelinghuysen Road
Piscataway, NJ 08854

Dale Hattis, Ph.D.
George Perkins Marsh Institute
Clark University
Worchester, MA 01610

Jeanne Harry, Ph.D.
National Institute of Environmental Health Science
111 Alexander Drive
Research Triangle Park, NC 27709

Steven Heeringa, Ph.D.
Institute for Social Research
University of Michigan
PO Box 1248
Ann Arbor, MI 48106

Ernest McConnell, DVM
President
Toxpath Inc.
3028 Ethan Lane
Raleigh, NC 27613

Peter MacDonald, D. Phil.
Professor of Mathematics and Statistics,
Department of Mathematics and Statistics,
McMaster University
1208 Main Street West
Hamilton, Ontario, Canada L8S4K1

Lorenz Rhomberg, Ph.D.
Gradient Corporation
238 Main Street
Cambridge, MA 02142

R. Peter Richards, Ph.D.
Director, Water Quality Laboratory
Heidelberg College
310 E. Market Street
Tiffin, OH 44883

Nu-May Ruby Reed, Ph.D.
Staff Toxicologist
California Environmental Protection Agency
Department of Pesticide Regulation
1001 "I" Street
Sacramento, California 95814-2828

FRIDAY, FEBRUARY 8, 2002
SHERATON CRYSTAL CITY HOTEL
1800 JEFFERSON DAVIS HIGHWAY
ARLINGTON, VIRGINIA 22202
703-486-1111

Methods Used to Conduct a Preliminary Cumulative Risk Assessment for Organophosphorous Pesticides

Risk Characterization

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Center for Environmental & Human Toxicology
Building 471 Mowry Road
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National Institute of Environmental Health Sciences
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Professor of Mathematics and Statistics,
Department of Mathematics and Statistics,
McMaster University
1208 Main Street West
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Tiffin, OH 44883

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Supplemental Material for:
February 5-8, 2002 SAP
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Comparison of Acute NOAELs and Benchmark Doses for Female Brain Cholinesterase Inhibition

In cumulative risk assessment, it is important to characterize both the time frame for exposure (e.g., What is the exposure duration?) and for the toxic effect (e.g., What are the time to peak effects and the time to recovery?). In the Preliminary Cumulative Risk Assessment of the Organophoshate Pesticides (OPs) relative potency factors (RPFs) for 29 chemicals and points of departure (PODs) and the index chemical were determined based on whole brain cholinesterase (ChE) data from toxicity studies of 21 days and longer. The Office of Pesticide Programs has argued that the use of steady state data for relative potency determination generates relative potency factors (RPFs) that are reproducible and reflect less variability than RPFs derived from single-dose or short-term studies where the extent of inhibition changes rapidly immediately following dosing.

OPP has posed a question to the FIFRA SAP for the February 5-8, 2002 review concerning how best to evaluate risk, taking into account the temporal characteristics of the hazard endpoint (i.e., cholinesterase inhibition) and the temporal characteristics of the exposure patterns for the food, drinking water, and residential/nonoccupational pathways. In order to facilitate the panel discussion, a table listing the available single dose toxicity studies performed with OPs has been made. Most of the studies are acute neurotoxicity (ACN) studies (OPPT Guideline 870.6200, OPP Guideline 81-8) administered by gavage. Acute lethality studies were not included. Dose levels, no-observed-adverse-effect levels (NOAELs), and no-observed-adverse-effect levels (LOAELs) for female brain ChE are also listed in the table. The NOAELs and LOAELs were extracted from study reviews called Data Evaluation Records prepared by toxicologists of OPP. Benchmark doses (BMD) from the Preliminary Cumulative Risk Assessment for OPs calculated from 21 days and longer are included for comparison.

- *Single dose oral toxicity studies with female whole brain ChE data* are not available for 19 OPs in the Preliminary Cumulative Risk Assessment (acephate, chlorethoxyphos, chlorpyrifos, chlorpyrifos-methyl, diazinon, dichlorvos, dimethoate, disulfoton, ethoprop, fosthiazate, malathion, methidathion, methyl-parathion, mevinphos, naled, pirimiphos-methyl, profenofos, tetrachlorvinphos, and tribufos);

- *Single dose oral toxicity studies with whole brain ChE data* are available for 13 OPs in the Preliminary Cumulative Risk Assessment (azinphos-methyl, bensulide, dicrotophos, fenthion, fenamiphos, methamidophos, ODM, phorate, phosalone, phosmet, phostebupirim, terbufos, and trichlorfon);

- As of 1/22/2001, calculation of the BMD_{10} for whole brain ChE measured from female rats from oral studies of 21 days and longer was on-going for chlorethoxyphos, profenofos, and phostebupirim;

- For the remaining 12 OPs, acute NOAELs are available for female whole brain ChE:

  - Acute NOAELs and the BMD_{10} from the >21 day studies for are *within approximately 3-fold* for 7 OPs (azinphos-methyl, bensulide, methamidophos phorate, phosmet, terbufos, and trichlorfon);

  - Acute NOAELs and the BMD_{10} from the >21 day studies for are *within 4-7-fold* for 2 OPs (fenthion and phosalone);

  - Acute NOAELs were not established for 3 OPs (dicrotophos, fenamiphos, and ODM) making comparisons to the BMD_{10} from the >21 day studies difficult.

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Acephate	ACN [c]	44203302	0, 0.5, 2.5, 5, 25, 125, 500	2.5 hours post dose	0.5 (Brain sections NOT whole brain)	2.5 (78-87%)	0.63	0.57
	ACN	44203303	0, 10, 100, 500	2.5 hours, 7 and 14 days post dose	< 10 (Brain sections NOT whole brain)	10 (39-44%)		
Azinphos-methyl	**ACN**	**43360301**	**0, 1, 3, 6**	**1.5 hours post dose**	**1 (5%)**	**3 (51%)**	**0.9**	**0.8**
Bensulide	**ACN**	**43195901**	**0, 15, 50, 150**	**6.75 hours and 15 days post dose**	**50 (0%)**	**150 (18-27%)**	**32.85**	**24.32**
Chlorethoxyphos	ACN	42559210	0, 0.32, 0.76, 0.746,	ChE not measured			N/A*	N/A*
Chlorpyrifos	ACN	42669101 42495401	0, 10, 50, 100	ChE not measured			0.83	0.57
Chlorpyrifos-methyl	ACN study not available						7.51	5.23
Diazinon	ACN	431302203	0, 2.5, 150, 300, 600	3, 9, and 24 hours post dose	2.5 (10%-0%) (Brain sections NOT whole brain)	150 (26- 73%)	3.43	1.03
	ACN	43132204 43132201	0, 2.5, 150, 300, 600	Brain ChE only measured 15 days post-dose				
Dichlorvos	ACN	42655301	0, 0.5, 35, 70	ChE not measured			2.25	1.39
Dicrotophos	ACN	43759801	0, 0.5, 5, 10	3 hours post dose	<0.5	0.5 (21%)	0.04	0.03

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CHEMICAL	STUDY	MRID no.	Female Dose Levels (mg/kg)	Time of ChE measurement	Acute NOAEL Female Brain ChE (% decrease in ChE)	Acute LOAEL Female Brain ChE (% decrease in ChE)	FEMALE BMD_{10}[a]	FEMALE BMDL[b]
Dimethoate	ACN	42865102	0, 2, 20, 200	ChE not measured			0.25	0.21
Disulfoton	ACN	42755801	0, 0.24, 0.76, 1.5, 5.2	Brain ChE not measured			0.07	0.05
Ethoprop	ACN	43197701	0, 5, 25, 50	Brain ChE only measured 15 days post-dose			1.7	0.87
	ACN	43442402	0,15.7, 33	1, 3, 8, 15 days post dose	<15.7 (Brain sections NOT whole brain)	15.7 (50 - 72%)		
Fenthion	**ACN**	**44326401**	**0, 1, 75, 225**	**5.5 hours post dose**	**<1**	**1 (9%)**	**0.24**	**0.2**
Fenamiphos	ACN	44041501	0, 0.37, 1.52, 2.31	50 min post dose	> 2.31 (1%)	> 2.31	2.11	1.12
Fosthiazate	Brain sections NOT whole brain (Study review on-going)						0.50	0.28
Malathion	ACN	43146701	0, 500, 1000, 2000	15 minutes, days 7 and 14 post dose	2000 (Brain sections NOT whole brain)	>2000	326.37	269.66
Methamidophos	ACN	42770301	0, 0.9, 3, 9	2 hours post dose	< 0.9	0.9 (24-39%)	**0.08**	**0.07**
	ACN	**43025001, 43445801**	**0, 0.3, 0.7**	**2 hours post dose**	**0.3**	**0.7 (15-27%)**		
Methidathion	ACN	43145903	Brain sections NOT whole brain (Study review on-going)				0.22	0.19
	ACN	43145901	ChE not measured (Study review on-going)					

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CHEMICAL	STUDY	MRID no.	Female Dose Levels (mg/kg)	Time of ChE measurement	Acute NOAEL Female Brain ChE (% decrease in ChE)	Acute LOAEL Female Brain ChE (% decrease in ChE)	FEMALE BMD_{10}[a]	FEMALE BMDL[b]
Methyl parathion	ACN	443254401	0, 0.025, 7.5, 15	1.5 hours, 7 and 14 days post dose	0.025 (Brain sections NOT whole brain)	7.5 (76-85%)	1.41	1.05
Mevinphos	ACN	42985402, 42985401	0, 0.025, 0.1, 2.0, 3.5	45 minutes, 7 and 15 days post dose	0.1 (Brain sections NOT whole brain)	2 (25%)	0.06	0.05
Naled	ACN	42861301	ChE not measured (Study review on-going)				1	0.81
	ACN	43189601	ChE not measured (Study review on-going)					
ODM	ACN	43929901	0, 2.5, 10, 50	1.5 hours, 7 and 15 days post dose	< 2.5	2.5 (39%)	0.09	0.08
Phorate	**ACN**	**44719901**	**0, 0.25, 0.50, 1.0**	**4-5 hours and day 15 post dose**	**0.5**	**1 (65.2%)**	**0.21**	**0.19**
Phosalone	**ACN**	**44852503**	**0, 10, 25, 60**	**6 hours, days 8 and 15 post dose**	**25 (8%)**	**60 (22%)**	**3.38**	**2.6**
Phosmet	**ACN**	**44673301 44706501**	**0, 3, 4.5, 22.5**	**3 hours, 7 and 14 days post dose**	**4.5**	**22.5 (70%)**	**4.13**	**2.67**
Phostebupirim	ACN	43819801	0, 0.25, 0.5, 1	1 hour post dose	0.5	1.0 (53%)	N/A	NA
Pirimiphos-methyl	ACN	43594101	0, 15, 150, 1500	24 hours and 15 days post dose	15 (brain sections NOT whole brain)	150 (13-28%)	2.88	2.21
Profenofos	ACN	42939801 42939802	0, 95, 190, 380	Brain ChE only measured 14 days post dose			N/A	N/A
Terbufos	**ACN**	**44672003**	**0, 0.15, 0.30, 0.90**	**6 hours and day 15 post dose**	**0.30**	**0.90 (51%)**	**0.1**	**0.07**

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CHEMICAL	STUDY	MRID no.	Female Dose Levels (mg/kg)	Time of ChE measurement	Acute NOAEL Female Brain ChE (% decrease in ChE)	Acute LOAEL Female Brain ChE (% decrease in ChE)	FEMALE BMD_{10}[a]	FEMALE BMDL[b]
Tetrachlorvinphos	ACN	42912501	0, 65, 325, 650	ChE not measured			101.92	66.64
Tribufos	ACN	45194401		Brain ChE only measured 3 days post dose			1.81	1.54
Trichlorfon	**ACN**	**44578001**	**0, 10, 50, 200**	**1.5 hours post dose**	**10**	**50 (30%)**	**6.03**	**2.74**

*BMD_{10} and BMDL calculation for chlorethoxyfos, profenofos, and phostebupirim not yet complete as of 1/22/2002
a BMD_{10} = Benchmark dose resulting in 10% decrease in cholinesterase activity. Calculated from toxicity studies of 21 days and longer
b BMDL = Lower confidence interval on the BMD_{10}
c ACN = Acute neurotoxicity study

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Summary of Changes to the Dose-Response Modeling

Since the December 2001 publication of the Preliminary Analysis, the inability to fit more datasets with the expanded model prompted a reexamination of both the basic and expanded models. The resulting analyses and small changes in RPFs will be discussed in more detail in the February meeting of the FIFRA SAP.

1) Reparameterization of Basic and Expanded Models

The difficulty in fitting the expanded model caused a reexamination of the models used. In the parametrization used in the Preliminary Analysis (December 2001), the parameters *m* (slope scale factor) and P_B (horizontal asymptote) were highly correlated. In marginal datasets, this could cause a complete failure to estimate all the parameters, or, in less severe cases, could result in somewhat less than optimal estimates being returned. Reparameterizing the basic and expanded models in terms of *BMD* (benchmark dose) instead of *m,* as was described in the technical appendix (III.B.1), considerably reduces this correlation. Profile likelihoods for P_B have been recomputed using this alternative parameterization and will available at the February 5-8, 2002 meeting of the FIFRA SAP.

2) Sensitivity Analyses

The sensitivity of estimates of *BMD* to different characterizations of the random and fixed effects models, and to different plausible values for P_B when it is not directly estimable, has been evaluated. The sensitivity analysis has shown that when it was not possible to estimate P_B it was because of the experimental designs used, specifically, that the highest dose used was not high enough to allow precise estimation of P_B.

3) Programming Errors in R Code

The programming code released in the Preliminary Cumulative Risk Assessment (III.B.4) includes two programming errors. These programming errors impact the computation of the SD profiles. One of these errors is responsible for the inability to estimate the SD profile when that estimation failed. This error has been corrected.

The other error caused profile likelihood plots (for S and D only) to have incorrect axis labels, and the incorrect initial guesses for these parameter values to be read off the graphs. As of 1/22/2002, this error was corrected and recalculation of S and D was on-going. Revised SD profiles will be available for the February 5-8, 2002 SAP meeting.

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Revision to SAP Question #1 For Food Session and Associated Background Material for "Preliminary Cumulative Risk Assessment for Organophosphorous Pesticides: Review of Methodology"

Questions on Food Assessment

1. In the Preliminary OP Cumulative Risk Assessment, OPP used all available PDP monitoring data generated since 1994 as the basis for the residue distributions of pesticides in treated foods. As a result, some foods have multiple years of data (as many as 5), while others have only a single year of data. All years of data were included to provide the most robust residue data set possible. These data were extended to cover foods and processed forms of foods for which data are not directly available. Additionally, some foods were included in the analysis based on less robust data from FDA.

   OPP is conducting a sensitivity analysis in which the residue contributions from specific foods (either one at a time or in combination with other foods) are removed from the analysis. This analysis is being conducted as part of an effort to determine the contributions of specific food commodities and chemicals to the upper tail of the exposure distribution. Some preliminary results are shown in Table 1 of the addendum to this document.

   Partly as a result of this exercise, OPP has observed that the more variables (e.g., commodities, chemicals, years of data) that are included in the exposure distribution, the more difficult it becomes to affect the tail of the distribution by removing commodity/pesticide combinations from the calculations. While removal of most exposure contributors results in a demonstrable change in the lower portion of the distribution, the exposures at the upper end of the tail (for example the 99.9^{th} percentile) are relatively unaffected by removal of a single commodity, even if it is identified by DEEM as a frequent contributor to the high end of the exposure distribution.

   Please discuss the significance of this observation and its potential impact on interpretation of the output distributions and results from highly complex distributional analyses such as the Preliminary OP Cumulative Risk Assessment.

Addendum

Background material for Revised Question #1 for OP Cumulative Food Assessment

This addendum is being provided as additional background for discussion of revised question 1 on the food assessment.

Table 1 summarizes the results of 10 separate assessments of cumulative OP exposure distributions from food consumption by children 1-2 years old. The conditions for the 10 assessments were as follows:

1. **Preliminary Cumulative Assessment** is the assessment as published for comment on Dec 3, 2001. These results were based on, among other things, all PDP residue data available on foods analyzed between 1994 and 2000.

2. **Preliminary with reduced PDP data set** was conducted as part of an evaluation of the impact of removal of older residue data from the assessment for those foods with several years of data. Only the most recent analyses were included for each food commodity with a maximum of 2 years of data for any given commodity.

3. **No Translated Commodities** represents an assessment from which all foods were removed that were not directly supported by PDP data or PDP data adjusted by a processing factor. These results are consistent with similar ones summarized in the OP Case Study presented to the SAP in December of 2000. They demonstrate that foods included by translation (for example parsnips based on carrots) or from other data sources (such as beef, pork, and other meats based on FDA TDS data) do not impact significantly at the higher end of the exposure/risk distribution. This is also supported by data summarized in the public document related to the relative per capita consumption of foods that were based on surrogate data or less robust monitoring data than those collected by PDP.

4. **Minimum Assessment (only food forms analyzed by PDP)** represents a lower boundary of the preliminary assessment as affected by residue data. The only foods included in the analysis were those that closely matched the actual commodity that PDP analyzed. Cooked and processed food forms were excluded unless they were actually analyzed

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by PDP. Therefore, this assessment included no foods based on processing factors, surrogate data, or FDA data.

5. **No Baby Foods** was conducted as a check on the impact of residue assumptions related to these food commodities. In the preliminary assessment it was assumed that commercial baby foods are derived from crops with the same pesticide treatment history as adult foods. This is a conservative estimate of residue levels on these commodities; however, this assessment confirms that the impact of this assumption on the overall assessment is negligible.

6. **No Forms of Food A** excluded all of the foods derived from Food A, which was the most frequent contributor to the upper end of the exposure distribution.

7. **No Forms of Food B** excluded all of the foods derived from Food B, which was the second most frequent contributor to the upper end of the exposure distribution.

8. **No Forms of Food C** excluded all of the foods derived from Food C, which was the third most frequent contributor to the upper end of the exposure distribution.

9. **No Forms of Foods A or B** excluded food forms of both A and B.

10. **No Forms of Foods A, B, or C** excluded food forms of A, B and C.

Assessments 6 through 10 represent analyses of the relative impact of the contribution to the exposure distribution for the three foods (foods A, B and C) that were found to contribute most frequently to the extreme upper portion of the distribution (99.8th-100th percentile). Residues were removed from the assessment for all food forms of foods A, B, and C. It can be seen that, even for the three top contributors to the upper end of the exposure distribution, removal of the contribution of exposure from one food had very little effect at the 99.9th percentile. Similar results are observed for the other top contributors to exposure. As seen in assessment 10, all of the food forms for all three top contributors had to be removed from the analysis to obtain a two-fold reduction in risk at the 99.9th percentile.

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Table 1. Sensitivity Analysis of Various Exposure Parameters in Cumulative Assessment.

Assessment	Description	MOEs for Children 1-2 at Selected Points in the Exposure Distribution [1,2]				
		Mean	95th %	99th %	99.5th %	99.9th %
1	Preliminary Cumulative Assessment	2001	457	160	110	52
2	Preliminary with Reduced PDP Data set	2205	503	181	125	58
3	No Translated Commodities	2082	470	165	114	53
4	Minimum Assessment (only food forms analyzed by PDP)	4895	988	293	188	77
5	No Baby Foods	2087	471	164	112	52
6	No Forms of Food A	2925	651	222	149	63
7	No Forms of Food B	2183	495	178	121	56
8	No Forms of Food C	2920	652	192	126	55
9	No Forms of Foods A or B	3330	727	255	174	75
10	No Forms of Foods A, B, or C	7063	1666	428	268	105

1. MOE = Point of Departure/Exposure
2. Point of Departure =BMD_{10}=0.08 mg/kg body wt./day

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Background Paper

Rolling Time Frame Approach

One important aspect of the preliminary cumulative risk assessment for the organophosphate pesticides (OPs) is the manner in which estimated exposure is compared with toxicity endpoints. This paper briefly describes and compares two different "modes" of analysis in DEEM/Calendex which are available and permit consideration of either a single day or varying time frames of analysis. It is hoped that this document will provide sufficient background material for the Panelists to address the various questions and concepts relating to rolling time frames during the February 5-8, 2002 FIFRA Scientific Advisory Panel Meeting. The concepts discussed here have specific applicability to Question #2 of the Food Exposure session and Question #1 of the Risk Characterization session.

DEEM/Calendex Time Frames of Analysis

The DEEM/Calendex program can perform analyses by either of these two options.

- Under the first option (termed the single consecutive day option), separate, independent estimates are made for each day of the year (January 1, January 2, etc.). These can be arrayed into an exposure timeline for any selected percentile and graphed. That is, for example, the estimated 99th (or any other percentile) percentile exposure value is calculated by DEEM/Calendex for each day of the year from January 1 through December 31. These represent independent daily estimates of the 99th percentile exposures on each day of the year and do not necessarily represent the same individual on consecutive days. Thus, it is NOT possible (with this mode of analysis) to interpret an extended period (or series) of elevated exposures over time as necessarily representing extended exposures to the *same* individual, and comparison of any estimated exposure to multi-day endpoints (e.g., a multi-day BMD_{10}) would be expected to provide a very conservative estimate of risk to the extent that exposures on consecutive days at any given percentile are unlikely to be the same individual.

- Under the second option (termed the multiple sequential day option), a rolling (or sliding) time frame is used and multi-day average exposures are calculated for each

individual (e.g, average exposures for each individual for January 1 through January 7, January 2 through January 8, etc.). Under this mode, average exposures over multiple consecutive days (e.g., January 1 through 7, January 2 through 8, etc.) are assessed for the same individual. It is then this distribution of multi-day average exposures at any given percentile which serves as a basis of comparison with the (multi-day) BMD_{10}. DEEM/Calendex permits rolling time frames of 7-, 14-, 21-, and 28-days duration.

In the Preliminary Cumulative Risk Assessment, exposures were estimated on a single-day basis (the first option) and a comparison made of each independent DEEM-estimated single-day exposure with the steady-state (21 day) equilibrium BMD_{10} value (see the exposure profile plots presented in the Preliminary Cumulative Risk Assessment in Figures III.I.2-1 to III.U.2-20). That is, separate exposure estimates were made for January 1, January 2, etc. for each individual in the CSFII survey *for each (single) day of the year* with exposure at a given percentile (e.g., 99^{th}) calculated and compared to a multi-day BMD_{10}. In viewing these figures, and despite their one-day exposure basis, OPP is NOT concerned with exposure spikes lasting only one or perhaps a few days since the MOE's associated with these "spikes" are based on multi-day toxicity endpoints. Rather, OPP is interested in extended periods of high exposure (or, equivalently, low MOEs) which indicate not that an *individual* is being exposed to high levels of OP pesticides over a multi-day time period, but instead that the overall level of exposure to the sub-population in the tails of the distribution has increased. This is an important distinction which brings up two issues:

- comparing a series of elevated single-day exposures to multi-day endpoint may have less relevance than comparing a multi-day average exposure (at any given percentile) to a multi-day endpoint.

- Consecutive single-day estimates of exposure are likely to significantly overestimate multi-day exposures to an individual (at the higher percentiles) i.e., the individuals at or around the 99^{th} percentile are unlikely to appear there on consecutive days.

The alternative option is to estimate multi-day rolling average exposures in which average exposures over multiple consecutive days (e.g., January 1 through 7, January 2 through 8, etc.) are assessed for the same individual. It is this multi-day average exposure which then serves as a basis of comparison with the (multi-day) BMD_{10}. There are a number of advantages to this alternative. In addition to providing a means of estimating exposure which is more directly comparable to a multi-day endpoint, the multiple sequential day mode of analysis better incorporates variability in exposure for an individual across multiple days and is likely to provide a more realistic estimate of exposures for individuals across multiple days. It is also flexible with

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individuals for many commodities might be assumed to consume on subsequent days foods obtained from the same source and the DEEM/Calendex calculations instead assume that the residues contained in these foods are independent. For example, if oranges were eaten on two consecutive days, the OP pesticide residues would be assumed in the DEEM/Calendex program to be independent. In reality, if these oranges were purchased at the same time (or selected from the same bag), it is not likely that these residues are entirely independent as both oranges likely share a common treatment history.

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Supplemental Material for:
February 5-8, 2002 SAP
25 January 2002

Background Paper

Rolling Time Frame Approach

One important aspect of the preliminary cumulative risk assessment for the organophosphate pesticides (OPs) is the manner in which estimated exposure is compared with toxicity endpoints. This paper briefly describes and compares two different "modes" of analysis in DEEM/Calendex which are available and permit consideration of either a single day or varying time frames of analysis. It is hoped that this document will provide sufficient background material for the Panelists to address the various questions and concepts relating to rolling time frames during the February 5-8, 2002 FIFRA Scientific Advisory Panel Meeting. The concepts discussed here have specific applicability to Question #2 of the Food Exposure session and Question #1 of the Risk Characterization session.

DEEM/Calendex Time Frames of Analysis

The DEEM/Calendex program can perform analyses by either of these two options.

- Under the first option (termed the single consecutive day option), separate, independent estimates are made for each day of the year (January 1, January 2, etc.). These can be arrayed into an exposure timeline for any selected percentile and graphed. That is, for example, the estimated 99th (or any other percentile) percentile exposure value is calculated by DEEM/Calendex for each day of the year from January 1 through December 31. These represent independent daily estimates of the 99th percentile exposures on each day of the year and do not necessarily represent the same individual on consecutive days. Thus, it is NOT possible (with this mode of analysis) to interpret an extended period (or series) of elevated exposures over time as necessarily representing extended exposures to the *same* individual, and comparison of any estimated exposure to multi-day endpoints (e.g., a multi-day BMD_{10}) would be expected to provide a very conservative estimate of risk to the extent that exposures on consecutive days at any given percentile are unlikely to be the same individual.

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individual (e.g, average exposures for each individual for January 1 through January 7, January 2 through January 8, etc.). Under this mode, average exposures over multiple consecutive days (e.g., January 1 through 7, January 2 through 8, etc.) are assessed for the same individual. It is then this distribution of multi-day average exposures at any given percentile which serves as a basis of comparison with the (multi-day) BMD_{10}. DEEM/Calendex permits rolling time frames of 7-, 14-, 21-, and 28-days duration.

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The alternative option is to estimate multi-day rolling average exposures in which average exposures over multiple consecutive days (e.g., January 1 through 7, January 2 through 8, etc.) are assessed for the same individual. It is this multi-day average exposure which then serves as a basis of comparison with the (multi-day) BMD_{10}. There are a number of advantages to this alternative. In addition to providing a means of estimating exposure which is more directly comparable to a multi-day endpoint, the multiple sequential day mode of analysis better incorporates variability in exposure for an individual across multiple days and is likely to provide a more realistic estimate of exposures for individuals across multiple days. It is also flexible with

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respect to matching time-frame associated with BMD_{10} in that multi-day averages can be calculated over 7, 14, 21, or 28 days.

Importantly, however, the USDA's Continuing Survey of Food (CSFII) does not provide consumption data across the multiple consecutive days which would be of interest. That is, the USDA food consumption survey does not provide *longitudinal* data in which the consumption of the same individual is followed and traced for any extended period of time. The CSFII consumption data which serves as a basis of DEEM/Calendex exposure estimates is limited to two non-consecutive days of data (i.e., two days separated by 3-10 days) for each interviewed individual. This means that any multi-day average exposure for any given individual (as calculated by DEEM/Calendex's multiple sequential day rolling time frame approach) repeats, for each individual on each day of the time frame of interest, one of that individuals' two reported diets (randomly) in a sequential series (e.g., Day 1 diet, followed by Day 2 diet, then Day 2 diet again, Day 1 diet, etc.)[1]. Two issues become apparent with the use of CSFII data in this way:

(1) The DEEM/Calendex method assumes that the food contribution to exposure is the result of eating an ongoing diet that, for each individual, corresponds only to one of the two, non-sequential, daily diets reported for a person in the USDA Continuing Survey of Food Intake by Individuals (CSFII). This assumption does not correspond to reality in that a person will likely have greater variability in his or her eating habits than would be reflected by randomly selecting from two days of food choices. Thus, any consecutive day period of interest will contain in Calendex a series of repeated diets which do not reflect the true variability that likely exists in any given individual's diet.

(2) Since residue values are drawn at random (and anew) for each day's selected diet during the time frame of interest, true correlations that may exist between residues on subsequent days may not be accurately reflected in the DEEM/Calendex analysis. Specifically, the DEEM/Calendex method also cannot account for either the "leftover" phenomenon, i.e. the fact that there is likely to be some correlation between foods consumed by an individual on consecutive days, or the fact that there is likely to be some correlation between the residue levels found on fresh foods consumed on consecutive days. For example, left-overs eaten on subsequent days might be expected to contain similar or equivalent residues to those eaten on a previous day. The DEEM/Calendex program would draw residues anew from its residue distribution file for the food commodity of interest which would thereby not be reflective of actual residues to which individuals consuming leftovers would be exposed. In addition, as another example,

[1] Note that while each individual's two days or reported diet is repeated for the time frame of interest, residues for each commodity comprising that diet are randomly drawn so that each day's exposure is different.

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individuals for many commodities might be assumed to consume on subsequent days foods obtained from the same source and the DEEM/Calendex calculations instead assume that the residues contained in these foods are independent. For example, if oranges were eaten on two consecutive days, the OP pesticide residues would be assumed in the DEEM/Calendex program to be independent. In reality, if these oranges were purchased at the same time (or selected from the same bag), it is not likely that these residues are entirely independent as both oranges likely share a common treatment history.

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U.S. Environmental Protection Agency

Revised OP (Organophosphate) Cumulative Risk Assessment

June 10, 2002

Executive Summary

Glossary / Acronyms

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Cover page created by EPA Region 9 Library staff, January 14, 2004.

Executive Summary

A. Introduction

In 1996 Congress enacted the Food Quality Protection Act (FQPA), which among other things, requires EPA to take into account when setting pesticide tolerances (maximum residue legally allowed on a food) "available evidence concerning the cumulative effects on infants and children of such residues and other substances that have a common mechanism of toxicity." Also, FQPA mandates that by 2006, EPA must review the safety of all existing tolerances that were in effect as of August 1996. The law requires EPA to place the highest priority for tolerance reassessment on pesticides that appear to pose the greatest risk, such as the organophosphorus (OP) pesticides.

To implement the cumulative provision of FQPA, EPA has been working to develop methodologies for conducting cumulative risk assessments and then conduct its first such risk assessment on the OP pesticides. This has been a challenging task given that historically, the potential health risks associated with exposure to pesticides has focused on *single pathways of exposure* (e.g., exposure from food, or water, or pesticide use in and around the home) for individual chemicals and not on the potential for individuals to be exposed to *multiple (common mechanism) pesticides by all pathways concurrently*, as is required under FQPA.

This scientific assessment of OP pesticide food safety contains good news for American consumers. After years of rigorous scientific work, it strongly supports our confidence that the United States has one of the safest food supplies in the world. Specifically, with this groundbreaking work, EPA has evaluated over 1,000 OP pesticide tolerances and virtually all of them are now consistent with the highest levels of safety. Please note that EPA is still evaluating the tolerances for a few of the OP pesticides.

This finding comes after years of scientific work, countless scientific and public meetings, and an existing regulatory process to ensure these pesticide tolerances meet the tough food safety standard in the Food Quality Protection Act. In the last several years, EPA has taken a variety of regulatory actions on the OP pesticides, ranging from lowering application rates to complete cancellations of specific uses. These actions have substantially reduced the risks and have contributed to the high level of safety found in the cumulative risk assessment.

On December 3, 2001 EPA issued for public comment its "Preliminary OP Cumulative Risk Assessment." That assessment was a preliminary review of the results of a new way of analyzing data regarding potential exposure to pesticides. The focus of the assessment was on the methods used to assess the risk. In contrast this revised risk assessment describes the potential risks of OP's by presenting a range of estimates that reflect the variability inherent in an assessment of this scope. Table 1 provides a side-by-side comparison of the major changes between the December 2001 and current documents. The changes were made due to comments submitted during the public comment period, suggestions from the FIFRA Scientific Advisory Panel (SAP), and issues that EPA was aware of at the time the preliminary cumulative risk assessment was issued but had not yet addressed. These major changes are discussed under "Hazard Assessment" and "Exposure Assessment," below.

With the release of this document the Agency has met its deadline obligation under a Consent Decree with the Natural Resources Defense Council to issue a revised risk assessment of the OP pesticides by August 3, 2002. As existing analyses are revised or new information is obtained, EPA will review this assessment and will make further changes as appropriate.

Not all of the changes result in quantitative impacts on the risk assessment. For example, in February 2002 the FIFRA SAP suggested that the Agency conduct more "sensitivity analyses" to assure the quality and robustness of the model being used (see text box). While these analyses provide valuable information on the reliability of the models, they do not change the quantifications of risk (e.g., MOEs). On the other hand, other changes do impact the risk quantification. During the public comment period food processing factors were submitted; EPA has updated its food exposure estimates using this information.

Sensitivity Analysis is the study of how the variation in the output of a model can be apportioned to different sources of variation–it aims to ascertain how the model depends upon the information fed into it, upon its structure, and upon the assumptions made to build it. Overall, sensitivity analysis is used to increase the confidence in the model and its predictions by providing an understanding of how the model response variables respond to changes in the inputs.
http://sensitivity-analysis.jrc.cec.eu.int/default.htm

It has become evident that addressing issues such as the FQPA Safety Factor and the threshold of concern are both dependent on the available data. The decisions made regarding these two issues involve risk management considerations and will be made on a case-by-case basis. EPA intends to use a systematic approach in making these decisions to reflect such factors as the quality of the available data and the characteristics of the modeling analysis.

Table ES-1. Major Differences Between the Preliminary OP Cumulative Risk Assessment and the Revised OP Cumulative Risk Assessment

	December 2001	June 2002
Toxicity		
Relative Potency Factors (RPF's)	Used best available data	Additional RPF's were calculated: chlorethoxyphos, phostebupirim, profenofos and omethoate (a metabolite of dimethoate)
FQPA Factor	Not addressed	FQPA Safety Factors were assigned based on available information; 1X for three OP's and one metabolite; 3X used for the others
Treatment of Animal Data	Used means and standard deviations	To see how the results would be affected, single animal data were used in a sensitivity analysis
Exposure		
Food: Processing Factors	Used best available data	Revised based on data provided during the public comment period
Consumption Data	Used the CSFII data "as is"	Conducted a sensitivity analysis to look for 'extreme' outliers
Residue Data	Did not use any over-tolerance residues	Included over-tolerance residue values
Impact of High-End Exposure	Not considered	Conducted an analysis to determine whether specific high-end consumption and/or residue values are significantly responsible for the exposure estimates at the higher percentiles of the exposure distribution
Duration of Exposure	One-day	One - and seven-day rolling average. Also, a sensitivity analysis was conducted using 14- and 21-day rolling averages
Populations Considered	The standard populations	Conducted a sensitivity analysis by looking at additional subpopulations
Drinking Water: Number of Regions*	13	7; EPA found that a number of the Regions could be combined due to similarities among geography, climate, and soil type
Sensitivity Analysis	Some performed	Extensive analyses conducted, as suggested by the SAP
Residential: Populations Considered	The standard populations	Conducted a sensitivity analysis by looking at additional subpopulations
Type of Distribution	Uniform	log normal, as recommended by the SAP
Number of Regions[1]	13	7; EPA found that a number of the Regions could be combined due to similarities among geography, climate, and soil type
Pet Uses	Not included	New data on tetrachlorvinphos
Risk		
Risk Quantification	Summary results; MOE's for single-day exposures at various percentiles of exposure	Identified pestide/crop combinations that have significant roles in the estimates. Risk presented as ranges of MOEs at various percentiles reflecting one- and seven-day exposures, and 14 and 21-day rolling averages

[1]A Note on "Regions." Because the United States is so climatologically and geographically diverse, EPA has divided the country into different risk assessment "Regions" so that this diversity could be factored in to the assessments.

B. Hazard Assessment

1. RPF's

The RPF's were revised and relative potency factors for four additional chemicals have been calculated (chlorethoxyphos, phostebupirim, profenofos, and a metabolite of dimethoate).

2. FQPA Safety Factor

In the December 2001 preliminary cumulative risk assessment, EPA discussed and characterized the potential multiple sources of exposure to children but did not address the FQPA Safety Factor. The decision regarding the Safety Factor is determined based on the available data for the specific chemicals in this assessment. The Revised OP Cumulative Risk Assessment provides an analysis on the sensitivity and susceptibility of infants and children to cholinesterase (ChE) inhibition (the common mechanism of toxicity) caused by OP pesticides.

In summary, based on available information, the FQPA Safety Factor is 1X for three OP's and one metabolite (dimethoate; omethoate, a metabolite of dimethoate; chlorpyrifos; and methamidophos) and 3X for the remaining OP's. A summary of the rationale is provided below; please note that these Safety Factors are appropriate for this risk assessment only.

- In making an FQPA Safety Factor decision, EPA considers both the potential for pre- and postnatal toxicity and the completeness of the toxicology and exposure databases (USEPA, 2002a). Looking at the exposure side of the equation–there is a high degree of confidence in the exposure data and methodologies used–EPA believes that it is not necessary to retain the default 10X FQPA Safety Factor based on the exposure database.

- The toxicity endpoints for this assessment were developed in consideration of a 10X uncertainty factor to account for interspecies variability and a 10X uncertainty factor to account for intraspecies variability. Because some OP pesticides show age-dependent sensitivity and there are missing comparative ChE inhibition data in young animals for many of the OP's, EPA chose an FQPA Safety Factor of 3X for most of the OP pesticides. There were a few whose data supported a 1X FQPA Safety Factor:

  - Age-dependent susceptibility data are available for seven of the OP's. The data for dimethoate, omethoate (a metabolite of dimethoate), chlorpyrifos, and methamidophos support an FQPA Safety Factor of 1X.

On June 25 to 27, 2002 EPA is consulting with the FIFRA Scientific Advisory Panel on this sensitivity and susceptibility analysis for children. For more information see: http://www.epa.gov/fedrgstr/EPA-MEETINGS/2002/May/Day-31/.

For future cumulative risk assessments the FQPA Safety Factor may be retained, reduced, or removed, based on the available data which are specific to the chemicals examined.

C. Exposure Assessment

1. Regions

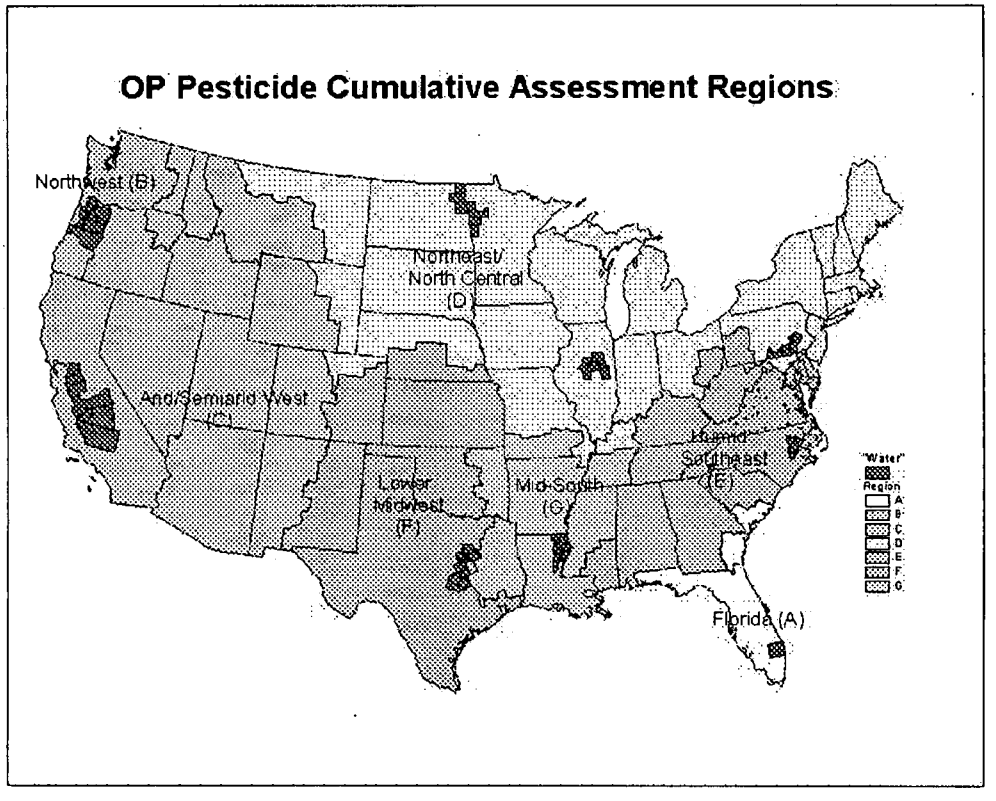
Because the United States is climatologically- and geographically-diverse, EPA divided the country into Regions so that it could account for factors such as weather and soil type (these affect the amounts and types of pesticides used). In the December 2001 analysis 13 Regions were used; the current analysis has seven. The reason for this reduction is that EPA realized that some of the Regions were not truly distinct so they were combined. Provided in Figure ES-1 is a map of the United States that shows the seven Regions.

As mentioned in the "Introduction" sensitivity analyses were conducted for a number of variables. The exposure data used for these analyses were from Region A. EPA chose Region A because it has the highest estimated exposure.

2. Food

The amount of pesticide to which an individual is exposed (i.e., exposure) is determined by combining the amount of pesticide that is in or on the food (i.e.,

ES-1. Regions Used for Exposure Assessment



residue levels) and the amount and type of foods that people eat (i.e., food consumption). In the Revised OP Cumulative Risk Assessment EPA conducted a number of sensitivity analyses on the data and models supporting the food risk assessment.

Consumption Data. EPA uses USDA's Continuing Survey of Food Intake by Individuals (CSFII) for its food consumption data. One of the criticisms that has been raised regarding the food consumption data is that it may include individuals who have "extreme" diets. EPA scientists, including a nutritionist, have conducted a sensitivity analysis on the food consumption database; no outliers were identified. Consumption data that appeared unusually high and were associated with high exposures in the cumulative risk assessment were fully investigated.

Although they did not identify any outliers, it is important that appropriate sensitivity analysis be conducted so that any outliers are evaluated. Please note that several individual OPs are still undergoing individual assessments and for these pesticides future analysis on food consumption will continue.

Residue Data. All of the residue data in this assessment came from USDA's Pesticide Data Program (PDP) and FDA's Center for Food Safety and Applied Nutrition (CFSAN) monitoring data. In the Revised OP Cumulative Risk Assessment EPA incorporated over-tolerance residue values from the PDP data.

Impact of High-End Exposure. The December 2001 document pointed out that:

> The data inputs and assumptions need to be verified, and the results at the tail end of the distribution at the higher percentiles of exposure for children's age groups need to be evaluated to ensure they reflect reasonable consumption patterns. Additionally, OPP is in the process of conducting sensitivity analyses that will permit a fuller characterization of the contributors or sources of potential risks associated with the food pathway.

The Revised OP Cumulative Risk Assessment includes an analysis of the upper tail of the exposure distribution to determine whether specific high-end consumption and/or residue values are significantly or mainly responsible for the exposure estimates at the higher percentiles of the exposure distribution. In addition, a range of percentiles of exposure as well as the percentiles at which the MOEs approach 100 (100 because the toxicity endpoints for this assessment were developed in consideration of a 10X uncertainty factor to account for interspecies variability and a 10X uncertainty factor to account for intraspecies variability) are presented in the body of the risk assessment. This information provides the basis for bounding and characterizing exposures.

Duration of Exposure. In the December 2001 risk assessment EPA used one-day as the duration over which an individual would be exposed to a pesticide residue in food. However, this analysis overestimates risk because the toxicity data and consumption reflect different time frames. For the current analysis EPA added a second exposure duration, that of the seven-day rolling average in an attempt to better match the time frames for the toxicity data with the consumption data which are not directly comparable. EPA also believes using these time intervals will bound the risk (i.e., the potential risk is best represented by a range of values for different exposure durations). In addition the Agency evaluated 14- and 21-day averages for one Region (Region A). EPA conducted these additional analyses to determine whether estimates of average daily exposure changed significantly over longer durations.

The chart provided below (Table ES-2) provides a discussion of how the one- and seven-day durations are affected by four key factors.

Table ES-2. How the One- and Seven-Day Durations Are Affected

Factor	Impact on Durations
The degree to which the exposure and toxicity time frames correspond to each other.	The use of a steady state hazard endpoint–based on toxicity studies that are 21-days or longer–tends to overstate the risk for the one-day analysis. Use of the steady state value is more appropriate with the 7-, 14-, and 21-day analyses.
The degree to which the Agency has captured the previous day's cholinesterase inhibition.	For the one-day analysis, the consideration of only a single day's exposure may underestimate risk, to the extent an individual's previous days' exposures continue to cause ChE inhibition. For the same reason, multiday exposures may also underestimate risk.
Day-to-day variation in individuals' diets.	Day-to-day variability in an individual's diet does not affect the one-day estimate. Limited data about such variability requires EPA to make assumptions that tend to underestimate the potential exposures for the seven-day analysis.
Possible correlation among residues on different days.	EPA's multiday analyses do not account for the possibility that a person may be more likely to encounter high residues in food because some portion of their consumption comes from the same source. This limitation means that multiday analyses may underestimate food exposure somewhat. This limitation does not affect the one-day analysis.
Interpretation of Model Outputs	The one-day analysis assumes that an individual is exposed to OP residues from the tail of the distribution every day. This assumptions overestimates risk. The seven-day analysis incorporates day-to-day variability in exposure and is more representative of anticipated exposures.

The Agency believes the timeframe considerations, as they relate to both hazard and exposure, to be among the most important for the OP cumulative assessment. This is not surprising since the essence of the cumulative assessment is to estimate likely co-occurrence in exposure to multiple chemicals and the likely combined effect of those exposures.

Populations Considered. Standard population subgroups that EPA considers in dietary risk assessment include: children one- to two-years-old; children three- to five; adults 20 to 49; and adults 50 and older. Upon SAP's recommendation, EPA looked at other subpopulations such as infants less than one year and teenagers. This was done to demonstrate that indeed children one- to two-years-old are the most highly exposed, due to their high consumption-to-body weight ratio.

3. Drinking Water

EPA evaluated the contribution to overall exposure resulting from OP pesticide residues in drinking water across different Regions and found that drinking water is not a significant source of exposure. EPA looked at the impacts that periods of high-volume runoff (e.g., during the spring and storm events) have on the level of pesticide residue estimated in drinking water. It was found that there are higher concentrations of pesticides in the drinking water during such periods. The analysis shows that, even considering such events, drinking water is not a significant contributor to overall risk.

4. Residential

Populations Considered. The population subgroups that EPA considers for residential exposure are the same as those considered for the food exposure. Similar to the food assessment, EPA conducted sensitivity analyses by looking at additional subgroups such as infants. This was done to see how including more population subgroups would change the risk estimates. The Agency is still working to evaluate individual residential uses (as part of the cumulative assessment) where additional risk mitigation will likely be necessary. In the next several weeks, EPA will continue the scientific and regulatory work to evaluate and address these potential risks.

Type of Distribution. EPA reassessed residential exposure using log-normal distributions of the available data (instead of a uniform distribution), wherever possible. This change was made because, according to the SAP, a log-normal distribution better represents the data set. Some of the resulting residential exposure estimates, and in turn risk, are lower than the December 2001 estimates.

Pet Uses. New data on exposure from the pet uses of tetrachlorvinphos have been used to quantitatively include tetrachlorvinphos in the residential assessment.

D. Risk Characterization

The risk characterization summarizes and integrates all of the information from the various components of the assessment. Risk characterization looks at the strengths and weaknesses of the data used, including any potential biases in input parameters and the direction of that bias, reliability and availability of the data, as well as the characteristics of the exposure models, and attempts to bound that uncertainty. The revised assessment discusses in great detail what data have been used; how the data have been used; and the strengths and weaknesses of the resulting analysis.

The risk estimates presented in this Revised OP Cumulative Risk Assessment are the culmination of several years of Agency analyses, outside input, and risk mitigation efforts on the part of the regulated community. Beginning in the summer of 1998 EPA started to seek public input on its individual OP risk assessments by issuing *Federal Register* notices asking for comment. In addition, EPA actively sought the advice of the regulated community, environmental groups, and others through two Federal advisory committees, the Tolerance Reassessment Advisory Committee (TRAC) and the EPA-USDA Committee to Advise on Reassessment and Transition (CARAT).

Throughout this period of public review and scrutiny, a good deal of risk reduction has been achieved through the risk mitigation measures taken on the individual OP's. In 1996 49 OP pesticides were registered for use in agriculture and residential settings. Today, 14 of those pesticides have been canceled completely and for another 28, considerable risk mitigation actions have been taken. For example:

- Methyl Parathion. Methyl parathion had been one of the most widely used OP's. In 1999 the registrants voluntarily canceled many methyl parathion uses that contribute most to the children's diet. These included: apples, peaches, pears, grapes, nectarines, cherries, and plums, carrots, succulent peas, succulent beans, and tomatoes.

- Ethyl Parathion. Before 2000, ethyl parathion had been one of the most highly restricted pesticides registered for use in the United States. A 2000 agreement canceled all remaining uses of the OP pesticide ethyl parathion, which included use on nine agricultural crops. Use of parathion on corn grown for seed was to stop immediately, with the use on other crops to be phased out over the next few years.

- Chlorpyrifos. Before the risk mitigation measures were taken, chlorpyrifos had been one of the most widely-used pesticides in and around the home. It is also one of the most widely used OP pesticides in agriculture. In 2000 the registrants agreed to cancel nearly all indoor and outdoor residential uses, as well as use on several food crops that contributed most to children's dietary exposure.

- Diazinon. Diazinon is one of the most widely used agricultural insecticides and until 2000, one of the most widely used insecticides for household lawn and garden pest control. In 2000 all indoor residential uses were terminated; outdoor residential uses will be phased-out over the next several years. Additionally, many agricultural uses of diazinon also are being canceled.

Without these measures, pesticide exposure through food and in and around the home would have been more significant. December's preliminary analysis and now the revised analysis reflect all these important risk mitigation measures.

1. Risk Quantification

This version of the cumulative risk assessment presents results showing a range of estimated risks depending on the exposure period considered (one-day or seven-day average) and the percentile of exposure. Ranges of estimated risk at various percentiles of exposure are also presented for 14- and 21-day averages for Region A. The selection of the range for the percentile of exposure must take into account the data from the particular group of chemicals in the assessment. For most portions of the ranges presented from the different exposure periods, the estimated Margins of Exposure (MOEs) do not represent levels of potential concern. After careful analysis, the Agency believes that the potential exposures are bounded by the estimates for the one- and seven-day exposure durations, and generally the margins of exposure in this assessment do not represent major concerns.

In considering the possible need for risk mitigation actions, EPA believes that it is important to consider the range of risk assessment values, which in turn take into account different exposure periods, for different age groups, living in different Regions, with risks shown at different percentiles of estimated exposures. It is also important to consider risk characterization, including the factors that may tend to overestimate or underestimate risk, and the identification of major sources contributing to potential exposure.

It appears that one of the major factors influencing the results at the highest portion of the range derives from the fact that, for a few individual OP's, risk assessments and mitigation actions have not been finalized. This is particularly true for DDVP and dimethoate. The Agency expects to complete these risk assessments and possible mitigation actions very soon.

Finally, it is important to remember that portions of this document are currently under review by the FIFRA SAP. For instance, EPA intends to present preliminary results of cumulative risk using two additional models–CARES and Lifeline™–to the SAP during the June 2002 meeting. EPA will evaluate SAP's comments, as well as other comments or data that it receives, and will modify this assessment, as appropriate. In addition, as existing analyses are revised or new information is obtained, EPA will review this assessment and will make further changes as appropriate.

E. Conclusion

This scientific assessment of OP pesticide food safety contains good news for American consumers. Regulatory actions taken over the last six years have considerably reduced the risks posed to Americans from OP residues that may be found in food, drinking water, and in and around the home. After years of rigorous scientific work, the Revised OP Cumulative Risk Assessment strongly supports our confidence that the United States has one of the safest food supplies in the world.

F. Road Map

The Revised OP Cumulative Risk Assessment is divided into three parts: (1) the actual risk assessment which draws on the regional risk assessments and the supporting toxicology analyses (I. Revised OP Cumulative Risk Assessment); (2) the seven regional risk assessments (II. Revised Regional Assessments); and (3) the detailed toxicology analyses such as the derivation of the RPF's and how the FQPA Safety Factors were determined (III/ Appendices).

Glossary

BMD_{10} is a Benchmark Dose associated with a 10% response adjusted for background.

Benchmark Response (BMR) is a designated level or percent of response relative to the control level of response used in calculating a BMD

Common Mechanism of Toxicity pertains to two or more pesticide chemicals or other substances that cause a common toxic effect(s) by the same, or essentially the same, sequence of major biochemical events (i.e., interpreted as mode of action).

Comparative effect level (CEL) is a dose by which potency of chemicals may be compared; *e.g.* the dose causing a maximum of 15% cholinesterase inhibition.

Cumulative Assessment Group (CAG) is a subset of chemicals selected from a common mechanism group for inclusion in a refined quantitative estimate of risk.

Cumulative risk is the risk of a common toxic effect associated with concurrent exposure by all relevant pathways and routes of exposure to a group of chemicals that share a common mechanism of toxicity.

Dose additivity is the Agency's assumption when evaluating the joint risk of chemicals that are toxicologically similar and act at the same target site. In other words, it is assumed that each chemical behaves as a concentration or dilution of every other chemical in the CAG (or chemical mixture). The response of the combination is the response expected from the equivalent dose of an index chemical. The equivalent dose is the sum of the component doses, scaled by each chemical's toxic potency relative to the index chemical.

Index chemical is a chemical used as the point of reference for standardizing the common toxicity of the chemical members of the CAG.

Lowest-Observed-Adverse-Effect Level (LOAEL) is the lowest dose in a toxicity study resulting in adverse health effects

No-Observed-Adverse-Effect Level (NOAEL) is the highest dose in a toxicity study which does not result in adverse health effects

OPCumRisk is a computer program developed at ORD's NHEERL to determine relative potency estimates and PoDs for the index chemical.

Pathway of Exposure is the physical course a pesticide takes from the source to the organism exposed (e.g., through food or drinking water consumption or residential pesticide uses).

Point of Departure (PoD) is a dose that can be considered to be in the range of observed responses, without significant extrapolation. A PoD can be a data point or an estimated point that is derived from observed dose-response data. A PoD is used to mark the beginning of extrapolation to determine risk associated with lower environmentally relevant human exposures.

Relative Potency Factor (RPF) is the ratio of the toxic potency of a given chemical to that of an index chemical in the CAG. Relative potency factors are used to convert exposures of all chemicals in the CAG into their exposure equivalents of the index chemical.

Route of Exposure is the way a chemical enters an organism after contact (e.g., ingestion, inhalation, or dermal absorption).

Steady state inhibition is the time point at which continued dosing at the same level results in no further increase in cholinesterase inhibition.

Acronyms

A	Estimate of A (background cholinesterase activity)
AChE	Acetylcholinesterase
B	Estimate of B (horizontal-asympote from July 2001 analysis)
B/A	Ratio of estimate of B/estimate of A
BMD_{10}	A Benchmark Dose associated with a 10% response adjusted for background
BMDL	Lower 95% confidence limit on the BMD_{10}
BMR	Benchmark Response -a designated level or percent of response relative to the control level of response used in calculating a BMD
CEL	Comparative effect level - Dose level used to compare potencies
ChEI	Cholinesterase inhibition
CL	Confidence limit
CNS	Central nervous system
D	Displacement parameter in expanded model
DER	Data evaluation record, a review of a toxicity study
F	Female
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FQPA	Food Quality Protection Act
GOF	Model goodness-of-fit
HED	Health Effects Division
idose	Scaled internal dose
m	Estimate of absolute potency for a single cholinesterase measurement in the July 2001 analysis
*l*A	Log of background cholinesterase activity
*l*m	Log slope-scale factor
M	Male
MOE	Margin of exposure
MRID #	Study identification number
NA	Not available
NERL	National Exposure Research Laboratory
NHEERL	National Health and Environmental Effects Laboratory
nlme	Non-linear mixed effects model
NOAEL	No-Observed-Adverse-Effect Level - the highest dose in a toxicity study which does not result in adverse health effects
OP	Organophosphorous pesticide
OPCumRisk	Computer program developed at ORD's NHEERL to determine relative potency estimates and PoDs for the index chemical.
OPP	Office of Pesticide Programs
OPPTS	Office of Prevention, Pesticides, and Toxic Substances
ORD	Office of Research and Development
P_B	Limiting value of minimum cholinesterase activity (horizontal asymptote)
P_{BF}	Female specific value of P_B
P_{BM}	Male specific value of P_B
PBPK	Physiologically Based Pharmacokinetics
POD	Point of Departure

PNS	Peripheral nervous system
RBC	Red blood cells
RfD	Reference Dose - A dose not expected to cause adverse health effects in humans
RPF	Relative Potency Factor
S	Shape
SAP	Scientific Advisory Panel
*t*B	Transformed horizontal asymptote

Part I.

Revised OP Cumulative Risk Assessment

I. Revised OP Cumulative Risk Assessment

A. Introduction

The Food Quality Protection Act of 1996 significantly amended the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) and the Federal Food, Drug, and Cosmetic Act (FFDCA). One of the major changes is the requirement that EPA consider risk posed by pesticides acting by common mechanism of toxicity.[1] For such groups of pesticides, EPA's Office of Pesticide Programs has treated cumulative risk, under FQPA, as the risk of a common toxic effect associated with concurrent exposure by all relevant pathways and routes.

Since the enactment of FQPA, EPA's Office of Pesticides Programs (OPP) has been working to develop new methodologies in a number of risk assessment areas. The steps necessary to complete the Revised OP Cumulative Risk Assessment were:

- Development of approaches for grouping chemicals by a common mechanism of toxicity (USEPA, 1999a) and
- Conducting aggregate (USEPA 1999c and 2001d) and cumulative risk assessments (USEPA 2000a and 2001a)

At each major step in development OPP consulted with the FIFRA Science Advisory Panel (SAP) to seek expert review, advice, and recommendations. We held several external peer review meetings with the SAP and asked for comment on our approaches to grouping chemicals based on common mechanism of toxicity, grouping chemicals for the purpose of cumulative assessment, improved methods for exposure assessment, approaches to aggregating food, drinking water and residential exposure and proposed models for combining these exposures. We also held several meetings with the FQPA Federal Advisory Committee Act (FACA) Groups of stakeholders (public interest groups, state agricultural agencies, pesticide industry representatives, growers, USDA and others) to present our methodologies as they were developed, and to seek comments and recommendations. All of the new science policies which are a foundation of this assessment were proposed for public comment. The work to develop the methodology was completed with the publication of the Revised Guidance Document for Cumulative Risk Assessment USEPA 2001a). The document was proposed for public comment on June 30, 2000 (65 FR 127:40644-40650). The SAP and public comments were reconsidered and the Guidance was revised in December, 2001. All of these documents played roles in preparation at the Preliminary OP Cumulative Risk Assessment which was issued

[1] For details see The Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), 7U.S.C. §§ 136 et seq., and Federal Food, Drug, and Cosmetic Act (FFDCA) 21 U.S.C. § 346a.

in December 2001and presented to the public in a technical briefing in January 2002. The assessment was reviewed by the SAP in February 2002. Public comment was also solicited for ninety days. The comment period closed in March 2002.

OPP proceeded with the methodology and risk assessment development in a step-by-step process. The approach to the risk assessment was evaluated using a case study of three organophosphorus pesticides. That assessment was reviewed by the SAP (September and December 1999 see FIFRA SAP 2000a,b), who recommended that OPP proceed with a more comprehensive case study. OPP developed the hazard, dose-response and exposure assessment for 24 OP pesticides and brought it to the SAP for comment in September and December of 2000 (FIFRA SAP 2001a,b). Based on the comments, the hazard and dose-response assessment was revised and again reviewed by the SAP in September of 2001(FIFRA SAP 2001c). The SAP was very supportive of the approach, calling it both 'skillful' and 'creative.' The recommendations made by the September 2001 SAP were addressed in the Preliminary Risk Assessment. In February 2002, OPP brought the Preliminary OP Cumulative Risk Assessment to the SAP. Once again the panel was generally supportive of the preliminary document while suggesting some revisions. These revisions have been incorporated in this current document, the Revised OP Cumulative Risk Assessment.

Cumulative Risk Assessment is a complex analysis and OPP needs to emphasize that the results are not a collection of numbers or bright lines. Quantitative methods have been used throughout the analysis but the results need to be interpreted with a full understanding of the assumptions made and the uncertainties introduced by making these assumptions. As the regulatory managers and the stakeholders look for guidance in reading the document, it is especially important to consider the Risk Characterization Chapter of the Risk Assessment.

I. Revised OP Cumulative Risk Assessment

B. Hazard/RPF

1. Introduction

Since the passage of the FQPA, the Office of Pesticide Programs (OPP) has presented proposed guidance, tools and methodologies for conducting cumulative risk assessments to the FIFRA Scientific Advisory Panel (SAP). Specifically, the hazard and dose-response sections have been presented to the FIFRA SAP four times between 1999 and 2002 including the February 5-8, 2002 meeting on the methods used in the Preliminary Cumulative Risk Assessment (PCRA) of the Organophosphorus Pesticides (FIFRA SAP, 2000a, 2001a, 2001b, 2002a). Following the previous SAP reviews, constructive comments and recommendations have been incorporated into revisions and refinements of the hazard and dose-response assessment for the organophosphorus pesticides (OPs). Key recommendations from SAP reports have included the utilization of the exponential model for fitting the cholinesterase data, the derivation of relative potencies from several relatively consistent studies rather than a single study, and further exploration of low dose modeling issues. In collaboration with EPA's Office of Research and Development (ORD) National Health and Environmental Effects Research Laboratory (NHEERL), OPP released a Preliminary Dose-Response Assessment for OPs on July 31, 2001 (USEPA 2001b) followed by a revised dose-response assessment on December 3, 2001. At the February 5-6, 2002 meeting, the SAP was very supportive of the approach used in the PCRA for OPs. The panel commended the Agency for its progress in modeling of dose-response relationships of OP exposure to cholinesterase inhibition. The panel indicated that remaining issues concerning cumulative hazard and dose-response assessment reflect the evolving nature of the field and do not need to be specifically addressed in the cumulative risk assessment of OPs.

Revised relative potency factors (RPFs) for 33 OPs were released to the public on April 17, 2002 (http://www.epa.gov/pesticides/cumulative/pra-op/rpf_final.htm). EPA has calculated RPFs for four OPs not included in the hazard and dose-response assessment of the PCRA: chlorethoxyphos, omethoate, phostebupirim, and profenofos. After issuing its PCRA, the Agency identified computer programming errors in its statistical modeling procedure. EPA discussed them at the February 5-8, 2002 meeting of the FIFRA SAP. These errors impacted the curve-fitting procedure for some OPs. In addition, EPA received additional toxicology data for disulfoton, fenamiphos, phosalone, tetrachlorvinphos, and tribufos, which were used in the revision of the RPFs for these chemicals.

2. Methods

a. Overview

Before the cumulative risk of exposure to OPs can be quantified, the relative toxic potency of each OP must be determined. The determination of relative toxic potency should be calculated using a uniform basis of comparison, by using, to the extent possible, a common response derived from the comparable measurement methodology, species, and sex for all the exposure routes of interest (USEPA 2001a, 2002).

b. Endpoints and Toxicology Studies

i. Selection of Endpoints

As part of the hazard analysis, all relevant responses were evaluated to identify the most appropriate endpoint pertaining to the common mechanism of toxicity and to determine which endpoint(s) provide(s) a uniform and common basis for determining the relative potency of the cumulative assessment group. OPs exert their neurotoxicity by binding to and phosphorylating of the enzyme acetylcholinesterase in both the central (brain) and peripheral nervous systems (Mileson *et al.,* 1998). There are laboratory animal data on OPs for cholinesterase activity in plasma, red blood cell (RBC) and brain, as well as behavioral or functional neurological effects in submitted guideline studies. Measures of acetylcholinesterase inhibition in the peripheral nervous system (PNS) are very limited for the OP pesticides. As a matter of science policy, blood cholinesterase data (plasma and RBC) are considered appropriate surrogate measures of potential effects on PNS acetylcholinesterase activity and of potential effects on the central nervous system (CNS) when brain cholinesterase data are lacking (USEPA, 2000c). Behavioral changes in animal studies usually occur at higher doses compared to doses needed to inhibit cholinesterase. Also, behavioral measures are limited in terms of the scope of effects assessed and the measurements employed. **Plasma, RBC, and brain cholinesterase inhibition were considered potential endpoints for extrapolating risk to humans in the OP cumulative risk assessment.**

ii. Selection of Routes and Duration of Exposure for Potency Determination

Humans may be exposed to the OPs through diet, in and around residences, schools, commercial buildings, etc. Therefore, the potency of OPs needs to be determined for the oral, dermal, and inhalation routes of exposure. Cholinesterase inhibition can result for single or short-term exposures. The Revised Cumulative Risk

Assessment for OPs (RCRA) has evaluated both single-day and multiple sequential days (i.e., 7-day rolling average) exposures for integrating multiple sources of OPs.

Various toxicokinetic and toxicodynamic factors influence an individual OP's time to peak effect of inhibition, persistence of action following acute exposure, and the duration of exposure required to reach steady state inhibition. OPP has elected to estimate relative potencies and points of departure (POD) using measurements where cholinesterase inhibition in the laboratory animal is not changing with time. OPP defines this point where continued dosing at the same level results in no further increase in enzyme inhibition as steady state. The use of cholinesterase data for single-dose or short duration studies to model the comparative potency is problematic because the extent of inhibition is rapidly changing immediately following dosing. Measures of cholinesterase taken during this time will be highly variable and uncertain. Cholinesterase inhibition will continue to increase until steady state is reached. When the measurements are taken at steady state, the differences in toxicokinetics among the OPs are less likely to impact the assessment. At this point in the dosing scheme, it is possible to develop a stable estimate of relative inhibitory capacity (i.e., relative potency) between compounds.

OPP has elected to use data reflecting steady state conditions to estimate relative potencies for the OPs in the interest of producing RPFs that are reproducible and reflect less uncertainty due to rapidly changing, time-sensitive measures of cholinesterase. Although the data selected do not directly reflect the time frames of interest (single-day and multiple sequential days), they are preferred to short-term estimates for developing comparative potencies among OPs. OPP has shown previously that steady state is reached by approximately 21 to 28 days of exposure (USEPA, 2001b). No further analysis of the time course data was performed in the revised cumulative risk assessment. **The current focused on studies of a duration of 21 days or greater in order to use cholinesterase data that has attained steady state.** Twenty-one days of exposure was selected instead of 30 days because of the duration of exposure of available guideline toxicity studies; specifically, most dermal toxicity studies are 21 or 28 days in duration.

iii. Toxicity Database

As stated previously, relative potency should be based whenever possible on data from the same species and sex to provide a uniform measure of relative potency among the cumulative assessment group (USEPA, 2002). Under FIFRA, toxicology studies in various species (e.g., dog, mouse, rat and rabbit) are submitted to OPP. For the OP's,

toxicology studies in the rat provided the most extensive cholinesterase activity data for all routes, compartments, and both sexes. **Thus, the focus of this analysis was on cholinesterase activity data derived from male and (non-pregnant) female rats**. EPA used rabbit studies for five chemicals with residential/nonoccupational exposure potential because dermal toxicity data in rats were not available. The cholinesterase data considered in this analysis were extracted from the study types listed in Table I.B-1.

Studies used in this analysis were identified by their source MRID number. Studies submitted to OPP are reviewed for their quality of cholinesterase measurements and consistency of their experimental protocol with the OPPTS Guidelines (http://www.epa.gov/opptsfrs/home/guidelin.htm).

When assessing cholinesterase activity, it is important to carefully consider methodological issues that may affect the accuracy and variability of the data. There are many methods available for measuring cholinesterase activity. These methods include colorimetric, electrometric, titrimetric, radiometric, fluorimetric, gasometric, and immunochemical assays. The colorimetric method, based on the Ellman reaction, is the most commonly used method for measuring brain, plasma and erythrocyte cholinesterase activity (Ellman et al., 1961; USEPA 1992; ASCP, 1994). For this preliminary assessment, if the Data Evaluation Record (DER) for a particular study indicated that the study was acceptable, it was assumed that the methodology was also acceptable.

A comprehensive list of all the studies utilized in the present analysis is given in Appendix III.B.2. The cholinesterase data are available to the public at http://www.epa.gov/pesticides/cumulative/.

Table I.B-1. Test Guideline Studies Evaluated for Cholinesterase Activity.

Test Guideline Studies Evaluated for Cholinesterase Activity	
Study Type	**Guideline Type**
Oral	
90-day oral toxicity study in rat	OPPTS 870.3100 OPP 82-1
Chronic oral toxicity in rat	OPPTS 870.4100 OPP 83-1
Carcinogenicity in rat	OPPTS 870.4200 OPP 83-2
Combined chronic toxicity/carcinogenicity in rat	OPPTS 870.4300 OPP 83-5
Subchronic neurotoxicity study in rat	OPPTS 870.6200 OPP 82-7
Range finding oral toxicity study in rat	Not applicable
Other —Special studies	Not applicable
Dermal	
21/28-Day dermal toxicity in rat or rabbit	OPPTS 870.3200 OPP 82-2
90-Day dermal toxicity in rat	OPPTS 870.3200 OPP 82-2
Inhalation	
90-Day inhalation toxicity in rat	OPPTS 870.3465 OPP 82-4
21/28-Day inhalation toxicity in rat	OPPTS 870.3465 OPP 82-4
Inhalation carcinogenicity in rat	OPPTS 870.3320 OPP 83-5

c. Collection of Cholinesterase Activity Data

i. Oral Route

Oral relative potency values were needed for all OP pesticides included in the RCRA because of potential dietary exposures from food and drinking water and hand to mouth exposures associated with residential/nonoccupational uses. Numerous oral studies with comparable methodologies were available and suitable for quantitative dose-response analysis. An electronic spreadsheet is needed to perform quantitative dose-response analysis. Study type, duration of exposure,

number of animals per dose group, sex, compartment, and the measured effect for each dose group (mean cholinesterase activity, activity units, and standard deviation) were compiled into an electronic spreadsheet. In feeding studies, average compound intake (mg/kg/day) over the entire study was used. At least one oral toxicity study of the appropriate duration was available for all the OPs. Time of measurement was expressed as number of days on study where: number of days = number weeks x 7 and number of days = number months x 30.

ii. Dermal and Inhalation Route

Relative potency factors were needed for 10 OPs with residential exposure. Unlike the database of oral toxicity studies, the database of dermal and inhalation studies with cholinesterase measurements is limited. However, using the CEL approach is adequate for the RCRA. Comparative effect levels (CELs) have been used to compare the relative potency of the OPs. CELs are dose levels from a given study with a defined range of effects. The CEL was defined as the dose causing a maximum of 15% brain cholinesterase inhibition. Quantitative dose-response analysis for estimating a common benchmark response is the preferred method for determining relative potency.

d. Selection of Relative Potency Factors for the Female Brain Cholinesterase Data Set

A key component of cumulative hazard assessment is to select an endpoint pertinent to the common mechanism of toxicity that can be used to quantify cumulative risk. In the July 2001 dose-response assessment, OPP prepared a dose-response analysis for 25 OPs in which a large body of toxicity data on a common mechanism endpoint for these OPs – the ability to inhibit cholinesterase in plasma, RBC, and brain – was analyzed. To determine which compartment would provide a strong basis for determination of relative potency, OPP reviewed data in each compartment. In the July 2001analysis, RPFs based on the male RBC database were proposed. It was stated in that document that the RBC RPFs proved to be a reliable and sensitive endpoint considered protective of both the peripheral and central nervous systems for the majority of the chemicals. The major advantage of the RBC database was its large size compared to the whole brain ChE database; this large database allowed the examination of time course information and observation of a steady state response.

After considering the comments from the September 2001 SAP meeting in addition to the comments from the public and stakeholder groups, OPP has decided to use female brain ChE data for quantifying cumulative risk for OPs. OPP has decided to estimate cumulative risk based on RPFs and PODs from the female brain ChE database for

several reasons. Principally, compared to relative potency estimates based on RBC, estimates of relative potency based on brain ChE have tighter confidence intervals and therefore will confer less uncertainty on cumulative risk estimates. Also, these data represent a direct measure of the common mechanism of toxicity as opposed to using surrogate measures. The toxic potencies and PODs for brain cholinesterase inhibition for these OPs are generally similar to the RBC data for the oral, inhalation, and dermal exposures (USEPA, 2001b). The SAP recommended the Agency address the issue of repeated measures in its revised analysis. This issue concerning repeated cholinesterase activity measures only pertains to the plasma and RBC ChE data because blood can be collected several times from a single animal, whereas brain ChE can only be collected once. Finally, in the present analysis, although male and female rats were equally sensitive for 30 OPs, female rats were more sensitive to three OPs. Therefore, OPP has chosen to based its RPFs on female brain measurements.

In the RCRA, potency estimates have been recalculated only from the brain ChE database. The plasma and RBC databases were thoroughly examined in the July 2001 analysis (USEPA, 2001b). Re-analysis of the plasma and RBC databases using the revised methodology is unlikely to significantly change potency estimates from these compartments (USEPA, 2001c).

e. Determination of Chemical Potency: Oral Route

In their review of the September, 2000 pilot analysis, the SAP suggested that EPA consider Michaelis-Menton kinetics or the exponential model to fit cholinesterase data from OPs (FIFRA SAP, 2001a). Preliminary simulations using a subset of studies (one study per 24 chemicals) were performed using both the rectangular hyperbola (i.e., Michaelis-Mention kinetics) and the exponential function. The exponential model was selected over the rectangular hyperbola based on statistical criteria such as goodness of fit (USEPA, 2001b). Based on the results presented to the SAP in September, 2001, the panel indicated that no alternative to the exponential model would be more appropriate at the present time (FIFRA SAP 2001b).

i. Exponential Equations Used To Determine Potency

The simplified and general exponential equation used for modeling the effect of the OPs on cholinesterase activity is:

Equation I.B-1a

$$y = A\left[P_B + (1 - P_B)\mathrm{e}^{-m \times Dose} \right]$$

where ***y*** is cholinesterase activity,
Dose is the dose level of the OP, in mg/kg/day,
A is the background (similar to control) ChE activity,
m is the slope-scale factor,
and P_B is the horizontal asymptote (i.e., limiting value of minimum cholinesterase activity), expressed as a fraction of the background activity.

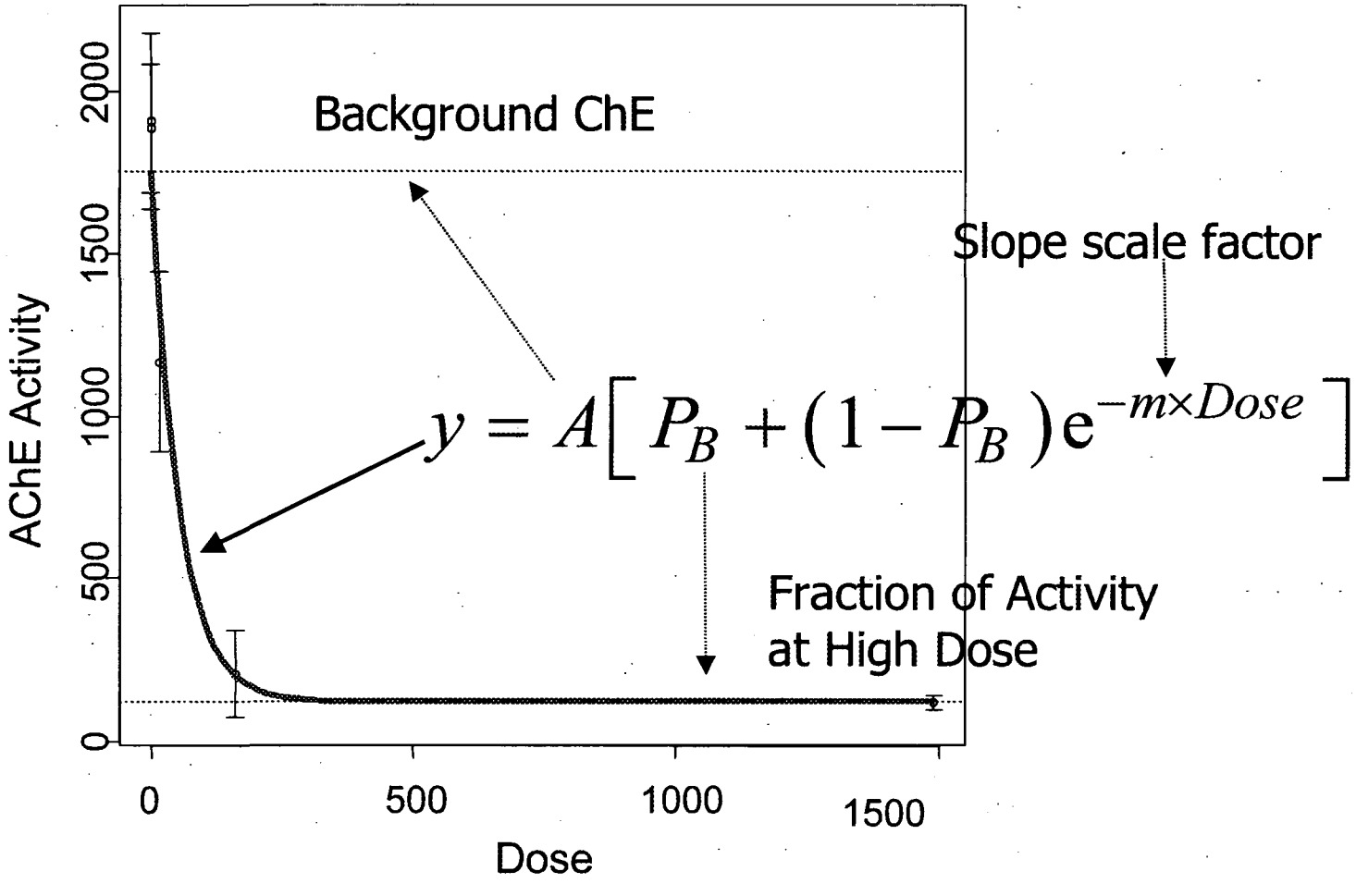
Both *y* (cholinesterase activity) and *dose* were extracted from the oral toxicity studies. P_B expresses the horizontal-asymptote as a fraction of background cholinesterase activity. P_B does not have any units. As described in detail in the technical appendix (III.B.1), Equation I.B-1a was reparameterized to Equation I.B-1b, where benchmark dose is an explicit parameter, to simplify the statistical calculations.

Equation I.B-1b

$$y = A\left[P_B + (1 - P_B)\,e^{-\frac{\log\left(\frac{1-P_B-BMR}{1-P_B}\right)}{BMD}\times Dose}\right]$$

where **A** is the level of cholinesterase activity in the absence of exposure to organophosphate (i.e., control),
P_B is the fraction of cholinesterase activity remaining at a very high dose of organophosphate,
BMR is the level of inhibition at which to estimate the benchmark dose (in this study, *BMR* is always 0.10),
BMD is the benchmark dose, and
Dose is the dose of organophosphate pesticide, generally in units of mg/kg/day.

Figure I.B-1. Plot of basic equation.



The exponential function in Equation I.B-1a/b decreases in a linear fashion in the low dose region (Figure I.B-1). Considerable discussion at the August 2001 Technical Briefing and the SAP meeting of September 5-6, 2001 centered around the potential for a flat region in the low dose portion of the dose-response curve. This potential low-dose flat region was explored and a revised equation was developed. This revised equation is a modified version of the exponential function in Equation I.B-1b which includes two additional variables, *S* (shape) and *D* (displacement). S and D together describe a low-dose flat region of the dose-response curve (Figure I.B-2). The second equation results from combining Equation I.B-1b with an equation which describes the relationship between administered dose and calculated internal dose (Equation I.B-2). The value *idose* replaces *Dose* in Equation I.B-1b. The SAP called this revised equation "elegantly simple" and pointed out that the equation improved fit for many OPs with little response at low dose levels. For ease of discussion, Equation I.B-1b will be called the '*basic*' model (low dose linear) and Equation I.B-2 will be called the '*expanded*' model (low dose flat).

Equation I.B-2

$$idose = g(Dose; S, D) = 0.5\left[(Dose - S - D) + \sqrt{(Dose - S - D)^2 + 4 \times Dose \times S}\right]$$

where ***idose*** is the scaled internal dose,
Dose is the administered dose level (mg/kg/day),
S controls the low-dose shape of the curve, and
D controls the ultimate horizontal displacement of the curve relative to the identity line (i.e., the line with *idose* = *Dose*).

As shown in Figure I.B-2, for the basic model, the low dose region decreases in a linear fashion. For the expanded model, the low-dose end of the dose-response curve has a more shallow slope (more flat). As *S* grows small, or *D* grows large, the estimated benchmark dose increases in magnitude. As *S* grows large, or *D* approaches 0, the relationship between *idose* and *Dose* approaches the line *idose = Dose. In other words, as S increases or D decreases, the shape of the expanded equation approaches the shape of the basic equation.* The technical discussion of the expanded model and its derivation are described in more detail in Appendix III.B.1.

Figure I.B-2 shows the relationship between the basic and expanded models and also how the shape and displacement variables impact the dose-response curve.

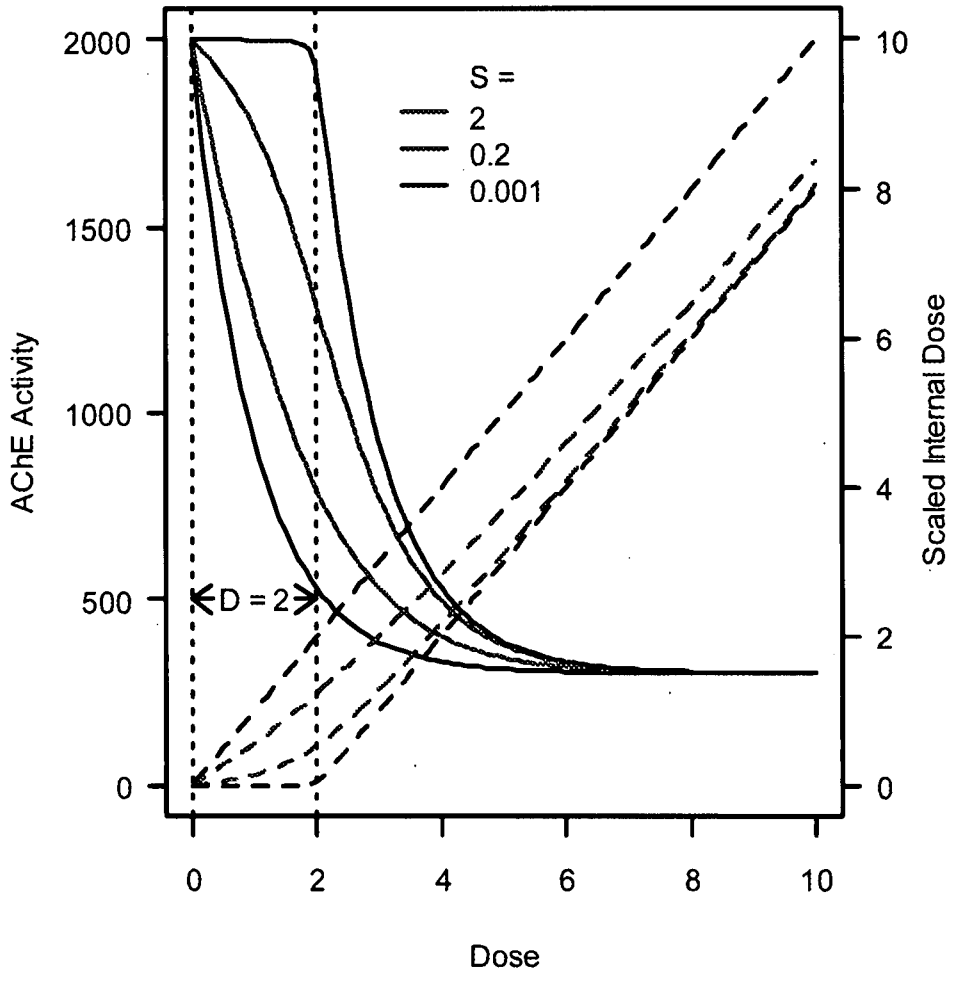


Figure I.B-2. Basic and expanded equations. The black solid curve is the basic equation of Equation I.B-2 with A = 2000, P_B = 0.15, and m = 1. The colored solid curves show the results of the expanded equation with 3 different values of S and D=2. The dotted curves shows the relationship between *idose* (blue, purple, and red) and *Dose* (black).

ii. Joint Analysis of OP Cholinesterase Data

In the joint dose-response analysis, the cholinesterase data for various time points for a specific chemical are modeled *together* all at once. For example, there are five measurements of female rat brain cholinesterase following exposure to methamidophos. All five datasets were analyzed together to determine the benchmark dose (although studies are plotted separately in Appendix III.B.2). This approach allows information about the shape of the dose-response curve to be "shared" among individual studies and results in benchmark dose estimates which are representative of a given OP. To perform the joint analysis of all the datasets for each chemical, several aspects of the data need to be accommodated . First, measurements of cholinesterase activities can have different units (mainly U/G, U/L, and ΔpH), which need to be accommodated in the same analysis. Model parameters may also differ between males and females. Finally, it is likely that model parameters vary randomly among studies and within a study. When more than measurement of brain cholinesterase was available, the approach to nonlinear mixed effects (nlme) modeling developed in Lindstrom and Bates (1990) was used to fit the cholinesterase data to Equations I.B-1b and I.B-2. Only one measurement of brain cholinesterase was available for four OPs; for these OPs generalized least squares (*gnls*) was used to fit the cholinesterase data. Profile likelihood plots were used to estimate the horizontal asymptotes, shape, and displacement parameters. All estimated parameters, including the shape and displacement parameters, were estimated separately for each OP and vary among OPs. The technical statistical methodology used to fit the cholinesterase data to the exponential model are not discussed here. The statistical methodology are discussed in detail in Appendix III.B.1.

Thirty-two OPs were fit to both the basic and expanded models. In cases where the expanded model resulted in a significantly improved fit ($P < 0.05$), the expanded model was used to estimate potency. The basic model was used to estimate the potency of the remaining OPs. Omethoate was modeled using only the basic model. At the time of public release for the revised RPFs only one measurement of brain cholinesterase in female rats with the appropriate duration of exposure was available for omethoate. In this dataset, ***all*** treatment groups exhibited reduced brain ChE activity compared to the control. Three other OPs have one dataset for female rat brain cholinesterase inhibition was available. For only one of these, dichlorvos, reduced cholinesterase activity was observed at all treatment groups. The expanded model did not improve the fit for dichlorvos; the basic model was used to estimate the potency. In addition, the potency of dimethoate, the parent chemical, of omethoate was estimated using the basic model. At this time, it is reasonable to assume that the expanded model would not improve the fit for omethoate.

iii. Use of BMD_{10} for Relative Potency Determination

Potency determinations of the OPs for the oral route exposure are based on the benchmark dose where cholinesterase activity is reduced 10% compared to background activity (BMD_{10}). The BMD_{10} was selected as the effect level for potency determination because this level is generally at or near the limit of sensitivity for discerning a statistically significant decrease in cholinesterase activity across the blood and brain compartments and is a response level close to the background cholinesterase.

At the February 5-8, 2002 meeting of the FIFRA SAP some members of the panel in addition to some public commenters discussed the Agency's selection of the BMD_{10} as the benchmark response level. In response to this discussion, the Agency analyzed the detection limits of the studies assessing female brain cholinesterase levels used in the RCRA of the OPs. This analysis has shown that generally these studies can reliably detect around 10% cholinesterase inhibition, that such levels were generally achieved in the studies, and that therefore, the Agency's use of the BMD_{10} as the benchmark response is appropriate. This analysis is described in detail in Appendix III.B.3

iv. Software Used in Oral Potency Determination

The programming code in R-language used to develop the relative potency factors and the PODs for the index chemical in the current analysis has been included in Appendix III.B.4.

In the July 2001 dose-response analysis, a computer program, OPCumRisk, was used to determine relative potency estimates and PODs for the index chemical. OPCumRisk was developed at ORD's NHEERL specifically for use in the July 2001 OP dose-response assessment and is available at http://www.epa.gov/scipoly/sap/index.htm. OPCumRisk is written in R (Ihaka and Gentleman, 1996), a freely distributable implementation of the S programming language available for download on the internet at http://www.R-project.org. Minor revisions recommended by the SAP have been incorporated into the OPCumRisk program (See Appendix III.B.3). The statistical methodology used in the present document has **not** been incorporated into the OPCumRisk program.

f. Determination of Chemical Potency: Dermal Route

Chemical potency was determined using CELs for the dermal route of exposure. These CELs are experimental dose levels which elicit a similar toxicological response to the selected endpoint.

Cholinesterase activity data were collected from dermal toxicity studies for nine chemicals with residential/nonoccupational exposure and the index chemical (methamidophos). Five OPs were tested by the dermal route in rats. Only rabbit studies were available for the other five OPs. Thus, it was not possible to compare cholinesterase activity data from dermal studies in only one species. Of the chemicals with potential dermal exposure, only three chemicals (acephate, disulfoton, and naled) had more than one dermal toxicology study which could be used for assessing relative potency. One chemical, dichlorvos, had no dermal exposure study. The requirement for a dermal toxicity study with dichlorvos was waived because the volatility of the chemical renders it technically difficult to conduct such a study.

Relative potencies of the chemicals with residential/non-occupational uses were determined by using CELs derived from data on inhibition of cholinesterase activity in female rat brain. The CEL was defined as the lowest dose where a maximum 15% brain cholinesterase inhibition (compared to control) occurred.

g. Determination of Chemical Potency: Inhalation Route

Chemical potency was determined using CELs for brain cholinesterase activity for the inhalation route of exposure. Cholinesterase activity data were collected from inhalation toxicity studies for seven chemicals with residential/nonoccupational exposure and the index chemical (methamidophos). Two inhalation exposure studies were available for acephate whereas only one suitable study was available for the other OPs. Although all of the inhalation studies were performed with the same species (rat), four different strains of rats were used. Furthermore, the exposure conditions varied among the chemicals tested. There were four whole-body exposure studies, one head-nose, and three nose only exposure studies. No inhalation toxicity study was available for three chemicals, bensulide, fenthion, and tetrachlorvinphos.

Relative potency was calculated from CELs for brain cholinesterase activity determined from inhalation toxicity studies. The CEL was defined as the lowest dose where a maximal response [brain cholinesterase inhibition] of 15% (compared to control) occurred.

h. Selection of the Index Chemical (Methamidophos)

The cumulative risk assessment guidance document (USEPA, 2002) states that the index chemical should be selected based on the availability of high quality dose-response data for the common mechanism endpoint and that it acts toxicologically similar to other members of the common mechanism group. High quality dose-response data allows the calculation of points of departure (POD) for oral, dermal, and inhalation exposures with confidence. A POD is a point estimate on the index chemical's dose-response curve that is used to extrapolate risk to the exposure levels anticipated in the human population. Thus, any error or uncertainty in an index chemical's POD value will be carried forward in the cumulative risk estimates. For the cholinesterase inhibiting OP pesticides, the ideal index chemical should exhibit high quality dose-response data in plasma, RBC, and brain for both sexes of a single species for all exposure routes of interest.

In the July 2001 dose-response assessment, methamidophos was selected as the index chemical for the OPs. The selection criteria and the potential candidates for the index chemical were discussed in detail in the July, 2001 document (USEPA 2001b). **Methamidophos remains the index chemical for the RCRA OPs because this chemical has a high quality database for the common mechanism endpoint of inhibition of acetylcholinesterase for the oral, dermal, and inhalation routes of exposure.**

i. Points of Departure (POD)

The oral, dermal, and inhalation PODs for the index chemical are based on the benchmark dose where cholinesterase activity is reduced 10% compared to background activity (BMD_{10}). The BMD_{10} was selected as the effect level for the POD because this level is generally at or near the limit of sensitivity for discerning a statistically significant decrease in cholinesterase activity across the blood and brain compartments and is a response level close to the background cholinesterase.

j. Calculation of Relative Potency Factors (RPF)

Oral RPFs were calculated from oral BMD_{10}s for female brain cholinesterase activity by the Equation I.B-3.

$$Oral\ RPF_{\text{Chemical X}} = BMD_{10\ \text{Index Chemical}} / BMD_{10\ \text{Chemical X}}$$

Equation I.B-3

where $BMD_{10\ \text{Chemical X}}$ is the BMD_{10} for Chemical X

and $BMD_{10\ \text{Index Chemical}}$ is the BMD_{10} of the index chemical.

CELs for brain cholinesterase activity measured in dermal studies were determined in order to calculate RPFs. Dermal RPFs were calculated using Equation I.B-4.

$$Dermal\ RPF_{\text{Chemical X}} = CEL_{\text{Index Chemical}} / CEL_{\text{Chemical X}}$$

Equation I.B-4

CELs for brain cholinesterase activity measured in inhalation studies were determined in order to calculated RPFs. Inhalation RPFs were calculated using Equation I.B-5.

$$Inhalation\ RPF_{\text{Chemical X}} = CEL_{\text{Index Chemical}} / CEL_{\text{Chemical X}}$$

Equation I.B-5

3. Results

a. Dose-Response Modeling: Oral Route of Exposure

The joint analysis using the exponential model served as good method for determining potency and provided confident estimates of the benchmark dose. The exponential model fits the cholinesterase data well. Plots of dose-response data, residuals, and profile likelihoods for all 33 OPs are given in Appendix III.B.2. BMD_{10}s and RPFs for the OPs are listed below.

i. Basic vs. Expanded Models

A joint analysis using the basic (low dose linear) and/or the expanded (low dose flat) equations of brain cholinesterase data for OPs was performed. The potency of 17 pesticides listed in Table I.B-2 were determined with the expanded model. The expanded model fit was significantly improved; i.e., the P-value of the likelihood test for the expanded model was ≤ 0.05 for all 17 chemicals. The potency of the remaining 16 were determined with the basic model.

Table I.B-3 shows the dose-response model parameters for the horizontal asymptote (P_B), shape (S), and displacement (D) parameters for each OP. These parameters vary among OPs.

Table I.B-2. Listing of OPs which were modeled with basic and expanded models

Listing of OPs which were modeled with basic and expanded models.		
Chemical	**Expanded vs. Basic**	**P value for the Improvement in Model Fit for Expanded vs. Basic**
Acephate	Basic	0.999
Azinphos-methyl	Expanded	3.04E-21
Bensulide	Expanded	0.0002
Chlorethoxyfos	Expanded	7.05E-24
Chlorpyrifos	Expanded	1.88E-13
Chlorpyriphos-methyl	Basic	0.96
Diazinon	Expanded	8.05E-21
Dichlorvos	Basic	0.77
Dicrotophos	Basic	0.998
Dimethoate	Basic	0.81
Disulfoton	Expanded	2.06E-10
Ethoprop	Basic	0.78
Fenamiphos	Basic	0.46
Fenthion	Basic	0.998
Fosthiazate	Expanded	2.73E-09
Malathion	Expanded	9.29E-13
Methamidophos	Basic	0.17
Methidathion	Basic	0.86
Methyl-parathion	Expanded	1.03E-07
Mevinphos	Expanded	0.0001
Naled	Basic	0.62
Omethoate	Basic	NA
Oxydemeton-methyl	Basic	0.9996
Phorate	Expanded	4.23E-28
Phosalone	Expanded	0.01
Phosmet	Expanded	5.20E-05
Phostebupirim	Expanded	0.001
Pirimiphos-methyl	Basic	0.99997
Profenofos	Basic	0.9999
Terbufos	Expanded	1.14E-32
Tetrachlorvinphos	Basic	0.39
Tribufos	Expanded	8.79E-13
Trichlorfon	Expanded	8.90E-06

Table I.B-3. Exponential model parameters for female and male brain cholinesterase data

Exponential model parameters for female and male brain cholinesterase data				
Chemicals	**Displacement[a] (D)**	**Shape[b] (S)**	**P_B Male[c]**	**P_B Female**
Acephate	--	--	0.295	0.286
Azinphosmethyl	0.597	0.001	0	0.082
Bensulide	22.066	0.110	0	0
Chlorethoxyfos	0.603	0.002	0	0
Chlorpyrifos	0.764	0.015	0.287	0.249
Chlorpyriphos-methyl	--	--	0.383	0.413
Diazinon	18.725	0.212	0.457	0.428
Dichlorvos	--	--	0.672	0
Dicrotophos	--	--	0.115	0.109
Dimethoate	--	--	0.331	0.364
Disulfoton	0.043	0.001	0.168	0.133
Ethoprop	--	--	0.304	0.313
Fenamiphos	--	--	0.720	0.750
Fenthion	--	--	0.230	0.200
Fosthiazate	11.560	0.006	0.128	0.098
Malathion	1415.734	2.913	0.800	0
Methamidophos	--	--	0.204	0.207
Methidathion	--	--	0.331	0.288
Methylparathion	0.351	0.007	0	0
Mevinphos	0.057	0.001	0.320	0.343
Naled	--	--	0.256	0.267
Omethoate	--	--	0	0.414
Oxydemeton-methyl	--	--	0.211	0.210
Phorate	0.235	0.002	0	0
Phosalone	4.502	1.222	0.090	0
Phosmet	1.379	0.027	0	0
Phostebupirim	0.097	0.005	0	0.052
Pirimiphos-methyl	--	--	0.769	0.610
Profenofos	--	--	0	0.496
Terbufos	0.211	0.005	0	0
Tetrachlorvinphos	--	--	0	0
Tribufos	1.775	0.046	0	0
Trichlorfon	28.437	0.189	0	0.400

a. *D* controls the horizontal displacement of the curve; b. *S* controls the low-dose shape of the curve; c. P_B is the horizontal asymptote, expressed as a fraction of the background activity. Parameters for S and D are only available for those chemicals with the expanded model

ii. Benchmark Dose Calculations

The BMD_{10}s for brain cholinesterase measured in male and female rats using the joint analysis procedures are listed in Table I.B-4 and shown graphically in Figures I.B-3 and I.B-4. Among the OPs, BMD_{10}s range widely over approximately five orders of magnitude.

Ratios of the male to female BMD_{10}s are plotted in Figure I.B-5. For 30 of 33 OPs the ratio is approximately one indicating that male and female rats exhibit similar sensitivity to the OPs for brain cholinesterase activity. For these three OPs (terbufos, tetrachlorvinphos, and trichlorfon) the females rats were ~2- to 7-fold more sensitive compared to male rats.

Table I.B-4. Oral BMD_{10}s and BMDLs (mg/kg/day) estimated for brain ChE activity

Oral BMD_{10}s and BMDLs (mg/kg/day) estimated for brain ChE activity				
Chemical	Female		Male	
	BMD_{10}	BMDL	BMD_{10}	BMDL
Acephate	0.99	0.53	0.77	0.41
Azinphos-methyl	0.86	0.79	1.14	0.98
Bensulide	31.91	30.44	40.88	37.11
Chlorethoxyfos	0.65	0.61	0.69	0.62
Chlorpyrifos	1.48	1.26	1.50	1.27
Chlorpyriphos-methyl	16.20	4.77	14.26	4.21
Diazinon	6.24	2.89	9.62	5.39
Dichlorvos	2.35	1.61	1.71	0.08
Dicrotophos	0.04	0.04	0.04	0.03
Dimethoate	0.25	0.22	0.35	0.31
Disulfoton	0.07	0.06	0.10	0.09
Ethoprop	1.37	0.70	1.35	0.69
Fenamiphos	1.96	0.69	1.73	0.63
Fenthion	0.24	0.21	0.18	0.15
Fosthiazate	1.28	0.32	1.48	0.38
Malathion	313.91	221.12	212.02	119.31
Methamidophos	0.08	0.07	0.07	0.06
Methidathion	0.25	0.17	0.24	0.16
Methyl-parathion	0.67	0.50	0.70	0.51
Mevinphos	0.11	0.10	0.15	0.13
Naled	1.00	0.82	1.00	0.82
Omethoate	0.09	0.07	0.14	0.12
Oxydemeton-methyl	0.09	0.09	0.07	0.07
Phorate	0.21	0.20	0.29	0.26
Phosalone	6.93	6.27	7.88	7.05
Phosmet	3.56	2.03	4.15	2.25
Phostebupirim	0.37	0.24	0.40	0.26
Pirimiphos-methyl	2.25	1.61	1.58	0.93
Profenofos	20.58	17.64	24.98	21.86
Terbufos	0.10	0.08	0.18	0.17
Tetrachlorvinphos	60.69	20.97	369.27	102.31
Tribufos	4.27	3.31	4.52	3.47
Trichlorfon	31.74	28.62	58.49	45.39

Figure I.B-3. BMD_{10}s (mg/kg/day) for female brain ChE activity for 33 OPs

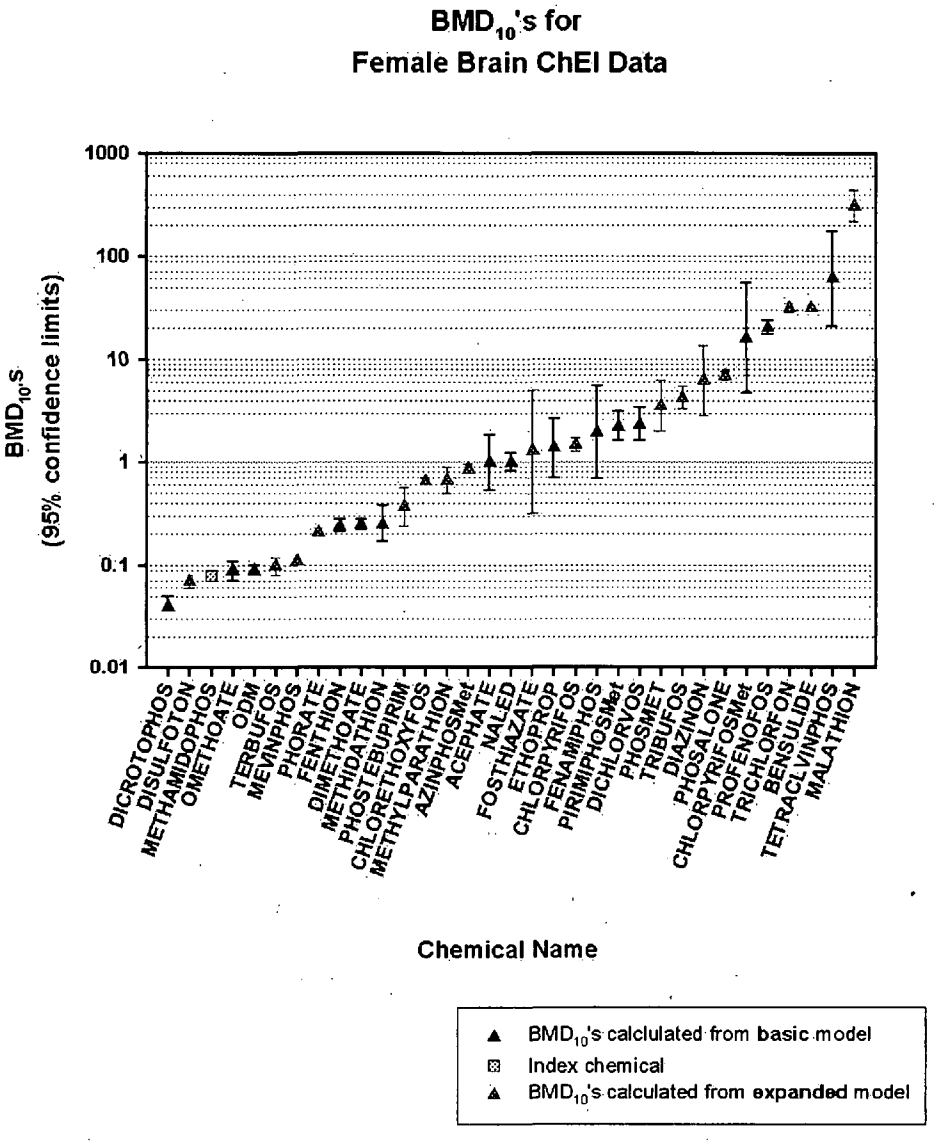


Figure I.B-4. BMD_{10}s (mg/kg/day) for male brain ChE activity for 33 OPs

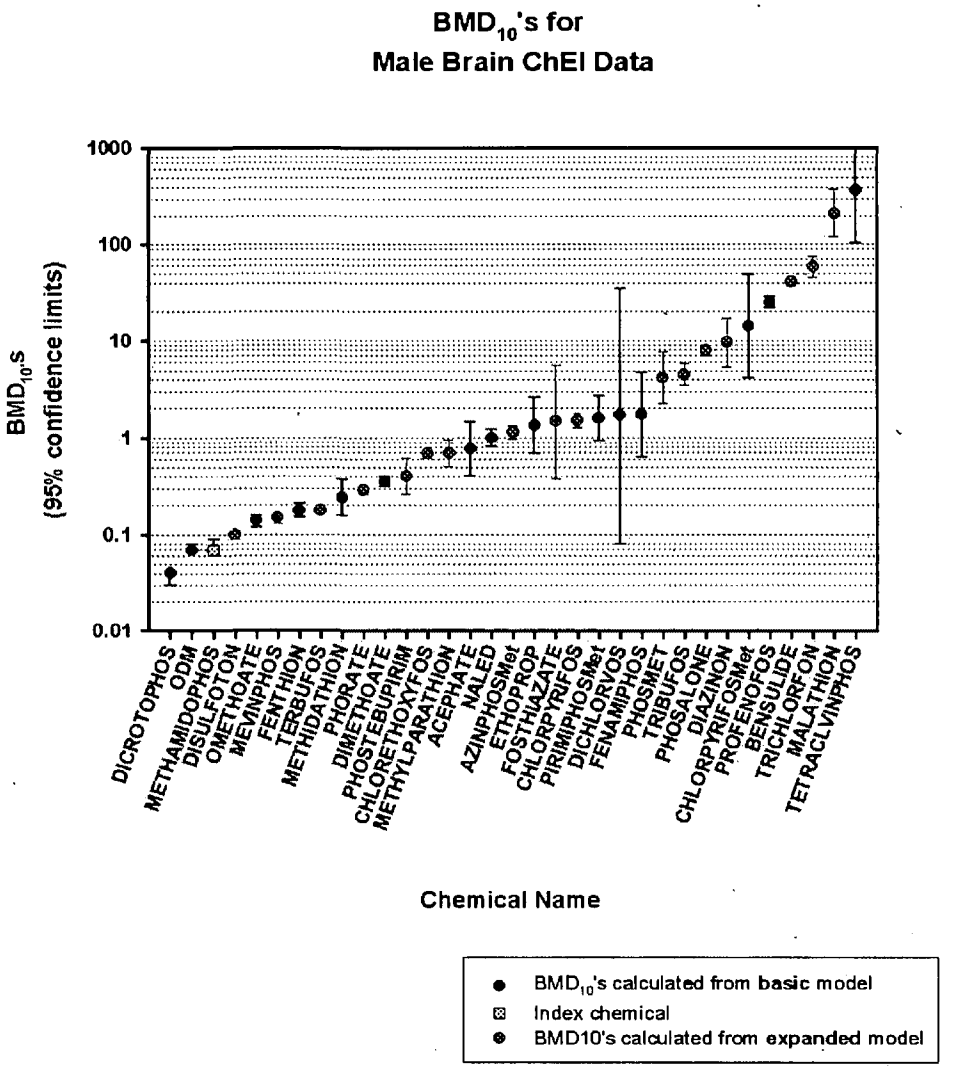
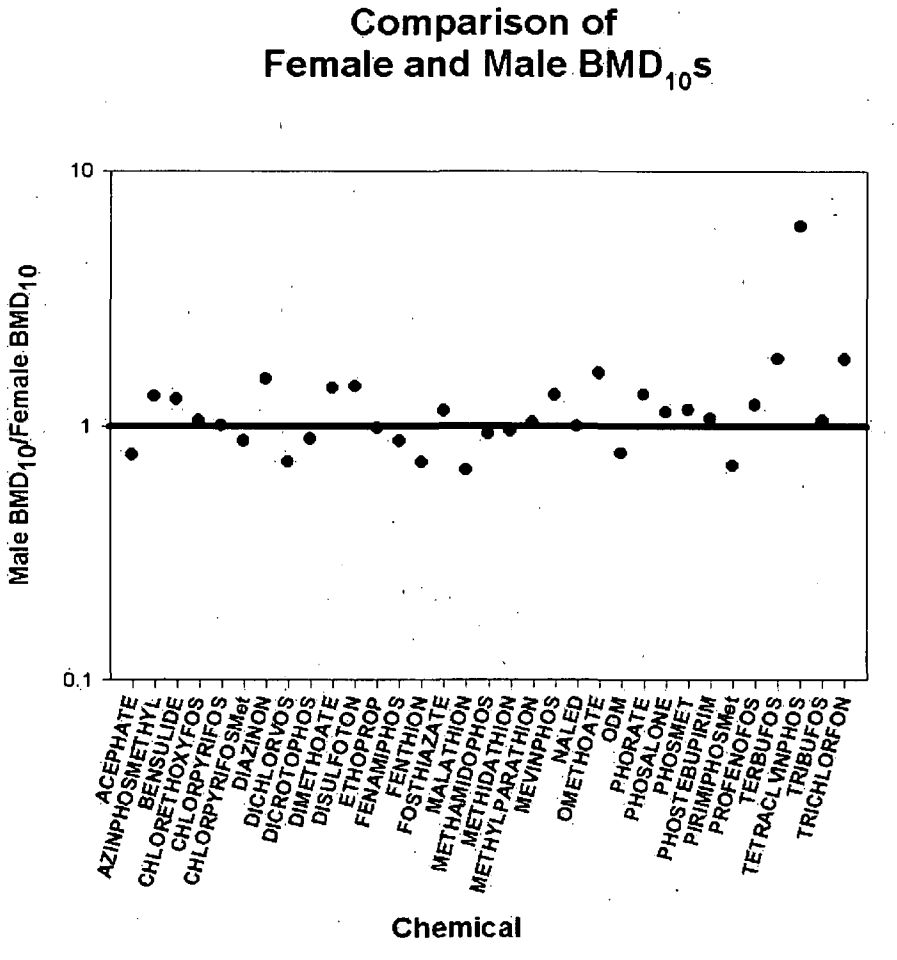


Figure I.B-5. Comparison of BMD_{10}s (mg/kg/day) for female and male brain ChE activity for 33 OPs



b. CELs Determined for Dermal Endpoints for OPs with Residential/Nonoccupational Exposure

Table I.B-5 lists CELs and the next higher dose levels for brain ChE inhibition from dermal exposure studies of OPs with residential/occupational exposure plus the index chemical, along with the level of ChE inhibition (compared to control values).

Table I.B-5. CELs for brain and RBC cholinesterase activity from dermal exposure studies (% cholinesterase inhibition compared to control value)

Chemical	Species	Male Brain CEL mg/kg/day	Male Brain Next Higher Dose mg/kg/day	Female Brain CEL mg/kg/day	Female Brain Next Higher Dose mg/kg/day
Acephate	rat	300 9%	>300* 9%	**300** **14%**	>300* 14%
Bensulide	rat	500[a] 0-9%	>500*[a] 0-9%	**500[a]** **2-10%**	>500*[a] 2-10%
Dichlorvos	Dermal exposure study waived due to volatility of compound.				
Disulfoton	rabbit	1.6 7%	3 55%	**1.6** **8%**	3 27%
Fenamiphos	rabbit	10 * 0%	>10 * 0%	**0.5** **0%**	2.5 18%
Fenthion	rabbit	100 13%	150 65%	**50** **13%**	100 24%
Malathion	rabbit	300[a] 2%	1000[a] 65%	**50[a]** **0%**	300[a] 19%
Methamidophos	rat	0.75 0%	11.2 41%	**0.75** **5%**	11.2 38%
Naled	rat	10 0%	20 60%	**10** **0%**	20 60%
Tetrachlorvinphos	rat	1000 0%	>1000 * 0%	**1000** **0%**	>1000 * 0%
Trichlorfon	rabbit	1000 0%	>1000 * 0%	**100** **4%**	300 18%

* Highest dose tested.

c. CELs Determined for Inhalation Endpoints for OPs with Residential/Nonoccupational Exposure

Table I.B-6 lists CELs for brain cholinesterase inhibition determined for inhalation toxicity studies for OPs with residential/nonoccupational exposure plus the index chemical, along with the level of cholinesterase inhibition (compared to control values).

Table I.B-6. CELs for brain and RBC cholinesterase activity from inhalation toxicity studies (% cholinesterase inhibition compared to control value)

Chemical	Method	Male CEL (mg/kg/day)	Male Next higher dose (mg/kg/day)	Female CEL mg/kg/day	Female Next higher dose (mg/kg/day)
Acephate	nose only	1.419 14%	1.419* 14%	**1.492** **13%**	1.492* 13%
Bensulide	No inhalation toxicity study was available for bensulide				
Dichlorvos	whole body	0.436 10%	0.436 10%	**0.458** **11%**	0.458 11%
Disulfoton	nose only	0.044 4%	0.384 24%	**0.047** **5%**	0.410 28%
Fenamiphos	nose only	0.928 0%	>0.928* 0%	**0.984** **0%**	>0.984* 0%
Fenthion	No inhalation toxicity study was available for fenthion				
Malathion	whole body	115 3%	514 17%	**121** **8%**	540 41%
Methamidophos	head/ nose	0.292 8%	1.432 29%	**0.310** **11%**	1.520 25%
Naled	whole body	0.354 0%	1.594 38%	**0.378** **4%**	1.702 46%
Tetrachlorvinphos	No inhalation toxicity study was available for tetrachlorvinphos.				
Trichlorfon	whole body	9.388 0%	27.44 21%	**3.574** **0%**	9.96 27%

*Highest dose tested.

d. Points of Departure for the Index Chemical (Methamidophos)

Table I.B-7 lists the PODs and no-observed-adversse-effect-levels (NOAELs) for the oral, dermal, and inhalation routes for methamidophos. The PODs for all three routes were calculated with dose-response modeling using the basic model of Equation I.B-1. OPP has used these endpoints in the RCRA.

Brain cholinesterase was only measured once (at study termination) in the methamidophos 21-day dermal and 90-day inhalation studies. Therefore only one data set was available for calculation of the PODs for these routes.

Within route of exposure, the BMD_{10}s for brain cholinesterase shown in Table I.B-6 were similar for males and females. The values of the BMDLs were close to the BMD_{10}s. This observation increases the confidence not only in the selection of methamidophos as the index chemical but also the utilization of the central estimate of the female data (BMD_{10}) for cumulative risk extrapolation rather than its lower limit (BMDL). It is notable that the BMD_{10} and BMDL values were similar to but slightly larger than NOAELs established for the oral (chronic NOAEL used for RfD derivation), dermal, and inhalation routes.

Table I.B-7. Points of departure for index chemical (methamidophos) by route of exposure for brain cholinesterase activity measured in female and male rats

Route of Administration	Sex	BMD_{10} (mg/kg/day)	BMDL (mg/kg/day)	NOAELs (mg/kg/day)
Oral[a]	F	**0.08** [d]	0.07	0.03*
	M	0.07	0.06	
Dermal[b]	F	**2.12** [d]	1.77	0.75
	M	1.88	1.41	
Inhalation[c]	F	**0.39** [d]	0.21	0.31
	M	0.30	0.20	0.29

[a]MRID nos. 41867201, 43197901, 00148452
[b]MRID no. 44525301
[c]MRID no. 41402401
[d]PODs for RCRA of OPs.
*NOAEL used for chronic RfD derivation in the single chemical assessment.

e. Relative Potency Factors (RPFs)

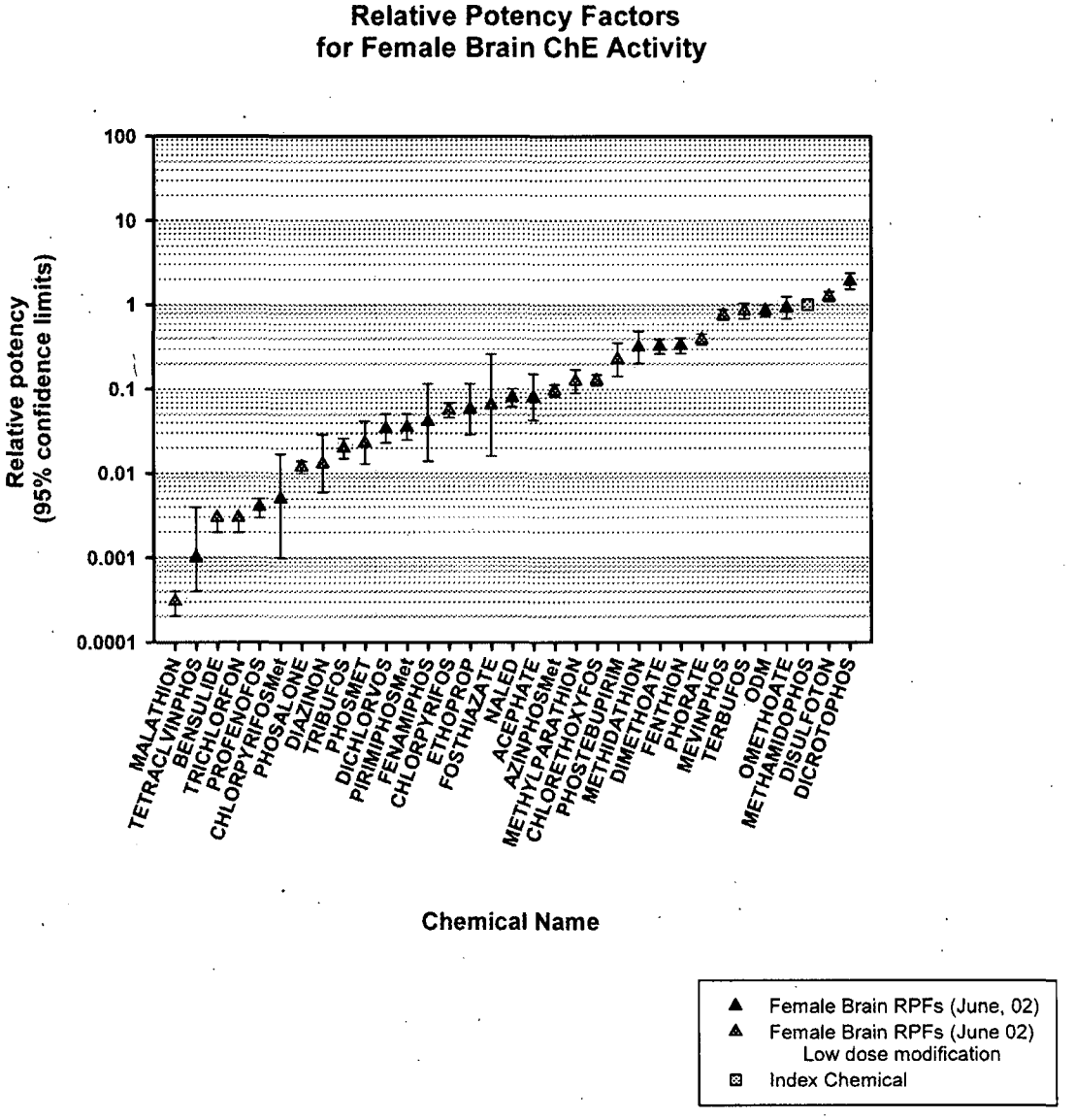
Table I.B-8 provides the RPFs for the oral, dermal, and inhalation routes of exposure based on brain cholinesterase in female rats which were used in the RCRA for OPs. Figure I.B-6 shows the oral RPFs with 95% confidence limits.

These values were calculated with Equations I.B-3, I.B-4, and I.B-5 for oral, dermal, and inhalation routes, respectively, and using methamidophos as the index chemical. BMD_{10}s for all of the chemicals are listed in Table I.B-4. Dermal and inhalation CELs are given in Tables I.B-5 and I.B-6. Although a model-derived oral RPF was determined for fosthiazate, this is a new OP that is not yet registered. Fosthiazate has no appropriate monitoring data to support characterization of exposure from food, and therefore, was not included in the quantification of cumulative risk.

Table I.B-8. Relative potency factors for the oral, dermal, and inhalation routes of exposure

Relative Potency Factors for Female Brain Cholinesterase Activity			
Chemicals	**Oral**	**Dermal**	**Inhalation**
Acephate	0.08	0.0025	0.208
Azinphos-methyl	0.10		
Bensulide	0.003	0.0015	
Chlorethoxyfos	0.13		
Chlorpyrifos	0.06		
Chlorpyrifos-methyl	0.005		
Diazinon	0.01		
Dichlorvos	0.03		0.677
Dicrotophos	1.91		
Dimethoate	0.32		
Disulfoton	1.26	0.47	6.596
Ethoprop	0.06		
Fenamiphos	0.04	1.5	0.315
Fenthion	0.33	0.015	
Fosthiazate	0.07		
Malathion	0.0003	0.015	0.003
Methamidophos	1.00	1.00	1.00
Methidathion	0.32		
Methyl-parathion	0.12		
Mevinphos	0.76		
Naled	0.08	0.075	0.82
Omethoate	0.93		
Oxydemeton-methyl	0.86		
Phorate	0.39		
Phosalone	0.01		
Phosmet	0.02		
Phostebupirim	0.22		
Pirimiphos-methyl	0.04		
Profenofos	0.004		
Terbufos	0.85		
Tetrachlorvinphos	0.001	0.00075	
Tribufos	0.02		
Trichlorfon	0.003	0.0075	0.087

Figure I.B-6. Relative potency factors for female brain ChE activity for 33 OPs



4. Discussion

a. Determination of Relative Potency

With the passage of the FQPA in 1996, EPA was faced with numerous challenges such as the reassessment of 66% of all tolerances by 2002 and notably the development of methodology for doing cumulative risk assessment. As part of the methodology development, EPA has participated in the public process with technical briefings and reviews by outside experts who make up the SAP. The SAP has offered constructive and thoughtful guidance in the development of the hazard and dose-response component of cumulative risk assessment. With each review, EPA has taken the recommendations into consideration and has made appropriate revisions or refinements. The analysis performed for the OPs represents an innovative and novel approach to hazard and dose-response assessment, and by taking advantage of the large database of oral toxicity studies in adult rats available to OPP, offer a comprehensive review of the common mechanism endpoint (i.e., cholinesterase inhibition) from available toxicity studies in adult animals. By incorporating dose-response information from multiple studies into one estimate of potency for the oral route, potency estimates are representative of the overall toxicity of each pesticide.

Adult cholinesterase data for many OPs has been extensively analyzed for plasma, RBC, and brain ChE response (USEPA 2001b, 2001c). OPP has generated an extensive database of ChE data that is available to the public. This large database has allowed OPP to investigate sex differences among rats, study-to-study variability for over 75 studies, time course data ranging from 21 days to > 2 years of exposure, and steady state response. The joint analysis allowed the exploration of low dose issues using a sophisticated model. The joint analysis using the exponential model resulted in high confidence RPFs and PODs that are representative of the OPs.

The data for the inhalation and dermal routes were less extensive compared to the oral route. Potency estimates using CELs from the dermal and inhalation studies are not as robust as those calculated for the oral route but are adequate for use in the cumulative assessment. It is also notable that the relative order of estimated potencies for all three routes of exposure are consistent with current knowledge about their toxicology.

The selection of methamidophos as the index chemical was supported by the SAP. Methamidophos had the highest quality database for the common mechanism endpoint in three routes of exposure and three biological compartments. The PODs calculated with methamidophos have narrow confidence limits which reduces overall uncertainty in the cumulative risk assessments. In this assessment, administered dose was used to estimate RPFs and PODs. At this time there are inadequate pharmacokinetic data for

these OPs to incorporate information about dose at the target site or species to species extrapolation.

b. Dose Additivity

The cumulative risk assessment for the OPs is based on the assumption of dose additivity. Dose additivity is the Agency's assumption when evaluating the joint risk of chemicals that are toxicologically similar and act at the same target site (USEPA 2001a). The SAP (FIFRA SAP, 2001a) indicated that substantial reliance would have to be placed on what is known about the mechanism of toxicity because it is very difficult to prove dose additivity at human exposure levels. They further pointed out that studies available on individual chemicals were usually not designed to address the issue of dose additivity.

The mathematical definition of dose addition requires a constant proportionality among the effectiveness of the chemicals (USEPA 2001a; Hertzberg et al.,1999). Thus, an important objective in the dose response assessment is to evaluate whether dose-response relationships are consistent with the assumption of dose additivity. There is some uncertainty surrounding the assumption. Two different versions of the exponential model have been used in this assessment. Approximately half of the pesticides were fit using a model with a flat low dose region while the remaining OPs were fit using a model which is linear in the low dose region. In addition, the OPs did not exhibit a common horizontal asymptotes (P_B); rather the P_Bs vary among chemicals. Both of these factors indicate that the dose-response curves are not parallel.

Dose additivity assumes that the common mechanism chemicals behave in a similar fashion (i.e., same pharmacokinetics and pharmacodynamics). In reality, these common mechanism chemicals may not behave ideally (i.e., the exact same pharmacokinetics and pharmacodynamics). Biotransformation of OPs is extremely complex and involves several metabolic systems in different organs (e.g., reactions involving cytochrome P450 isoenzymes, hydrolysis by esterases, and transferase reactions; see Nigg and Knaak, 2000). The differential activation and/or deactivation of OP pesticides has not been well documented in the literature, nor have the human metabolic pathways (Mileson et al., 1998). At this time, these pesticides can not be separated into subgroups based on pharmacokinetic or pharmacodynamic characteristics. Thus, current information on OP metabolism does not provide a sufficient basis to depart from dose additivity at low levels of exposure anticipated to be encountered environmentally.

The application of dose additivity requires the assumption of no interactions other than additive among the chemicals at low doses. There are a limited number of investigations of the toxicity of combinations of organophosphorus substances, not necessarily pesticides, that are known to

inhibit cholinesterase enzymes (For example see Dubois, 1961 and 1969; Frawley et al., 1957 and 1963; Calabrese, 1991; Cohen, 1984; Eto, 1974; Su et al., 1971; Casida et al., 1963; Keplinger and Deichman, 1967; Rosenberg and Coon, 1958; El-Sebee, et al., 1978; Seume and O'Brien, 1960; Singh, 1986; Mahajna et al., 1997; Serat and Bailey, 1974; Richardson, et al., 2001; Karanth et al., in press; Abu-Qare , et al., 2001a; Abu-Qare et al., 2001b). Most of the studies reviewed were high dose studies that investigated the acute lethality (LD_{50}) of combinations, mostly binary, and not the cumulative effects of low exposure levels from multiple OPs. A number of these studies were conducted using intraperitoneal (i.p.) administration which confounds interpretations of effects that may be expected by the oral, dermal, or inhalation routes.

Overall, the studies reported in the literature do not provide a basis for concluding that interactions between OPs will result in significant departure from dose addition at low doses. Nevertheless, this literature provides data showing that different types of interactions can occur between OPs and that the magnitude of the interaction appears to depend on the specific combination of OPs investigated, the dose-levels administered, and also the sequence of exposure (Singh, 1986; Pope and Padilla, 1990). In particular, the data available are not sufficient to establish the nature of interactive effects on cholinesterase activity that may be expected among OPs at low exposure levels.

The OPs all act on the same target site– namely, the inhibition of acetylcholinesterase by phosphorylation in nerve tissue, which elicits a variety of cholinergic effects. Dose addition is regarded as a reasonable and appropriate approach for estimating the cumulative risk associated with joint exposure to the OP common mechanism group. At this time, there is not sufficient basis to depart from dose additivity.

Although a biological or pharmacokinetic modeling approach would be preferred to determine the cumulative risk for these OPs, the input parameters for such an approach are not available. Thus, the pharmacokinetic (PK) characteristics of the OPs could not be incorporated in the dose-response assessment which would allow for a more refined estimate of the combined risk to humans. Therefore, OPP has applied simple dose addition and used an empirical curve fitting model (i.e., the exponential model) to determine RPFs and PODs.

c. Future Directions in Cumulative Dose-Response Assessment: Physiologically Based Pharmacokinetic (PBPK) Modeling

Physiologically based pharmacokinetic (PBPK) models, which describe the time course disposition of chemicals and their metabolites, are well suited to help assess cumulative risk. PBPK models are excellent tools to quantify the cumulative toxicity that can result from multiple exposures (multiple

exposures and multiple pathways) and from exposure to multiple chemicals with a common mechanism or mode of action. These models typically are systems of first order differential equations describing the mass balances and disposition of the chemicals and their metabolites in the body. While these models are excellent tools, numerous input parameters are necessary for each chemical. Organ specific thermodynamic parameters (such as tissue to blood equilibrium partition coefficients) are required for each pesticide entering the body and for each of its metabolites. Additionally, values for all of the metabolic rates governing all the biotransformation steps for each pesticide would be necessary. The complex processes for the common mechanism effect would be necessary. Using the OPs as an example, compound specific inputs such as binding constants and values for the rates of enzyme degradation, aging, and resynthesis would be needed.

ORD's National Exposure Research Laboratory (NERL) has formulated such a model that has been used to simultaneously model the disposition of three OPs and their metabolites (Blancato, et al., in review). Another PBPK model has been developed to describe the complex pharmacodynamics of acetylcholinesterase inhibition following OP exposure, based almost entirely on *in vitro* information (Gearhart, et al., 1994). Timchalk et al. (2002) developed a PBPK model for chlorpyrifos and and its major metabolites.

At present, these types of data/information on the majority of the OPs are not available to EPA. PBPK modeling techniques offer good promise despite the current limitations regarding the necessary input information. Continued development and testing of the models is necessary and should be pursued. Pharmacokinetic studies (*in vivo* and *in vitro* experiments to determine key values for PK parameters and the time course disposition of the compounds in the body) need to be done with many compounds to determine the key parameters of use in PBPK modeling. It is anticipated that data and methods will continue to improve and evolve as more experience is gained in this area.

I. Revised OP Cumulative Risk Assessment

C. Cumulative Risk From Pesticides in Foods

1. Introduction to Food

The cumulative dietary risk due to the use of Organophosphorus (OP) Chemicals on food crops was assessed using residue monitoring data collected by the United States Department of Agriculture's Pesticide Data Program (USDA-PDP) supplemented with information from the Food and Drug Administration Center for Food Safety and Applied Nutrition (FDA/CFSAN) monitoring data. The BMD10 for brain cholinesterase inhibition in female rats was chosen as the Toxicological Point of Departure (POD) for this assessment. Methamidophos served as the index chemical. The residue values for the other OP chemicals were converted to methamidophos equivalents by a Relative Potency Factor (RPF) approach. Residue data were collected on approximately 44 food commodities monitored by PDP between the years of 1994 and 2000. Food processing factors were applied to specific chemical/commodity pairs to extend these data for use on cooked and processed food/food forms in the analysis. The PDP residue data were further extended to other commodities identified as reasonable for translation of pesticide residue data per OPP/HED SOP 99.3 (USEPA, 1999b); see Appendix III.C.4. Other food commodities, not included in the PDP database, were incorporated using FDA monitoring data. The residue estimates incorporated in the assessment represent approximately 97 percent of the per capita food consumption for children aged 1 to 2 years (the most highly exposed age group) in the Continuing Survey of Food Intakes by Individuals for the years 1994-1998.

The residue data were compiled as distributions of cumulative residues of methamidophos equivalents and, after application of processing factors and FQPA factors, were summed on a sample-by-sample basis. These residue distributions were combined with a distribution of daily food consumption values *via* a probabilistic procedure to produce a distribution of potential exposures for multiple subpopulations in the CSFII 1994-1998 (Infants less than 1, Children 1-2, Children 3-5, Children 6-12, youth 13-19, Adults 20-49, and Adults 50+ years old). The most highly exposed age group was confirmed to be Children 1-2 years old.

2. Sources of Residue Data

a. USDA-PDP

The PDP program has been collecting pesticide residue data since 1991, primarily for purposes of estimating dietary exposure. The program is designed to focus on foods highly consumed by children and to reflect foods typically available throughout the year. Foods are washed and inedible portions are removed before analysis. This database is the primary source for residue data used in the current assessment, and data collected between 1994 and 2000 were included. A complete description of the PDP program and all data through 2000 are available on the Internet at http://www.ams.usda.gov/science/pdp. A summary of the PDP residue data on OP chemicals is shown in Appendix III.C.2. Appendix III.C.1 lists all of the food forms for which estimated residues were based on PDP data.

b. Market Basket Study of OP Residues in Apple Sauce

The Apple Processors Association sponsored a market basket study of OP pesticide residues in apple sauce samples collected in 1999. These data are incorporated in the current assessment for residue estimates on apple sauce and baby food apple sauce. The residue data on these samples are summarized in Appendix III.C.2.

c. FDA/CFSAN Surveillance Monitoring Data

The FDA Surveillance Monitoring Program is designed primarily for enforcement of EPA pesticide tolerances on imported foods and domestic foods shipped in interstate commerce. Domestic samples are collected as close as possible to the point of production in the distribution system. Import samples are collected at the point of entry into U.S. commerce. The emphasis in sample collection is on the agricultural commodity, which is analyzed as the unwashed, whole (unpeeled), raw commodity. Processed foods are also included in the program. A description of the program and residue data for recent years can be found on the Internet at http://vm.cfsan.fda.gov/~lrd/pestadd.html. Because the emphasis of this program is not on dietary exposure, it is being used in the current assessment mostly as a semi-quantitative check on the potential for residues and as support for data from other sources. The program has extensive data available on eggs and fish and these data support the judgement that the OP residues are negligible on these foods as consumed. Appendix III.C.1 indicates the food forms for which exposure estimates were supported by this program.

d. FDA/CFSAN Total Diet Study (TDS)

The TDS has provided data on dietary intake of food contaminants for about 40 years. A program description and residue data can be found at the same Internet site listed above for FDA Surveillance Monitoring Data. Foods are purchased in grocery stores, generally 3 or 4 times a year, prepared and cooked for consumption, and analyzed by highly sensitive multiresidue methods. Between 1991 and 1999 there have been 26 market baskets collected and approximately 260 foods analyzed for, among other things, OP pesticide contamination. A disadvantage of these data is that only one sample is analyzed of each food in each market basket. For this reason these data have been used primarily as semi-quantitative support for judgements on residues in foods. An exception is made in this assessment for the estimate for residues in meats other than poultry. Multiple forms and tissues of beef, pork, lamb, and meat byproduct cold cuts have been analyzed in all of the market baskets with only limited residues of OP pesticides on a few of the meats at low levels. In an effort to include residue estimates for all highly consumed foods, a conservative estimate for meat commodities was based on the TDS Data. A maximum residue level was used for each meat based on the TDS. The meat commodities included on this basis are identified in Appendix III.C.1 and the residue data are summarized in Appendix III.C.3.

3. OP Pesticides Included in Cumulative Assessment

All of the OP analytes detected in the PDP program are included in the current assessment. See Appendix III.C.2 for a complete summary of the analyses for OP pesticides and metabolites on each food commodity in the database. There have been significant numbers of analyses for 67 OP active ingredients, degradates, or metabolites between 1994 and 2000. A total of 39 of these OP analytes have been detected in at least one of the foods analyzed. After exclusion of data on pesticides that have been canceled or do not have food uses, and combining data for metabolites and degradates, there are positive analytical data being used for 20 OP pesticides. These are the following:

acephate	azinphos methyl	chlorpyrifos
diazinon	dichlorvos	dimethoate
disulfoton	ethoprop	malathion
methidathion	methamidophos	mevinphos
oxydemeton-methyl	methyl-parathion	phorate
phosalone	phosmet	pirimiphos-methyl
terbuphos	tribufos	

Naled has not been separately analyzed generally and residues from this use would be reflected in the dichlorvos analyses. Bensulide is not included in the PDP data; however, negligible residues would be expected in foods based on field trial data submitted for registration purposes. Cadusafos is not represented in the PDP data but the only registered use that could potentially result in food residues is as a nematacide soil application on bananas that are imported into the United States. Field trial data submitted for registration/tolerances purposes indicate that residues will not occur in the edible portion of the banana. Chlorethoxyfos is not included in PDP data but its only food use is soil application to corn crops at a low rate; therefore, significant residues in edible portions and processed foods from corn would not be expected. Dicrotophos, not included in PDP data, has one food use on cotton. Cottonseed oil is the only food commodity of cotton and it is not included in the current assessment, but the impact of the chemical on dietary (food) exposure is expected to be low due to the extent of refining and blending of the oil. Tebupirimphos (phostebupirim) has one food use on corn, mainly to control root worm. Significant contribution to cumulative food exposure is not expected. Profenofos is used on cotton, which is not included in the current assessment for the reasons stated above. Trichlorfon has no food uses except for an overseas use as pour-on treatment of beef cattle. Tetrachlorvinphos is used only on livestock or livestock premises. Potential residues from the two latter livestock uses are anticipated to be covered by the conservative cumulative residue estimate for meat commodities.

4. Foods Included in the Food Risk Assessment

The universe of foods included in the cumulative dietary exposure assessment is defined by the USDA CSFII for the years 1994-1996 with supplementary data on children obtained in 1998. The survey data, CSFII 1994-1998, is integrated into DEEM-FCID™. Appendix III.C.1 lists all of the foods in CSFII 1994-1998 in decreasing order of their relative per capita consumption by children 1-2 years old and children 3-5 years old. Each food is assigned a percent of relative consumption which was estimated in the following manner: the per capita consumption of each food was summed for all children in the survey in the two age groups. These consumptions were totaled for all foods in the survey and the individual sums for each food were expressed as a percent of the total. This measure of relative consumption is used as a partial indication of the potential significance of a given food in the diet of children.

According to the above described measure of relative consumption, the available PDP data were used either directly or with processing factors to estimate cumulative residues in foods accounting for about 88% of the per capita consumption of children 1-2 years old. PDP data were used for the top 10 ranked foods and for 24 out of the top 30 foods. Apple sauce, which was supported by special study data, account for about 1% of the consumption by children 1-2 years old.

Residues in other foods were estimated using translated PDP data according to HED SOP 99.3, (USEPA, 1999b) as summarized in Appendix III.C.4. Translations included only residues for chemicals registered on the food being simulated. These foods account for about 1% of the per capita consumption of children 1-2 years old.

Surveillance monitoring data from FDA include extensive analysis of eggs and fish with the implication that OP residues would not be expected to occur in significant amount on these two categories of foods. The TDS data from FDA indicate a similar situation for livestock meats. In this case a conservative estimate of residues was incorporated into the assessment, i.e., meats were assumed to always be contaminated with OP residues equal to the maximum values found in the TDS market baskets (see Appendix III.C.3 for a summary of TDS data used). These foods being supported by FDA data, i.e., eggs, fish, and meat, account for about 5% of the per capita consumption of children 1-2 years old.

PDP has analyzed high fructose corn syrup and found no OP residues but has not analyzed any other sugar or syrup sources. The FDA TDS has analyzed refined sugar and maple sugar and found no OP residues in 26 market baskets. A knowledge of the highly refined nature of sugars and syrups supported by the limited residue data mentioned above is the basis for assuming that negligible residues of OP pesticides would be expected to occur in sugars and syrups. Therefore, residues were assumed to be zero for these foods derived from sugarcane, sugar beet, and maple. These foods account for about 2% of the per capita consumption of children 1-2 years old.

The food forms not included in the current assessment account for almost 3% of the per capita consumption of children 1-2, distributed among many food forms. Table I.C-1 summarizes the relative consumption of foods in the assessment for children 1-5 years old. The information is provided in detailed form in Appendix III.C.1.

Table I.C-1. The Proportion of the Diet of Children (1-5 years old) Covered in the Cumulative Food Assessment

Source of Residue Estimate	Percent of Per Capita Consumption	
	Children 1-2	Children 3-5
PDP (RACs & processed)	88.4	85.0
Apple Sauce Study	0.9	0.7
Translation of PDP	1.1	1.3
FDA Monitoring and TDS	4.9	6.3
Assumed Negligible	2.0	3.1
Not Included in Current Assessment	2.7	3.6

5. Method of Estimation of Cumulative Dietary Risk

Dietary exposure was estimated using the Dietary Exposure Evaluation Model (DEEM-FCID™) software. A joint distributional analysis was conducted by combining representative data on concentrations of OP pesticides on foods with distributions of anticipated consumption of these foods by different segments of the U.S. population. The primary advantage of a joint distribution analysis is that the results are in the form of a simultaneous analysis (i.e., a distribution) of exposures that demonstrate both best-case and worst-case scenarios of exposure. The inputs were distributions or point estimates for residues, distributions for consumption, and a hazard endpoint. The output was a series of distributions of one-day dietary exposures and distributions of associated risks, i.e., margin of exposures (MOEs). The different components of the input data are discussed further in the remainder of this section.

a. Manipulation of Residue Data for Exposure Assessment

Commonly, the following two equations are used for estimating exposure and risk from a single chemical:

1) Exposure = Residue X Consumption

2) Risk = Hazard X Exposure

In the case of cumulative exposure assessment, the residue term in the first equation is changed to Index Equivalent Residue ($Residue_{IE}$), and the hazard end point in the second equation is based on the index chemical.

The calculated cumulative residue is a simple arithmetic addition of residues of different chemicals that have different toxicities (potency) and therefore simple addition of their residues is not appropriate. For that reason,

the amount of residue of each chemical is adjusted by multiplying by a ***RPF*** to get the equivalent residue of an index chemical. This new calculated residue is termed ***Residue***$_{IE}$ and the exposure value resulting from combining Residue$_{IE}$ and consumption is termed ***Index Equivalent Exposure (Exposure***$_{IE}$). The new central equation for exposure will then become:

$$\text{Exposure}_{IE} = \text{Residue}_{IE} \text{ X Consumption}$$

and in the risk equation (second equation) the toxic end point of the index chemical is used. The following discussion explains in more detail how this was accomplished for this cumulative risk assessment.

b. Generation of Cumulative Equivalent Residue (Residue$_{IE}$)

To determine a given one-day cumulative oral exposure to multiple OP chemicals, first an Residue$_{IE}$ for each residue value is calculated. On a given PDP sample, each residue value is multiplied by any applicable processing factor (PF) for that chemical on food sample of interest and the RPF for the same chemical to express it as a Residue$_{IE}$ for that chemical; this is step 1.

Step 1: **Residue$_{IE}$ (per chemical n) = Residue X PF$_n$ X RPF$_n$**

The cumulative Residue$_{IE}$ for all chemicals detected on one PDP sample will then be the sum of all the Residue$_{IE}$ for all the chemicals on that sample; this is step 2.

Step 2: **Cumulative Residue$_{IE}$ = $\sum$ Residue$_{IE}$** (per PDP sample)

For example, given 100 samples of apples, each analyzed for 22 OPs, there will be generated 22 Residue$_{IE}$ values for each sample. In step 2, each set of 22 Residue$_{IE}$ for a sample is summed to generate a cumulative Residue$_{IE}$ per one sample; hence 100 cumulative Residue$_{IE}$ points for 100 samples of apples are generated.

By summing on a sample-by-sample basis, the potential for capturing any co-occurrence on the same commodity is enhanced. Another very important advantage of this approach is that, using appropriate record keeping (see next section), the complete history of each cumulative residue value in the exposure assessment can be potentially traced back to its origins. All of the sample collection and analytical information associated with a given PDP sample and all arithmetic adjustments incorporated in producing a Residue$_{IE}$ can be traced in the process of sensitivity analysis or critical food commodity contribution analysis.

c. OPCRA Food Residue Database

The data manipulations necessary to prepare the PDP residue data for input into the risk equation are in principle very simple; however, the task of performing these calculations for multiple chemicals and food commodities is problematic. The residue data used in this assessment consist of approximately 1.5 million records of analytical data and sample information. The processing factors account for several thousand additional records of information. For this reason, and in anticipation of the need to make multiple uses of the data, to keep track of them, and work backward from the cumulative assessment results to determine contributors, all the data manipulations were conducted using relational database techniques. The OPCRA food residue database currently being used for this purpose consists of, among other things, four major data tables:

1. Residue data table(s); about 1.5 million records containing essentially all of PDP sample and analyses data for OP pesticides as well as other residue data compiled from FDA and the Apple Sauce Market Basket Survey.

2. Processing factor data table; containing all relevant processing factors for specific food form/chemical combinations. Appendix III.C.5 is extracted from these data.

3. RPF Table; containing the RPF for all chemicals of interest.

4. Translation Table; providing bridging links between PDP commodity codes, such as *AJ* (apple juice), and all corresponding DEEM™ food forms, such as *Apple, juice cooked:canned;cook meth N/S.* This table allows the assignments of translation of data between PDP commodities also, such as cantaloupe data to watermelon food forms. Appendix III.C.6 summarizes the links used in this assessment.

These four tables are linked through common fields, including pesticide codes and commodity codes. Calculation queries are coded into the database so that all the pertinent residue records can be extracted, each calculation outlined above can be performed, and the results can be sorted and stored in various formats for further analysis.

A cumulative residue calculation query performs the two-step process described earlier, extracting the various parameters needed from the four tables described above. The calculation is performed on all of the food samples that are of interest and the results are compiled in text files containing the cumulative distributions for each food commodity of interest.

Each text file contains a header with sample information (number of values, number of detects, number of zeros, average of residues) and all of the cumulative residue values for a single food form, sorted in descending order.

Residue distribution inputs to DEEM™ are converted to single average values for those foods that are highly blended before consumption.

By maintaining all of the calculation parameters in separate tables in the database, it is possible to repeat the above process with new inputs by simply replacing or adding data to the appropriate table. For example a specific chemical can be omitted from the entire process by assigning it a value of zero in the RPF table. Specific chemical/commodity combinations can be selectively omitted by entering a zero value for that pair in the processing factor table. These methods have been used extensively in the current assessment to adjust the inputs to reflect currently supported uses of OPs on food crops and to test the relative contributions of chemicals and commodities to the results of an assessment.

d. Generation of Exposure Values

The cumulative $Residue_{IE}$ values (text files described in the previous section) are treated as distributions of representative residues and linked to all appropriate food forms; cumulative residue values are then randomly picked and combined with a consumption record to generate a single exposure value which is termed $Exposure_{IE}$. This process (semi-Monte Carlo in nature and conducted by DEEM™ software) is repeated many times per each consumption record to generate a distribution of exposure values. This process has been described in public documents and proceedings of the FIFRA Science Advisory Panel (http://www.epa.gov/oscpmont/sap/2000/#february). For the food forms that are highly blended before consumption, the residue input consisted of the average of all the cumulative residues, i.e., a single average residue value was entered into the DEEM™ calculation.

e. Food Consumption Data

For this assessment, food consumption is being modeled on the USDA CSFII, 1994-1998. The consumption survey is included as an integral component of the DEEM-FCID™ software. The CSFII 1994-1998 contains survey data on 20,607 participants interviewed over two discontinuous days. It contains a supplemental children's survey conducted in 1998 in which an additional 5,459 children, birth through 9 years old, were added to the survey. This is the first dietary exposure assessment in which OPP has used this survey.

DEEM-FCID™ also has integrated new USDA/EPA recipes for conversion of foods reported eaten in the survey to food commodities on which residue data are available. These recipes, which are available to the public, replace proprietary recipes used in previous versions of DEEM™.

Separate assessments were conducted on the various segments of the population as represented in the CSFII 1994-1998. Among others, the current assessment included the following age groups:

- ❑ Infants less than 1 year old
- ❑ Children 1-2 years old
- ❑ Children 3-5 years old
- ❑ Children 6-12 years old
- ❑ Youth 13-19 years old
- ❑ Adults 20-49 years old
- ❑ Adults 50+ years old

The most highly exposed population group in this cumulative assessment is children 1-2 years old; subsequent analyses of the results reported in this document will emphasize results for this age group.

f. Hazard Data used in the Cumulative Food Assessment

Section II describes the hazard portion of this risk assessment in detail. Methamidophos was chosen as the index chemical for this assessment and relative potencies of the OP chemicals were based on female rat brain cholinesterase inhibition. The point of departure (BMD10) was 0.08 mg/kg body weight/day. The application of FQPA Safety Factors for this OP cumulative assessment is made for each individual chemical in the assessment. This is accomplished by incorporating these factors into the relative potency factors for each chemical in the assessment.

6. Results

The revised cumulative food exposure assessment for OP pesticides on food commodities was conducted for seven age groups, infants of less than one year, children 2-3 years old, children 3-5 years old, children 6-12 years old, youth 13-19 years old, adults 20-49 years old, and adults 50+years old.

Appendix III.C.7 contains a complete listing of the food forms in the DEEM-FCID™ software that were included in this assessment. This table also includes summary information on the residue distributions that were prepared from the OPCRA food residue database as input for each food form. Although most of the data inputs in this table are defined as residue distributions (rdf files), for highly blended commodities, a single average residue was estimated. The actual DEEM™ input file and necessary rdf files will be made available on CD ROM and on the internet for any interested party.

The most highly exposed age group in this assessment is Children 1-2 and the subsequent results reported in this chapter will focus on this group. Figure I.C-1a is a cumulative plot of the exposure distribution for this age group. Figure I.C-1b expands the portion of the cumulative distribution between the 99th and the 99.99th percentile. There are 4192 person-days (approximately half that many individuals with two reported days of food consumption) represented in the consumption records for this age group.

Figure I.C-1a. Cumulative Distribution of Food Exposure for Children 1-2 yrs

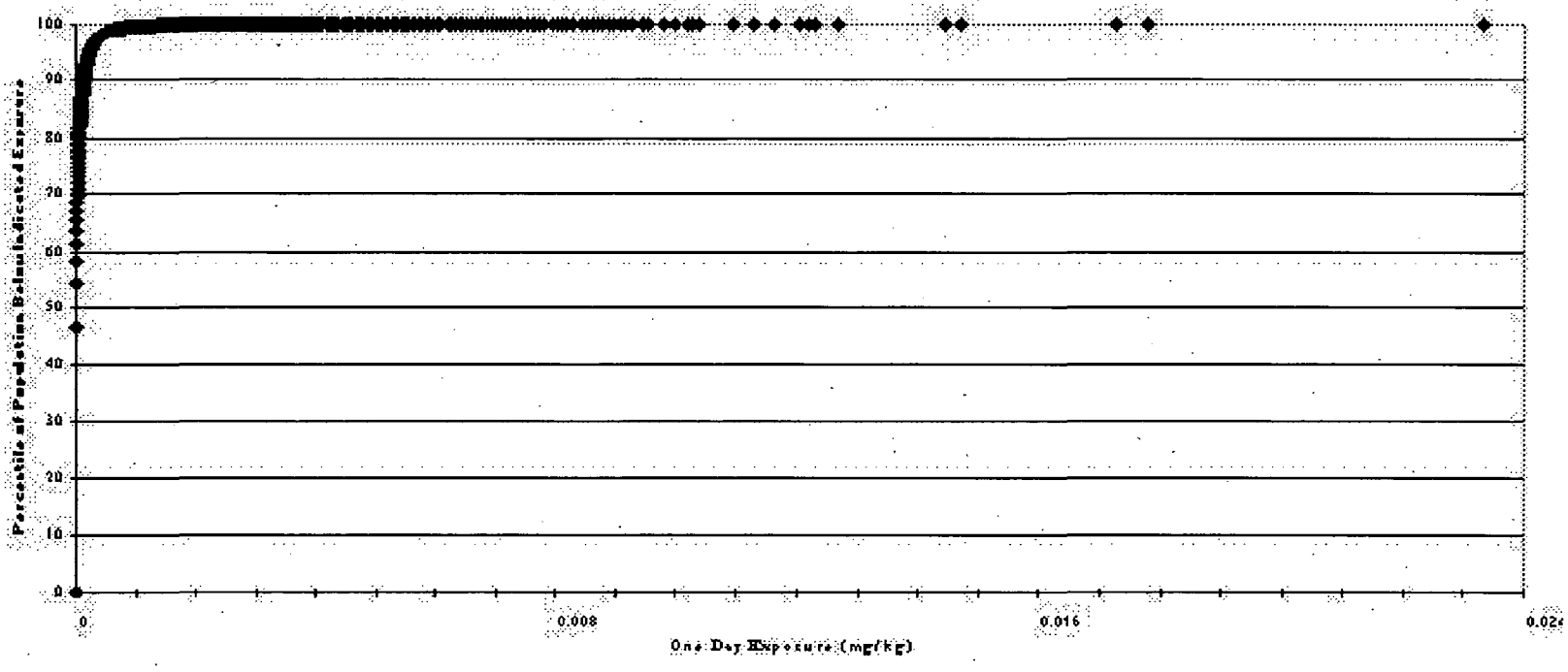


Figure I.C-1b. Cumulative Distribution of Food Exposure for Children 1-2 yrs - 99th percentile to 99.99th percentile of Exposure



a. Analysis of Significant Presence in The Upper Portion of the Distribution

The DEEM software has a provision for analyzing the foods and food forms that are contributing to the upper portions of an exposure distribution, up to a maximum interval of 5 percentile. This provision was used in the current assessment, in combination with the chemical/commodity specific information maintained in the database described above, to assess both foods and chemicals present in the tail of the distribution. The data summarized here were obtained by examination of the exposure distribution interval from the 99.8th percentile to the 100th percentile. Table I.C.2 lists all of the food forms appearing at or above the 99.8th percentile from a Monte Carlo assessment of the exposure of children 1-2 years old.

Table I.C-2. Partial Summary of Foods and Food Forms Occurring in the Top 0.2 Percentile of Exposure to an Exposed Sub-population in OP Cumulative Risk Assessment.*

[Monte Carlo Iterations =1000. Number of actual records in this interval = 8247. N=number of appearances in all records (including duplicates).]

Food	Food Form	N	Fraction of Total Exposure
Grape	Uncooked; Fresh or N/S; Cook Meth N/S	2600	0.33
Pear	Uncooked; Fresh or N/S; Cook Meth N/S	1549	0.16
Apple, fruit with peel	Uncooked; Fresh or N/S; Cook Meth N/S	2177	0.13
Apple, juice	Uncooked; Fresh or N/S; Cook Meth N/S	1510	0.10
Tomato	Uncooked; Fresh or N/S; Cook Meth N/S	584	0.05
Grape, raisin	Uncooked; Dried; Cook Meth N/S	376	0.04
Bean, snap, succulent	Cooked; Frozen; Boiled	397	0.03
Pepper, bell	Uncooked; Fresh or N/S; Cook Meth N/S	337	0.03
Bean, snap, succulent	Cooked; Canned; Boiled	383	0.02
Potato, tuber, w/o peel	Cooked; Fresh or N/S; Boiled	155	0.02
Spinach	Cooked; Frozen; Boiled	39	0.01
Bean, snap, succulent	Cooked; Fresh or N/S; Cook Meth N/S	58	0.01
Squash, summer	Cooked; Fresh or N/S; Boiled	33	0.01
Bean, lima, succulent	Cooked; Frozen; Boiled	76	0.01
Celery	Uncooked; Fresh or N/S; Cook Meth N/S	136	0.01
Cucumber	Uncooked; Fresh or N/S; Cook Meth N/S	42	0.01
Bean, lima, succulent	Cooked; Canned; Boiled	64	<0.01
Spinach	Cooked; Fresh or N/S; Baked	22	<0.01
Cucumber	Cooked; Canned; Cook Meth N/S	28	<0.01
Potato, tuber, w/peel	Cooked; Fresh or N/S; Fried	32	<0.01
Pepper, bell	Cooked; Canned; Cook Meth N/S	32	<0.01
Bean, snap, succulent	Cooked; Fresh or N/S; Boiled	110	<0.01
Bean, snap, succulent	Cooked; Fresh or N/S; Boiled/baked	31	<0.01
Potato, tuber, w/o peel	Cooked; Frozen; Fried	36	<0.01
Pepper, bell	Cooked; Fresh or N/S; Cook Meth N/S	46	<0.01
Potato, tuber, w/o peel	Cooked; Fresh or N/S; Fried	22	<0.01
Tomato	Cooked; Fresh or N/S; Boiled/baked	32	<0.01
Potato, tuber, w/o peel	Cooked; Fresh or N/S; Baked	23	<0.01
Apple, juice - babyfood	Cooked; Canned; Cook Meth N/S	37	<0.01
Apple, juice	Uncooked; Frozen; Cook Meth N/S	22	<0.01
Strawberry	Uncooked; Frozen; Cook Meth N/S	15	<0.01
Bean, lima, succulent	Cooked; Fresh or N/S; Boiled	36	<0.01
Bean, snap, succulent	Cooked; Fresh or N/S; Fried	13	<0.01
Cherry, juice	Uncooked; Fresh or N/S; Cook Meth N/S	11	<0.01
Bean, snap, succulent- babyfood	Cooked; Canned; Cook Meth N/S	19	<0.01
Tomato	Cooked; Fresh or N/S; Boiled	94	<0.01
Spinach	Uncooked; Fresh or N/S; Cook Meth N/S	7	<0.01
Peach	Uncooked; Fresh or N/S; Cook Meth N/S	42	<0.01
Grape, juice	Uncooked; Fresh or N/S; Cook Meth N/S	8	<0.01
Tomatillo	Uncooked; Fresh or N/S; Cook Meth N/S	7	<0.01
Apple, juice	Cooked; Canned; Cook Meth N/S	94	<0.01
Tomato, juice	Cooked; Canned; Cook Meth N/S	5	<0.01

Food	Food Form	N	Fraction of Total Exposure
Potato, tuber, w/peel	Cooked; Fresh or N/S; Baked	4	<0.01
Pepper, bell	Cooked; Fresh or N/S; Fried	21	<0.01
Cucumber	Uncooked; Cured etc; Cook Meth N/S	3	<0.01
Bean, snap, succulent	Cooked; Frozen; Baked	5	<0.01
Apple, peeled fruit- babyfood	Cooked; Canned; Cook Meth N/S	6	<0.01
Lettuce, head	Uncooked; Fresh or N/S; Cook Meth N/S	48	<0.01
Potato, tuber, w/peel	Cooked; Fresh or N/S; Boiled	5	<0.01
Broccoli	Cooked; Frozen; Boiled	3	<0.01
Celery	Cooked; Fresh or N/S; Boiled	64	<0.01
Potato, tuber, w/o peel	Cooked; Frozen; Baked	6	<0.01
Squash, summer	Cooked; Frozen; Boiled	2	<0.01
Squash, summer	Cooked; Fresh or N/S; Boiled/baked	1	<0.01
Tomato	Cooked; Fresh or N/S; Cook Meth N/S	11	<0.01
Spinach	Cooked; Fresh or N/S; Boiled/baked	1	<0.01
Grape	Cooked; Fresh or N/S; Cook Meth N/S	26	<0.01
Tomato	Cooked; Fresh or N/S; Baked	49	<0.01
Apple, sauce	Cooked; Fresh or N/S; Boiled	34	<0.01
Orange	Uncooked; Fresh or N/S; Cook Meth N/S	24	<0.01
Grape	Cooked; Canned; Cook Meth N/S	30	<0.01
Tomato, puree	Cooked; Canned; Cook Meth N/S	39	<0.01
Orange, juice	Uncooked; Fresh or N/S; Cook Meth N/S	17	<0.01
Strawberry	Uncooked; Fresh or N/S; Cook Meth N/S	2	<0.01
Celery	Cooked; Fresh or N/S; Cook Meth N/S	30	<0.01
Potato, chips	Cooked; Fresh or N/S; Fried	3	<0.01
Pepper, bell	Cooked; Fresh or N/S; Baked	19	<0.01
Orange, juice	Uncooked; Frozen; Cook Meth N/S	8	<0.01
Celery	Cooked; Dried; Boiled	3	<0.01
Celery	Cooked; Canned; Cook Meth N/S	17	<0.01
Pear	Cooked; Fresh or N/S; Cook Meth N/S	25	<0.01
Broccoli	Cooked; Fresh or N/S; Boiled	2	<0.01
Grape, raisin	Cooked; Dried; Cook Meth N/S	10	<0.01
Potato, tuber, w/o peel	Cooked; Fresh or N/S; Cook Meth N/S	2	<0.01
Pepper, non-bell	Uncooked; Fresh or N/S; Cook Meth N/S	8	<0.01
Celery	Cooked; Canned; Boiled	9	<0.01

*This table was prepared as part of the evaluation of the potential outliers and potential contributors and does not represent a judgement about the threshold of concern.

To evaluate the presence of chemicals in the tail of the distribution, all of the food forms in the above table were linked with the corresponding residue distributions that had been generated for the cumulative assessment. The individual chemical contributors to these distributions were extracted from the OPCRA food residue database used to generate the distributions. Thus the relative percent contributions of food forms derived from DEEM were combined with the relative percent contributions of chemicals to each food form's residue distribution to give an estimate of the relative contribution of each chemical to the interval being examined. These data were further reduced by combining all food forms to the crop level, for example, fresh grapes, raisins, and grape juice were all combined under the crop name grapes, and so on. All metabolites, degradates, and isomers were combined for each active ingredient in that assessment. The linkage of the DEEM output and the OPCRA food residue database information on chemical/food form specific contributions are summarized in Appendix III.C.8.

The most significant chemical presence in the exposure interval between the 99.8th percentile and 100th percentile is dimethoate/omethoate with a relative contribution of approximately 48% of the exposure, followed by azinphos methyl at 27%, acephate and its metabolite methamidophos at 11%, methamidophos, as active ingredient, at 5%, phosmet at 2.5%, phorate at 2.2%, and mevinphos at 1.8%. The most significant food crops are: apples, grapes, green peppers, pears, potatoes, spinach, succulent beans, and tomatoes.

7. Discussion

a. Changes Since the Preliminary Assessment

A preliminary cumulative assessment was published on December 3, 2001. Since that time a number of changes have been made in the input data, some of them as a result of public comments. All of these changes are captured in the data summaries included in the Appendices to this document. A summary of the major changes or categories of changes is provided in this section.

- Processing factors were updated. Several factors were added or changed based on public comments on the preliminary assessment. Appendix III.C.5 provides a summary of the processing factors currently being used. It should be noted that the absence of a processing factor in Appendix III.C.5 or a factor of zero indicates that the specific food form/chemical pair does not contribute to any residue distribution estimates. In some cases the absence of a factor is simply due to the fact that there are no detectable residues of that chemical in the database but in other cases it is due to the fact that a specific use is being excluded from the assessment because it is not being supported. Several commodities are not entered in the table at all because the residue

analyses conducted on these foods were uniformly below detectable levels. Therefore, one must not use this table as a means of determining the uses included in the assessment. The appropriate starting point for this determination is Appendix III.C.7, which lists every food form included in the assessment. A factor of zero in the processing factor table in some cases is due to a correction of a former entry and in some cases, such as for chlorpyrifos on apple and grape commodities, is a means of adjusting the assessment to account for mitigation negotiations. In the example of chorpyrifos, the use patterns are being altered to allow only pre-bloom applications, which are expected to yield essentially no detectable residues. The PDP data set contains many detects due to foliar applications; therefore, the processing factor was used as a use flag that was lowered to zero for this assessment. The residue data are still in the database and can be reactivated by raising the use flag.

- Apple sauce residue data have been added to the data set based on MRID 45432001: Data are from The National Food Laboratory and were sponsored by Apple Processors Association. The data have been incorporated in the PDP Data set in the OPCRA food residue database.

- Relative Potency Factors have been revised. Among the revisions, omethoate now has a factor different from that of dimethoate.

- FQPA Factors of 3 have been applied (via RPF adjustments) to all chemicals in the assessment except methamidophos, dimethoate/omethoate and chlorpyrifos, which have their FQPA factors reduced to 1.

- The bridging and translation of residue data from source to CSFII food forms have been updated. Several adjustments and corrections were made in these assignments. Among these was the changing of all tomato processed food forms to be derived from canned tomato residue data instead of fresh tomato residue data. All of the translations for the current assessment can be seen in Appendix III.C.6.

- Some inappropriate residue data were removed from the assessment. Lettuce residue data from 1994 were removed completely from the assessment because they contained residues from use patterns of methamidophos and mevinphos that are not current. Lettuce residues are now based solely on data from 1999 and 2000.

- Fenamiphos and chlorpyrifos-methyl have been removed from the assessment based on planned phase-outs. Appendix III.C.9 should be consulted for the complete summary of OP pesticide uses or import tolerances that are currently being supported in the reregistration process. It is important to note that this appendix provides the scope of use patterns that are being considered as having potential for producing OP

residues on foods. This list is based on reregistration actions up through March of 2002. If an OP use is not listed in this appendix then it is not considered in the current assessment.

- Tolerance exceeding residues were added back to the residue data as a result of discussion with SAP after release of the preliminary assessment. These violative residues are not a significant contributor to the assessment.

b. Major Assumptions in the Revised OPCRA for Foods

The following discussion of input assumptions is provided as a revision to the same discussion that was included in the preliminary assessment. The assumptions are revised to reflect their current status and thus some of the points covered in the previous section may be restated here.

The processes for exposure and risk assessment in the Office of Pesticide Programs (OPP) have been undergoing a rapid evolution. A number of choices and assumptions made in the conduct of the current assessment may differ from previous single-chemical assessments. The following discussion is intended to provide some background on the impact of choices that are unique to this assessment.

i. Some PDP Residue Data Were Excluded

The assessment includes only chemical/crop combinations currently being supported for registration in the United States or with import tolerances (see Appendix II.C.9). Therefore, residues representing canceled and phased-out uses are excluded. That is, residues in the OPCRA food residue database that do not represent supported section 3 registrations, SLN uses, or supported import tolerances, are excluded from the assessment. In a change from the preliminary assessment of 12/3/01, we are not excluding violative residues, i.e., tolerance exceeding residues, from the assessment. The criteria listed in this paragraph are intended to ensure that the cumulative assessment simulates the residue pattern that will result from ongoing mitigation actions in the reregistration of OP pesticides. Although this may appear to underestimate the food exposure as reflected by available residue data, it should be kept in mind that these data reflect past patterns of residue occurrence. The inclusion of violative residues in the assessment has no significant effect on the overall results of the assessment. Violative residues are rare in residue monitoring data.

ii. Composite Samples Were Used to Estimate Residues in Single-Servings as Consumed

Only the residue data from composite samples were utilized in this assessment. A single composite sample may contain several individual serving of some foods. For purposes of the present assessment, it is assumed that residues reported on composite homogenates adequately reflect the residues in any given single-serving contained in that homogenate. Therefore, no attempt was made to "decomposite" residue values to simulate residues that might be present in the single-servings contained in the PDP composite sample. PDP has conducted single-unit sampling for apples, pears, and peaches since 1998. A comparison of the residue levels on these single-servings to the residues on comparable composite samples indicate that use of composite samples will not result in a significant under- or overestimation of residues.

iii. PDP Samples Were Assumed to Reflect Residues in Foods Prepared for Consumption

The PDP generally collects foods at wholesale distribution centers and stores them frozen until analysis. Foods are washed and inedible portions are removed before analysis but these foods are not further cooked or processed. Processing factors (see Appendix III.C.5) were applied to the residue data in this assessment. These factors were taken from the most recent single-chemical dietary exposure assessments for the OPs. Information on these factors is somewhat limited; therefore, some storage or process related dissipation of residues may not be accounted for. In response to the preliminary assessment we have had several public comments with suggestions for improvements in the processing factors. These suggestions have been incorporated in the current assessment as appropriate. The processing factors in Appendix III.C.5 reflect these changes. The processing factors still probably result in some overestimation of residues in processed foods for which factors are not available, but the impact on this assessment of this possibility appears to be minimal according to the results reported here. Most of the food forms that appear to be significantly present in the upper ends of the exposure distribution are either uncooked food forms or are supported by residue data on food forms that have been processed in a similar manner.

iv. Residue Data Were Assumed to Reflect Co-occurrence of OPs in Single-day Diets

One reason for conducting the assessment of PDP residue data on a sample-by-sample basis is to maintain the connections in multi-analyte occurrences on these samples. In other words, it is assumed that the PDP sampling and analysis protocols capture the co-occurrence of OPs. Appendix III.C.10 demonstrates the extent of this measured co-

occurrence in the PDP program between 1994 and 1999. It can be seen in this table that a majority of PDP samples were reported as containing no detectable residues at all. For those that contained detectable residues, single residues were most prevalent but many multiresidue samples were found. The maximum number of OP analytes reported on a PDP sample is 5 (this occurred on only 5 samples during the period 1994-1999).

In addition to considering co-occurrence of different OPs on one food, the potential exists for co-occurrence from residues of one or more OPs on different foods consumed in one-day. This assessment is using residue data collected over a seven year period, 1994 through 2000. This is necessary in order to maximize the number of food commodities in the assessment but this raises issues of lack of co-occurrence. Co-occurrence in the food is important from the standpoint of all the food consumed in the same time period. One may question if it is appropriate to model exposure based on bananas grown in 1994 and apples grown in 1998. On the other hand, the consistency in appearance of residues in the monitoring data over time suggest that the uncertainty in this choice is probably not more significant than those in other aspects of the model.

A related choice in selection of residue data was to include all available data for a given food. This has resulted in data sets that span time periods of less than one year to as much as four years of data. At the time of the preliminary assessment we were exploring the impact of using reduced data sets for foods with a suggested maximum of 2 years of data for any given commodity. A decision was made to continue using the complete data set in the absence of specific information that a given subset of the data were inappropriate to consider for currently supported uses or import tolerances. Therefore, the complete data set is still being used (1994-2000 PDP) with the exception of data from 1994 on lettuce. These samples contained residues of methamidophos and mevinphos that could have resulted from applications that were not representative of current use patterns. The use of the complete data set from 1994 through 2000 increases the probability that variations in climate and pest pressures may have been captured in the residue distributions.

v. It Was Assumed That All OPs of Concern on an Analyzed Food Sample Were Accounted for in the Residue Analysis

All residue analyses are subject to the limitations of the sensitivity of the analytical methods. Many of the samples analyzed are reported as being below the analytical method reliable limit of detection (LOD). It has been usual practice in Agency assessments on individual pesticides to assume that residues in non-detectable samples are present at ½ LOD of the analytical method in samples that were harvested from treated fields. Thus, for purposes of estimating residues in samples reported as <LOD, a proportion of the samples equal to the estimated percent crop treated is assigned a residue level of ½ LOD and the remaining samples, which are assumed to come from untreated crops, are assigned a residue value of zero. This procedure becomes problematic for a cumulative assessment. It is not enough to simply estimate the percent crop treated for each of the pesticides in the cumulative assessment; it is also important to consider the potential for co-occurrence of residues of multiple residues on the same crop.

In the current assessment it is assumed that all OP residues reported as non-detectable are absent from the sample, i.e., they are assigned a value of zero. In a complex analysis such as this cumulative analysis, in which there are abundant samples with detectable residues, the assumption of zero for non-detects would not be expected to impact greatly the outcome of the exposure assessment at the highest percentiles. This was tested in an earlier stage of the assessment and reported in the case study that was presented to the SAP in December of 2000. Cumulative food exposure assessments were conducted using two extreme default assumptions: all non-detects = 0, and all non-detects = ½ LOD for the chemical with the greatest number of detectable residue findings on a given food. The most prevalent detected chemical was chosen because it is reasonable to assume that chemical would also have the greatest number of residues below the limit of detection. Under the conditions of the case study the two extremes showed essentially no significant difference in exposure above the 95th percentile of exposure. At the lower percentiles of exposure the impact of input for non-detectable residues on cumulative exposure became apparent; however, the overall exposure levels were so low they would not be considered to be of concern.

vi. PDP Residue Data Were Translated in Some Cases to Foods for Which No Residue Data Were Available

In chemical-specific dietary exposure assessments the Agency routinely translates residue data from one food commodity to related ones if the pesticide use patterns are similar on these commodities (USEPA, 1999b). For example, data on cantaloupes is often used as surrogate data for watermelons and other melons. For a cumulative assessment, in which a grower has a choice of several chemicals from the cumulative assessment group, these translations of data become more difficult to make. In the current assessment, translations of the residue data were made using the translation scheme in HED SOP 99.3 (USEPA, 1999b) in order to ensure representation of the maximum number of commodities possible. The allowable translation are summarized in Appendix III.C.4. In making these translations the only residues included were those that could occur on the simulated food from current registrations of OP pesticides. The uncertainty in this scheme is not expected to have a major impact on the assessment because the foods being translated comprise a relatively small portion of the per capita consumption by children (See Appendix III.C.1 for confirmation of this fact). An analysis of foods in the higher percentiles of exposure in this assessment has confirmed that translated foods do not significantly impact that portion of the distribution.

vii. The Food Exposure Portion of This Cumulative Assessment is Considered to be Constant Throughout the Year and Across Regions

It is currently assumed that the food distribution and storage systems in the United States result in essentially a national distribution of the major foods in our diet that is constant throughout the year. For some of the seasonal changes in availability of certain foods, PDP has designed its sampling program to concentrate on these time frames so that the residue data should reflect the foods as available to the consumer. This applies to imports also. For the water portion of dietary exposure it is recognized that the potential for residues is not constant nationwide. The national food estimate is combined with regional water assessments to provide a series of regional dietary assessments.

viii. Some Residue Data are Under Consideration But Not Included in This Assessment

A task force of pesticide producers has provided the Agency with an OP pesticide market basket survey. The results of this market basket survey, conducted in 1998, were submitted to the Agency in 2001. In this survey 13 foods were analyzed for 29 OP analytes. Samples were taken from grocery stores and single-serving size homogenates analyzed by methods with very low limits of detection. The foods collected, all of which

are also covered by PDP, were apples, broccoli, cherries, cucumbers, green beans, grapes, peaches, sweet corn, lettuce, oranges, potatoes, strawberries, and tomatoes. Preliminary examination of the data indicate that cumulative exposure assessment using market basket survey data are in general agreement with a similar assessment using PDP data. The impact of these data on the OP cumulative risk assessment are not included in this assessment.

I. Revised OP Cumulative Risk Assessment

D. Residential OP Cumulative Risk

1. Introduction

The Office of Pesticide Programs (OPP) has used a calendar based model (Calendex™) to address the temporal aspects of the residential use of pesticides in 7 geographic regions throughout the United States. These regions, based on major crop growing areas and their influence on surface and ground water, also present an opportunity to consider the unique climate patterns, pest patterns and potential socioeconomic patterns that influence residential pesticide use and expected exposure.

Calendex™ allows the OPP to delineate the critical timing aspects of seasonal uses of Organophosphate (OP) insecticides that result in exposure to pesticides. Calendex also enables OPP to identify potential co-occurrences from multiple sources. This includes the exposure from home lawn and garden treatments, pesticides used on golf courses and applications made by governmental entities for the control of public health pests such as wide area mosquito sprays.

In nearly all cases, the residential exposure scenarios were developed using proprietary residue and exposure data. Exposure factors such as breathing rates and durations of time spent indoors or outdoors were taken from various references including US EPA/ORD/NERL Consolidated Human Activity Database (CHAD), and the Agency's Exposure Factors Handbook (USEPA, 1997a). In this assessment, the full range of exposure values – expressed as uniform, log-normal or cumulative distributions -- are used, where appropriate, rather than relying solely on measures of central tendency. While the dietary and drinking water assessment address only the oral exposure route, the residential assessment considers the dermal and inhalation exposure routes as well as the oral route based on the mouthing behavior of young children.

EPA registered labels, while useful for establishing site/pest relationships and recommendations for applications, generally cannot provide the temporal aspects of regional pesticide use. Thus, OPP has relied on other sources of pesticide use information, including the National Home and Garden Pesticide Use Survey (NHGPUS) data and information available in State Cooperative Extension Service publications. These data resources were comprehensively used to identify information such as frequency of applications, the type of application equipment used, and the type clothing worn while making those applications. State Cooperative Extension Service recommendations were used to establish regional windows of pesticide applications based on the observed appearance of insects such as white grubs on lawns. For example, the timing for the treatment of white grubs occurs during mid-July in southern Texas (Region F-

Lower Midwest) and mid-August in areas such as New York (Region D – North East/ North Central).

2. Scope of Regional Assessments

The residential and drinking water assessments were developed for 7 distinct geographic Agricultural Production Regions (Figure I.D-1). EPA included ten OP pesticides with residential uses and potential for significant exposures in its assessment. Not included in the cumulative assessment were certain OP uses that result in low exposure and uses for which risk mitigation actions have been taken.

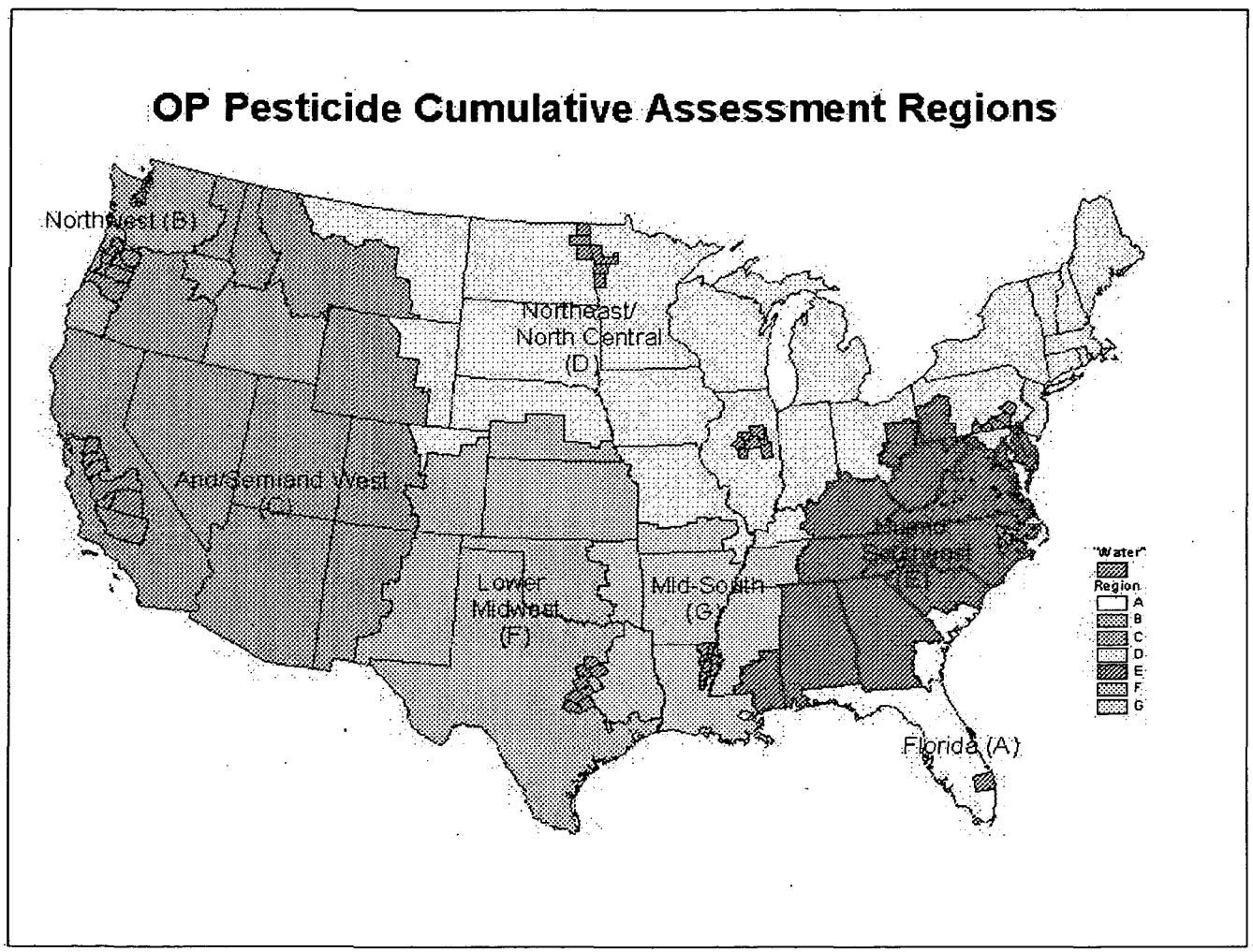
Two OP pesticides are currently registered for use on pets, tetrachlorvinphos (TCVP) (shampoo/dip and flea collar) and Dichlorvos (DDVP) (flea collars). OPP had insufficient data on DDVP or TCVP exposure for flea collar uses to include them in a calendar-based probabilistic assessment. However, OPP did assess TCVP through the shampoo/dip and powder use and these results are incorporated in this cumulative assessment.

Other OP uses were not included because they resulted in low exposures or because their single chemical REDs showed low risk. These low exposure uses include ant baits, paint additives and post application residential exposure from sod farm application of pesticides. Ant baits are contained inside enclosed packages. The treatment of individual fire ant mounds has very low applicator exposure and the reentry or significant play on fire ant mounds is unlikely. Low exposure is expected also because the treatments often take more than one day to produce results.

In case of paint additives, the diazinon additives in outdoor paints result in low potential for exposure because of the complexity of the paint/pesticide matrix as well as the dilution of airborne concentrations in the outdoor environment. For sod farm uses, post application exposure is mitigated by rapid dissipation of residues, residue removal during harvesting (cutting, rolling or stacking), and transportation. Installation of the sod requires considerable site preparation which is followed by watering in, further lowering potential for significant exposure in a post application scenario. OPP believes that children are unlikely to enter the lawn area immediately following the sod installation.

Finally, for wide-area public health treatments, the more significant uses such as fenthion, malathion and naled were included. Chlorpyrifos use for mosquito control was not included because very low exposures were estimated in the single chemical, screening level assessment.

Figure I.D-1. OP Pesticide Cumulative Assessment Regions



3. Residential Scenarios

The Residential Scenarios addressed in this document represent critical OP uses that have the potential for significant exposure or risk when considered in a cumulative assessment. These are:

- ❑ Golf course and lawn care applications,
- ❑ Home gardens,
- ❑ Wide area Public Health sprays,
- ❑ Pet Treatments (includes aerosol, liquid, and powder uses.), and
- ❑ Impregnated pest strips (limited to closets and cupboards.).

Table I.D-1. Summary of Changes Between December 3, 2001 Preliminary Cumulative Risk Assessment and Revised Cumulative Risk Assessment

Uses Included in the Preliminary Assessment That Have Been Removed from the Final Assessment	
Use Scenario	**Rationale for Change**
DDVP Crack and Crevice	Registrant is presently generating data
DDVP Pest Strips (currently under mitigation)	This assessment was limited to use of a small pest strip in closets and cupboards only. The uses in attics, basements, and garages were not considered in this assessment.
Malathion Lawn Spray	Registrant is no longer supporting this use.
Malathion Golf	Registrant is no longer supporting this use.
Malathion Vegetable Garden Dust	Registrant is no longer supporting this use.
Trichlorfon Lawn Care Spray – Applicator Scenario	This use has been limited to professional application by lawn care operators only. Only post-application scenarios will be considered.
Uses Included in the Final Assessment That Were not Included in the Preliminary Assessment	
Use Scenario	**Rationale for Change**
TCVP Aerosol, Powder, Pump Spray	Pet collars were not included in this assessment and are believed to pose less risk than the aerosol, powder, and pump spray uses considered in this assessment.

a. Golf Course and Lawn Treatments

Golf Course

Five OPs are registered for use on golf course fairways, greens and tees and/or residential lawns. Of the five pesticides, four may be applied on golf courses (Malathion golf course use is no longer supported by the registrant and was thus not included in the assessment). These pesticides are acephate, bensulide, fenamiphos, and trichlorfon. Acephate is used for surface feeding insects, like the chinch bug, which invade primarily warm season grasses such as St. Augustine grass. Bensulide is used for germinating weeds such as crabgrass on fairways, greens, and tees. Fenamiphos is a nematicide and is also watered. Trichlorfon is used for sub surface or thatch dwelling insects such as white grubs.

Lawn Treatments

On lawns, two pesticides may be applied by homeowners or by professional LCO. These pesticides are bensulide and trichlorfon. Bensulide is an herbicide used to control germinating weeds, and trichlorfon is labeled for insects such as white grubs, which damage turf when present in significant numbers. Both of these pesticides need to be watered in for effective control. Malathion is also registered for use on lawns applied as surface sprays to control nuisance pests such as fleas; however, this use is no longer supported by the registrant and was not included in the assessment.

b. Home Gardens

The home garden scenarios include ornamental and edible food gardens (including home fruit orchards). Due to the wide variety of plant/pest relationships that can exist in any given region, it was assumed that applications could be made throughout the growing season for a given area. Acephate and disulfoton are insecticides that have systemic properties and appear to be more widely recommended in the cooperative extension publications. However, malathion continues to be recommended for aphids by most cooperative extension services. In addition to use on ornamental gardens, malathion is also registered for use on home vegetable gardens and orchards.

c. Public Health Uses

Residential exposure from aerial and ground based applications for the control of public health pests made by regional or state personnel was addressed in this assessment. Malathion, fenthion and naled are applied to control mosquitoes. Fenthion is also applied to control black flies.

d. Indoor Uses

DDVP is the sole OP pesticide with indoor registrations. DDVP is used as both a crack and crevice spray and as a pesticide impregnated pest strip for the control of flying insects. Since OPP is currently in negotiations with the registrant regarding the use of DDVP crack and crevice applications, this scenario was not evaluated. The DDVP pest strip scenario, however, was

evaluated but was limited to use of smaller strips to control insects in closets and cupboards in which strip replacement occurred every 4 months.

e. Pet Uses

TCVP was evaluated in this assessment as an aerosol, pump, or powder flea and tick treatment for pets. TCVP is also available in impregnated from in pet collars. This assessment considered only TCVP pet treatment using the aerosol, pump, or powder form (and not the impregnated collar form), as these uses are believed to result in equal or higher exposures than the pet collar use. This is based on the assumption that shampooing a dog will result in greater exposure than merely securing a collar around a dog's neck. Post application exposure to the collar is also expected to be lower due to a smaller area being treated (area around the neck rather than the whole body).

4. Exposure Routes Considered

The routes of exposure considered in this cumulative assessment varied depending on certain application and post-application exposure activities which were determined to be age group-specific. The results of exposure are described in detail below:

Post-Application Oral Route of Exposure: Oral ingestion via hand-to-mouth activity of children was the only oral route of exposure considered in the residential portion of this assessment. Specifically, oral hand-to-mouth ingestion was considered only for the age groups Children 1-2 and 3-5 for their activities on treated lawns. OPP acknowledges that there is very limited data on exposure to very young children; in general, however, children ages six and older no longer exhibit mouthing behavior to the degree seen in younger children such as placing hands and /or objects into the mouth. In addition, while OPP recognizes that non-dietary pathways other than through hand-to-mouth activities do exist such as ingestion of soil and mouthing of grass, these latter two pathways are not considered because they had little impact on the exposure assessment when they were addressed in the individual chemical OP risk assessments.

Post-Application Dermal Route of Exposure: The dermal route of exposure was considered for both children and adults; however, the calculation for children adjusted by the appropriate surface area to body weight ratio. Children are considered in a separate group from adults because of the potential for additional exposures that result from a higher skin surface area to body weight ratio. In general children six and older have a surface area to body weight ratios that are similar to adults.

Post-Application Inhalation Route of Exposure: The inhalation route of exposure was considered for adults and children.

5. Data Sources

Three basic types of data were considered in this assessment: pesticide use data, residue concentration and dissipation/decay data, and residue contact and exposure factor data. Together, this information can be used to predict the potential for co-occurrence of exposure events in aggregate and cumulative

assessments. These data are described in more detail below and in Table I.D-2 (by application scenario).

Pesticide Use Data: Pesticide use information is critical to establishing windows of potential exposure when using a calendar-based exposure model. This information is needed to predict what pesticide will be used, the amount of pesticide which will be used, when the application will be made, how many times the pesticide will be applied (and for how long), and whether the applicator will be a professional or not. Other data such as frequency of applications, types of application equipment used, and types of clothing worn while making the applications are also used in developing exposure scenarios.

Several references were used to determine the application timing for lawn care pesticides and to estimate the number of pesticide users. To determine the percent of households that employ professional lawn care operators (LCO), the Agency used the 1996-1997 National Gardening Survey (Butterfield, 1997) conducted by the Gallup polling organization. For specific chemicals, regional percent of lawns treated were taken from the National Home and Garden Pesticide Use Survey (NHGPUS) (USEPA, 1992). Two other data sources, Kline Professional Markets for pesticides and Kline Consumer Markets for pesticides, were also used to check/confirm the NHGPUS estimates/data.

Residue Concentration Data: Residue concentration data and associated pesticide decay/dissipation parameters are used to define the sources and magnitude of exposure resulting from human contact.

Exposure Factor (Contact) Data: Exposure factors such as the amount of time spent in an area, whether the exposure is occurring indoors or outdoors, and whether the residue source is a golf course or a lawn (and if the latter, its size) are critical for estimating exposures to a given substance.

For example, an important variable for estimating home-owner applicator exposure is the size of the lawn. OPP considered the average and median lawn sizes reported in a journal article by Vinlove and Torla (1995). The means and medians were ~13,000 ft^2. However, the authors noted problems, interpreting the data since it is based primarily on low income houses and consists of adjustments of the lot size by the house's foundation (footprint) only. The data do not consider other structures such as decks or other green space such as gardens, which can reportedly reduce the lot size by up to 50%. Similar lawn sizes were noted in an extensive survey conducted by the Outdoor Residential Exposure Task Force (ORETF) with similar problems encountered with respect to confounding variables such as decks and other green spaces. For this assessment, OPP used a uniform distribution for lawn size bounded by 500 ft^2 and 15000 ft^2.

Another important variable for addressing post-application exposure from home lawn treatment is the duration of time spent on lawns. In this OP CRA, cumulative distributions of durations on lawns of up to two hours were used to address adult exposure on lawns. These data are presented in Table 15-64 in EPA's Exposure Factors Handbook; however, OPP notes that the percentiles above the 95^{th} have the same values (121 minutes). A similar cumulative distribution was given for children ages one to four. In order to be protective of children and to address the uncertainty of the upper percentiles of the exposure

factor data, OPP selected a cumulative distribution from the Exposure Factor Handbook's Table 15-80 with a bound of 3.5 hours for children.

This distribution represents the amount of time spent outdoors. This allows for the time that children spend outdoors not only at home but also in parks and near schools.

6. Lawn Care Exposure Data

a. Lawn Applicator Dermal and Inhalation Exposure Data

Residential applicator exposure was assessed for the applicator scenarios used in this assessment (i.e., commercial/professional applicator exposures were not included in the assessment). Both dermal and inhalation exposures were considered. Briefly, dermal exposures were calculated as the product of the Unit Exposure (mg/lb ai handled), application rate (lbs ai/ft^2), and area treated (ft^2). Unit exposure and area treated were inserted in the calculation as a log normal distribution and uniform distribution respectively, and application rate as a point estimate. Inhalation exposures to applicators were entered in the assessment as a uniform distribution bounded by high and low measured values.

Data concerning Unit Exposures (UE) (through both the dermal and inhalation routes) were generated by the ORETF. Specifically, this data consisted of exposure data from 30 volunteers using a push-type rotary spreader to apply 50 lbs of dacthal product to treat 10,000 ft^2 of turfgrass. Exposure data from these studies were used to generate normalized values expressed as milligrams exposure per pound of active ingredient of a pesticide handled (referred to as UE). Volunteers participating in these exposures studies were adult non-professionals who use pesticides on their own gardens and lawns. Many of the volunteers selected as subjects in these studies were members of garden clubs. All volunteers made their applications without specific instruction from the study investigators. Unit exposures from these studies were available for various clothing scenarios that consider individuals wearing short pants and short sleeved shirts, to long pants and long sleeved shirts. For this assessment, OPP assumed that all applications were performed using short pants.[1] Based on the Unit Exposure values generated in this study, UE's used in this assessment for the dermal and inhalation exposures were as follows: (i) for dermal exposure, a lognormal distribution with arithmetic mean of 0.69 mg/lb ai handled and arithmetic standard deviation of 0.36 mg/lb ai handled, truncated at the estimated 99th percentile of 1.93 mg/lb ai handled and (ii) for inhalation exposure, a uniform distribution bounded by the low and high measures values of 0.00019- and 0.0096 mg/lb ai handled, respectively.

[1] A survey conducted by Doane and Gallup (Johnson et al., 1999) on behalf of the ORETF identified 70% of those who treat their lawns wear short sleeved shirts while applying granular formulations. Likewise, 32% reported wearing short pants while applying granular formulations. Sensitivity analysis performed by OPP demonstrated that significant differences in Unit Exposures existed only between long pants and short pants, and that no significant differences existed between any of the other clothing scenarios (i.e., short- vs. long-sleeves did not impact estimated exposures). However, these significant differences in unit exposure between long pants and shorts had negligible effect on total MOEs, and thus, for this assessment, OPP assumed that all applications were performed using short pants.

Table I.D-1. Pesticides and Use Scenarios Considered in the Residential/Non-Occupational Regional Assessments

Pesticide	Golf Course	Lawn Care	Home Gardens	Public Health	Pest Strip	Pet Uses
Acephate	Used in Regions A, E, F, and G	None	Edible Foods: None Ornamentals: All Regions	None	None	None
Bensulide	Used in Regions A, C, D, E, F, and G	Used in Region F	Edible Foods: None Ornamentals: None	None	None	None
DDVP	None	None	Edible Foods: None Ornamentals: None	None	All Regions	None
Disulfoton	None	None	Edible Foods: None Ornamentals: All Regions	None	None	None
Fenamiphos	Used in Regions A, C, E, F, and G	None	Edible Foods: None Ornamentals: None	None	None	None
Fenthion	None	None	Edible Foods: None Ornamentals: None	Used in Regions A, and G	None	None
Malathion	None	None	Edible Foods: All Regions Ornamentals: All Regions	Used in Regions A, D, E, F, and G	None	None
Naled	None	None	Edible Foods: None Ornamentals: None	Used in Regions A and D	None	None
TCVP	None	None	Edible Foods: None Ornamentals: None	None	None	All Regions
Trichlorfon	Used in Regions C, D, E, F, and G	All Regions	Edible Foods: None Ornamentals: None	None	None	None

The application rate used in the assessment was taken as a point estimate equal to the maximum (label) application rate. For lawn size, OPP selected a uniform distribution of lot sizes ranging from 500 to 15,000 ft^2. This range considers smaller lawns for residences such as town houses. Information in a survey conducted by the ORETF also indicates that many pesticide users make spot treatments of insecticides. The upper bound of 15,000 ft^2 (~1/3 acre) appears reasonable given the type of application equipment assumed to be used by residential applicators (rotary granule spreaders). Information on frequency and timing of applications for pesticides were obtained from Representative Cooperative Extension Service publications and are described in each of the region specific section in Part II of this assessment.

Table I.D-2. Scenario-Specific Residential Exposure Data Inputs

Parameter		Value	Assumptions	Input Format	Data Source
Hand Pump Sprayer for Ornamentals					
Unit Exposure	-inhalation	0.002-0.0142 mg/lb ai handled	hand pump sprayer	Uniform Distribution	ORETF (Merricks, 1997)
	-dermal	mean of 78.2 and a SD of 75.7 mg/lb ai handled	hand pump sprayer	Lognormal Distribution	
Distribution includes wearing short pants and short sleeved shirt and were truncated at the 99th percentile.					
Area Treated		500-2000 ft^2	median home 2250 ft^2 assumed all one floor, with 2.5-10 ft. ornamental bed width	Uniform Distribution	US Census
Application Rate		label directions	rate per gallon treating 500-1000 ft^2	Uniform Distribution	(Merricks, 1997)
Treatments per Season		1-4	two-week intervals (on average based upon survey and label directions)	Cumulative Distribution	ORETF
Malathion on Edible Food Crops/Gardens and Home Orchards					
Area treated		135-8000 ft^2		Log Normal Distribution	ORETF with the National Garden Survey
Time Spent in Garden		0.083 -1 hour		Uniform Distribution	ORETF
Transfer coefficients		100-5000 cm^2/hr	activities=harvesting and maintenance of edible food crops. Accounts for a wide variety of gardens and activities	Uniform Distribution	(Korpalski and Bruce, 2000)
Number of applications		1-5	1 app.=32.6%, 2 app.=36.5%, 3 app.=14.3%, 4 app.=12.2%, 5 app. =4.4%	Cumulative	ORETF with the National Garden Survey

Parameter		Value	Assumptions	Input Format	Data Source
Ornamental Granular Incorporated Treatment-Disulfoton					
Unit Exposure	-inhalation	0.00001 mg/lb ai	Based on 1/2LOQ	point value	(Merricks, 2001)
	-dermal	mean of 0.18 and a SD of 0.29 mg/lb ai (trunc. at 99th%tile)	Distribution assumes the applicator is wearing short pants and short sleeved shirt.	Lognormal distribution	(Merricks, 2001)
Application rate		label		point value	
Frequency of application		1-3	1 app.=63%, 2 app.=32%, 3 app.=5% at six-week intervals		ORETF with the National Garden Survey
DDVP-Pest Strips					
Concentration in Air		0.005- 0.11 mg/m^3 over 120 days	samples taken at 1, 7, 14, 28, 56, and 91 day intervals and adjusted proportionately to account for smaller strips than measured in Collins and DeVries, 1973.	uniform distribution reflecting the range each sample day	Collins and DeVries, 1973

b. Post-application Dermal and Non-Dietary Exposure Data

i. Dermal Exposure-Residue Contact Data

The fate of pesticides applied to turf, and subsequent human contact, is a key variable for assessing post-application dermal exposure and can be an important exposure pathway to consider as part of a cumulative assessment. This exposure pathway was evaluated here in the OP Cumulative Risk Assessment by using data from a number of available studies (described in more detail below). Briefly, post-application dermal exposure (mg pesticide) is calculated by multiplying the transfer coefficient (cm^2/hr) derived from literature and other studies by the time spent on the lawn (hr) and the residue concentration on the lawn (mg/cm^2). For this assessment, the transfer coefficient and the time spent on lawn were represented by a distribution of values while the residue concentration on the lawn was represented by a time series of concentration values (which accounted for residue degradation over time). The transfer coefficients used in this equation were developed by dividing the hourly dermal exposure (µg/hr) obtained from a set of activities by the measurement commonly referred to as turf transferable residues (TTR) ($\mu g/cm^2$). Since none of the dermal exposure studies used to estimate hourly exposure in the above chemical specific residue studies permitted direct calculation of the TTR, the transfer coefficients for this assessment were instead for this assessment developed by assuming a transfer efficiency of 0.5% for granular formulations and 1% for spray formulation. This was done for two reasons:

- to make use of available dermal exposure measurements in the above studies which are not influenced by TTR method, and
- to make use of the available residue dissipation data for which there are no corresponding dermal exposure transfer coefficients.

The values of 0.5% and 1% are within the range of efficiency for the existing chemical specific TTR data. To account for the additional uncertainty of assuming a certain transfer efficiency to develop the transfer coefficients, TTR data having transfer efficiencies lower than 0.5% (granular) or 1% (spray) were adjusted upwards to make up the difference in efficiency. If the transfer efficiency of the TTR data was higher than 0.5% for granular formulations or 1% for spray formulations, they were not adjusted.

For a more detailed discussion of the relationship of transfer coefficients and TTRs please refer to the "Overview of Issues Related to the Standard Operating Procedures for Residential Exposure Assessment" presented to the FIFRA Scientific Advisory Panel on September 21, 1999.

Using the above-indicated calculation methodology, several exposure studies were used to assess post application dermal exposure to individuals reentering treated lawns. Separate studies are available, and used, for kids and adults. These studies are described in additional detail below:

Children's Exposure: Two studies were used to assess exposure to kids under granular and spray application scenarios. One study (Black,1993) investigated dermal exposure values of young children who are exposed to a non-toxic substance used to represent a spray application scenario. In this study, children performed unscripted activities on turfgrass treated with a non-toxic substance used as a whitening agent in fabrics. The subjects of the study were 14 children aged four to nine years old. The children performing the unstructured activities were provided toys and were observed in the treated area for a period of one half hour. Activities recorded included the following classifications:

- Upright (standing, walking, jumping and running)
- Sitting (straight-up, cross legged, kneeling, crouching and crawling)
- Lying (prone or supine)

Dermal exposure was measured by fluorescent measurement technology described in Fenske et al., (1986). Measurements on various body parts were expressed as μg/body part (e.g., hand, face, etc.) and as concentration ($\mu g/cm^2$). These concentrations were normalized to represent the surface area of children three to four years of age for use with a standardized body weight of 15 kg. Standard surface area values were taken from the Agency's Exposure Factors Handbook.

In a second study (Vaccaro, 1996) in which a granular formulation was used, seven adults performed structured activities intended to mimic a child's activities. These activities included:

- Picnicking
- Sunbathing
- Weeding
- Playing frisbee
- Playing touch football.

The subjects performed these activities for a period of four hours beginning after the turf had dried. Turf had been treated earlier with a granular form of chlorpyrifos and exposure was estimated in the study by monitoring the amount of a chlorpyrifos metabolite – 3,4,5, 6-TCP – excreted over the following period of 6 days. This method directly measures internal dose and was used to back-calculate a generic "to the skin" transfer coefficient by using chemical specific dermal absorption data for chlorpyrifos (Nolan et al., 1993) These data were further adjusted to account for differences in surface area of adults vs. children.

The transfer coefficients (cm^2/hr) for children estimated from these two studies are summarized below in Table I.D-3:

Table I.D-3. Transfer Coefficients for Dermal Exposure to Lawn and Public Health Uses for Children 1-6 Years of Age

Vacarro - Granular (scripted)	Black - Spray (unscripted)
714	2844
1042	3594
1042	3776
1485	4051
1736	4103
2758	4357
4785	4902
	6812
	8395
	8746
	9119
	9885
	10713
	16008

A lognormal distribution was used to fit these transfer coefficients values and an arithmetic mean and standard deviation for each distribution was calculated[2]. Specifically (for children's exposures) the OP cumulative assessment used a distribution for the transfer coefficient defined as a lognormal distribution with an arithmetic mean of 7265 cm^2/hr and a standard deviation of 4621 cm^2/hr for the spray application. For the granular application, the distribution used to define the transfer coefficient was a lognormal distribution with an arithmetic mean of 2225 cm^2/hr with a standard deviation of 2162 cm^2/hr. In each case, the lognormal distribution was truncated at the calculated 99th percentile of the distribution (i.e., 23,769 cm^2/hr for the spray application and 10,623 cm^2/hr for the granular application) in order to avoid a distribution which contained values that were well-beyond those that are deemed reasonable.

Adult Exposures: The Vaccaro study data discussed above were also used to assess exposure to adults under granular and spray application scenarios. These data are presented below in Table I.D-4:

[2] See Appendix 3 of "Guidance for Submission of Probabilistic Human Health Exposure Assessments to the Office of Pesticide Programs [draft dated 11/4/98] available at http://www.epa.gov/docs/fedrgstr/EPA-PEST/1998/November/Day-05/6021.htm for more information.

Table I.D-4. Transfer Coefficients for Dermal Exposure to Lawn and Public Health Uses for Adults 18 Years of Age and Older

Vacarro - Spray (scripted)	Vacarro - Granular (scripted)
3348	1229
6770	2813
7217	2813
8779	4010
9895	4688
11243	7446
13169	12920
13243	

A lognormal distribution was used to fit these transfer coefficients values and an arithmetic mean and standard deviation for each distribution was calculated (see footnote 2 in this chapter). Specifically (for these adult exposures), the OP cumulative assessment used a distribution of values for the transfer coefficient characterized by a lognormal distribution with an arithmetic mean of 9,784 cm^2/hr and a standard deviation of 5,515 cm^2/hr for the spray application. For the granular application, the distribution used for the transfer coefficient was characterized with a lognormal distribution with an arithmetic mean of 6,370 cm^2/hr with a standard deviation of 7,789 cm^2/hr. In each case, the lognormal distribution was truncated at the calculated 99th percentile of the distribution (i.e., 28,907 cm^2/hr for the spray application and 37,250 cm^2/hr for the granular application).

ii. Non-Dietary Exposure Data Hand-to-Mouth Behavior

The assessment also incorporated exposure from hand-to-mouth activity by children on lawns. Briefly, exposure through this pathway is calculated as the product of the following factors: hand-to-mouth contact frequency (hr^{-1}), surface area of inserted hand parts (cm^2), saliva extraction efficiency (unitless), wet hand adjustment factor (unitless), and hours spent on lawn (cumulative distribution)[3].

[3] The cumulative distribution used for hours spent on lawn by children was obtained from the Exposure Factors Handbook and represents a cumulative distribution for "do-ers" only, i.e., a cumulative distribution for only those children that reported spending at least SOME time on the lawn (i.e., it does not consider that some children on any given day DO NOT spend time on the lawn). Thus, the cumulative distribution assumes that some time is spent on the lawn by each child. To the extent that this overestimates time spent on the lawn, this overestimates exposure by this pathway. On the other hand, this cumulative distribution for time spent on the lawn is not stratified by season. To the extent that children spend time on the lawn during the seasons when applications occur, this may underestimate exposure. On balance, however, OPP believes that the distribution used is a reasonable, yet conservative estimate of time spent on the lawn during the relevant portions of the year.

Surrogate data to evaluate non-dietary ingestion through hand-to-mouth behavior in young children consist, in part, of observations reported in Reed et al., 1999 concerning the frequency of hand-to-mouth activity. This study addressed the mouthing behavior and other observations of children situated indoors, ages three to six at day care (n=20) and children ages two to five at home (n=10). The children were video taped and the frequency of hand-to-mouth events were enumerated after the taping. The hourly frequencies of the hand-to-mouth events reported were a mean of 9.5 events per hour, a 90th percentile of 20 events per hour and a maximum of 26 events per hour. These data were used to construct a uniform distribution to represent the frequency of hand to mouth activity bounded by a low value of 0 events/hr and a high value of 20 events/hour.

The observations reported by Reed, and discussed above, are based on children in real world settings. However, they provide little information regarding the characterization of the hand-to-mouth event, residue transfer efficiency, or extraction efficiency of the residues on the hands by saliva during the mouthing event. For these values, additional assumptions and studies to address the transfer efficiency of turf residues by wet hands are needed. Variables addressing this exposure pathway are discussed in the following below:

- Based on previous conversations with the SAP, each hand-to-mouth event has been estimated to equal one to three fingers or 6.7-20 cm^2 per event. To account for the fact that a child may touch nothing between successive events, and the fact that the event may not result in insertion of fingers at all (Kissel et al., 1998), a uniform distribution of 0 to 20 cm^2 per event was assigned.

- Hands wet from saliva are reportedly more efficient at residue transfer than dry hands. A uniform distribution of transfer efficiency multipliers of 1.5 to three times was selected to address the increased efficiency of wet hands. Wet hands had higher transfer efficiencies than dry hands and other TTR methods addressed in a study performed by Clothier et al., 1999. The TTR methods used in the study had similar efficiencies as the chemical specific lawn residue data (TTR data) used in this assessment.

- To address the removal of residues from the hands by saliva during the mouthing event several studies were considered. The removal efficiency of residues on hands by saliva and other substances (e.g., ethanol) suggests a range of removal efficiencies from 10% to 50% (Geno et al.,1995; Fenske and Lu 1994; Wester and Maibach 1989; Kissel et al.,1998). Thus a uniform distribution of 10% to 50% was used in this assessment.

- The time spent on the lawn was estimated as a cumulative distribution ranging from 0.25 hours to 3.5 hours. This data was obtained from the Exposure Factors Handbook and represents children aged 1 to 4 years old. To be protective of children and to address the uncertainty of the upper percentiles of the exposure factor data, OPP selected a cumulative distribution from Exposure Factors Handbook Table 15-80 with a bound of 3.5 hours for children. This distribution represents the

amount of time spent outdoors. This allows for the time that children spend outdoors not only at home but also in parks and near schools.

The percent contribution to total exposure via non-dietary ingestion continues to be difficult to quantify. This includes the variables discussed above as well as issues regarding the utility of using children's hand-to-mouth frequencies based on indoor activities for outdoor exposure scenarios. There are also differences in mouthing behavior based on active and quiet play with increased mouthing likely to be during activities of quiet play. Limited data evaluated by Groot et al.,1998 suggests there can be longer durations of mouthing activities for children aged six to 12 months (exceeding 160 minutes per day) than children 18 to 36 months (up to 30 minutes per day). However, children in this age group are not likely to be engaged in the higher post application lawn activities which OPP is currently modeling. Additional data for very young children (under the age of two) are needed in addition to delineating the frequency differences between hand-to-mouth events for children engaged in active and quiet play. The Agency recognizes this is an evolving field of study and that additional research is also needed to evaluate the distribution of behaviors across different age ranges with a view towards the influence of factors such as socioeconomic status.

7. Home Garden Applicator and Post Application Exposure Data

The US EPA National Home and Garden Pesticide Use Survey (1992), as well as various proprietary data sources were used to estimate dermal and inhalation exposure of individuals applying OPs to ornamental gardens, fruit and vegetable gardens, and home orchards. In addition, post-application dermal exposures were assessed for individuals harvesting or performing post application maintenance activities in home fruit and vegetable gardens and orchards. Both applicator and post-application scenarios are described in additional detail below.

Applicator Exposures: As described for dermal lawn applicator exposure, dermal exposures to applicators in home garden scenarios were similarly calculated as the product of the Home Garden Unit Exposure (mg/lb ai handled), application rate (lbs ai/ft^2), and area treated (ft^2). Both Unit Exposure and area treated were inserted in the calculation as a distribution, while application rate was entered as a uniform distribution .

For spray applications, Unit Exposure was estimated from a surrogate study with volunteers applying carbaryl to shrubs and trees using a small tank sprayer. This data was used in developing unit exposures for application of acephate and malathion to ornamentals. These data are presented below in Table I.D-5:

Table I.D-5. Applicator Unit Exposures for Using a Hand Pump Sprayer μg/lb ai handled for Ornamental Uses of Acephate and Malathion (also for home Vegetable/fruit Gardens (malathion only)

Replicate	Short-Sleeved Shirt, Short Pants	Inhalation
2	25348.3	2.3
4	51515.8	2.7
6	125828.3	2.0
8	26598.1	2.1
10	354396.6	3.2
12	55550.5	2.9
14	118695.9	2.3
16	173841.6	9.3
18	45160.0	5.7
20	39757.8	9.2
22	46075.7	2.1
24	14886.1	2.3
26	35911.5	2.3
28	81656.0	2.0
30	76548.2	14.2
32	74890.0	6.6
34	46498.0	2.1
36	36582.8	13.4
38	25014.7	2.0
40	63485.8	10.8

For dermal exposures, distributions for Unit Exposure through acephate and malathion ornamental uses (log normal with an arithmetic mean of 78 mg/lb ai handled, a SD of 76 mg/lb ai handled, truncated at 99th percentile value of 372 mg/lb ai handled, for application rate (uniform distribution specific to pesticide being assessed and detailed in Part II of this document), and for area treated (uniform distribution with a minimum value of 500 ft^2, and a maximum value of 2000 ft^2) were used. This latter value is based on US census data indicating a median house area of 2,225 ft^2. For this assessment, it was assumed this area was for one floor having a perimeter of ~200 linear feet. The ornamental beds were assumed to be 2.5 to 10 feet wide.

For granular disulfoton applicator exposures through the dermal route, chemical specific data measuring exposure of individuals using a shaker can of disulfoton granules to the soil around roses followed by soil incorporation are

available and were used in the OP CRA. Distributions for dermal unit exposure for applications to shrubs were developed from the following data in Table I.D-6:

Table I.D-6. Dermal Unit Exposures (μg/lb ai handled) for Applicator Using Disulfoton on Shrubs and Flower Beds

Replicate	Shrub
1	134
2	304
3	187
4	150
5	35.3
6	172
7	45.1
8	16.3
9	94.6
10	360
11	41.1
12	245
13	13.9
14	69.9
15	161

Note: all inhalation replicates were non-detect/loq - LOQ = 1.5 μg.

Specifically, a lognormal distribution with an arithmetic mean of 0.18 mg/lb ai handled, a SD of 0.29 mg/lb ai handled, and a truncation point at 1.31 mg/lb ai handled (99th percentile) was used for dermal Unit Exposure and a point estimate was used for application rate. This point estimate for application rate was specific to pesticide of interest and is detailed in Part II of this document. A uniform distribution was used for area treated bounded by a minimum value of 10 ft^2, and a maximum value of 2000 ft^2. As described above, this value is based on US census data indicating a median house area of 2,225 ft^2. For this assessment, it was assumed this area was for one floor having a perimeter of ~200 linear feet. The ornamental beds were assumed to be 2.5 to 10 feet wide.

Based on ORETF-submitted data, applicator inhalation unit exposures were represented by a uniform distribution for acephate and malathion ornamental uses, and as a point estimate for disulfoton ornamental use. Specifically, Unit Exposures for acephate and malathion ornamental uses were represented by a uniform distribution with a lower bound value of 0.002 mg/lb ai handled and an upper bound value of 0.0142 mg/lb ai handled (which represent the minimum and maximum measured values as per Table I.D-5 above) ; application rate was represented by a uniform distribution specific to the pesticide of interest and detailed in Part II of this document; and area treated was considered as a

uniform distribution with a minimum value of 500 ft^2, and a maximum value of 2000 ft^2 based on US census data indicating a median house area of 2,225 ft^2. For this assessment, it was assumed this area was for one floor having a perimeter of ~200 linear feet.

For applicator inhalation exposures for disulfoton, point estimates were used for unit exposure (0.00001 mg/lb ai handled) and application rate. The point estimate for inhalation Unit Exposure represents ½ the LOQ, since all measured inhalation unit exposures were less than the analytical limit of quantitation. The point estimate for application rate is specific to disulfoton and detailed in Part II of this document in the regional assessments. A uniform distribution with minimum value of 500 ft^2, and a maximum value of 2000 ft^2 was used to represent area treated. This value is based on US census data indicating a median house area of 2,225 ft^2. For this assessment, it was assumed this area was for one floor having a perimeter of ~200 linear feet.

Post-Application Exposures: Post-application exposure while harvesting or performing post application maintenance activities in home fruit and vegetable gardens and orchards was assessed using a wide range of transfer coefficients to account for the diversity of gardens and types of activities. Specifically, post application exposure was estimated as the product of a transfer coefficient (cm^2/hr), time spent in the activity (hrs), dislodgeable residue concentration (mg/cm^2), and the dermal absorption factor (unitless).

For the above calculation, the transfer coefficient was characterized as a uniform distribution ranging from 100 to 5000 cm^2/hr to account for and reflect a wide range of tasks for gardeners. The time spent harvesting or performing post-application maintenance activities was represented by a uniform distribution ranging from 0.0833 hr/day to 1 hr/day. These estimates of time spent in the garden performing post application activities (as well as the frequency of applications) were based on survey data performed by the Outdoor Residential Exposure Task Force (ORETF). Dislodgeable residue concentrations (expressed in mg/cm^2) were expressed as a time series of values collected from chemical-specific dislodgeable residue data obtained from studies performed in California (for Western regions) and Pennsylvania (for Eastern regions) and detailed in the region specific sections in Part II of this document. Timing and frequency aspects (on both a regional and chemical-specific) of post-application gardening activities were based on information available in representative state cooperative extension service publications, and regional use data was based on information available in the National Home and Garden Pesticide Use Survey and Kline Professional Markets Reports (1997-1998).

8. Golf Courses Post Application Exposure Data

The potential dermal exposure of individuals playing golf on treated golf courses was estimated using chemical-specific turf residue data and transfer coefficients derived from surrogate dermal exposure data. Specifically, post-application exposure to residues from golf courses (in mg) was calculated as the product of transfer coefficient (cm^2/hr), the time spent golfing (hr), and the turf residue value (mg/cm^2). The percent of the population playing golf and the percent of golf courses that are treated with any specified OP was also considered and incorporated into the assessment.

The surrogate data used to derive transfer coefficients were based on two measurements of four individuals playing golf on two golf courses treated with chlorothalonil (Ballee, 1990), and the exposure of golfers (four volunteers) to flurprimidol (Moran et al., 1987). The data are presented below in Table I.D-7:

Table I.D-7. Golfing Transfer Coefficients ($\mu g/cm^2$) for Post Application Dermal Exposure:

Chemical	Transfer Coefficient
Chlorthalonil	391
	329
	561
	547
	592
	533
	385
	508
	756
	522
Flurprimidol	264
	278

For both studies, an assumed transfer efficiency of 1% was used to calculate the transfer coefficients, since the studies were conducted using spray-able formulations. Based on these two studies, a lognormal distribution with an arithmetic mean of 483 cm^2/hr and an arithmetic standard deviation of 185 cm^2/hr was used to represent the transfer coefficient. This distribution was truncated at the calculated 99th percentile value of 1066 cm^2/hr. The exposure duration for individuals playing golf was assumed to be a uniform distribution bounded at the low end by two hours and at the upper end at four hours. The four-hour value was obtained from a 1992 survey conducted by the Center for Golf Course Management.

To establish the percent of individuals playing golf, the above-mentioned 1992 study was used. It was reported here that an average of 12.2% of the population plays golf. To determine the likelihood of playing golf on a treated golf course, percent of golf courses treated data provided by Doane's GolfTrak (1998-1999) was used. These data indicated anywhere from 5 to 85% of golf courses are treated with any specified OP depending upon the identity of the OP and the region of use. Additional details concerning the chemical- and region-specific use patterns used in the estimation of exposures through this pathway are present in Part II of this document.

9. Public Health Post Application Exposure Data

Assessment of post-application exposure to public health sprays was conducted in a manner similar to the method used to assess post-application exposure to lawn chemicals. That is, exposures to residues on lawns were estimated using the same dermal transfer coefficients, hand to mouth variables, and duration of time spent on the lawn. What differs between the public health spray scenario and post application lawn exposure scenario is the source strength of the residues deposited on the lawn from the public health sprays. The amount of residues that contact and may be present on the lawn can be predicted from the application rate for the various public health sprays and the application specifics, such as equipment type and spray nozzle settings. The percent of the application rate that is deposited on lawns following ground applications of public health sprays is based on a study by Tieze, et al. (1995) which measured the percent of the mosquito spray that is deposited on lawns following ground applications. These deposition values ranged from 3.8 to ~5%. For aerial applications, the percent of the application rate that is deposited on lawns were calculated using the spray drift model AgDrift which were reported (an discussed) in the individual risk assessments for malathion, naled and fenthion. These values ranged from approximately 15 to 30%. To address the uncertainty regarding the percent of use by ground equipment and or aerial equipment, a uniform distribution for deposition bounded by 3.8% and 30% was used. Inhalation exposure to public heath mosquitocide use was not addressed since there are no refined models to address this scenario. It is also expected that near-infinite dilution based on the outdoor location mitigates this exposure.

Timing aspects and estimates of percent of use are based on conversations with representatives of Florida Mosquito Abatement Districts (Whichterman) Florida A&M (Dukes) and Health Canada (Dr. Burke) for Black Fly. For other regions having public health spray uses, a spray schedule of once every two weeks was assumed for the summer season. Additional region-specific details regarding the application and timing of treatments and chemical-specific details regarding degradation are presented in Part II of this assessment.

10. Indoor Uses Inhalation Exposure Data

The only OP pesticide registered for indoor use is DDVP. This was assessed as a resin impregnated pest strip limited to unoccupied areas such as closets and cupboards. Exposures through crack and crevice treatments with DDVP were evaluated in the Preliminary Cumulative Risk Assessment, but not evaluate here in the Revised OP Cumulative Risk Assessment (Revised OP Cumulative) since OPP is currently in negotiations with the registrant regarding crack and crevice use.

Furthermore, estimated exposures through the DDVP pest strips were modified in this revised CRA to account for additional mitigation actions being taken and/or negotiated by the Agency. Specifically, use is expected to be limited to unoccupied areas such as closets and cupboards with the corresponding size of the pest strip reduced to account for the smaller spatial

volume being treated[4]. Exposure while handling the impregnated pest strips is expected to be minimal.

Thus, only post-application inhalation exposure was estimated for adults and children, with applicator exposure considered negligible and not evaluated.

Briefly, post application inhalation exposures (expressed in mg) were calculated in the OP CRA using the following equation:

$$E = C_{air} \times BMR \times H \times VQ \times MET_TIME$$

E = Exposure through the inhalation pathway (mg)

C_{air} = residue concentration in air (mg/m^3),

BMR= Basal Metabolic rate (MJ/hr) which is specific to a CSFII individual's age, sex, and weight

H = 0.05 m3/MJ, a constant representing the volume of oxygen consumed (at standard temperature and pressure) in the production of 1 MJ of expended energy.

VQ= 27 (unitless), a conversion factor reflecting the ratio between the amount of air breathed to the amount of oxygen obtained

MET_TIME (hr) which represents a distribution reflecting the sum (over a day) of the product of an unitless activity-specific metabolic factor and the amount of time spent in that activity (summed over all activities in a day).

The residue concentration in air (C_{air}) is represented by a time series of calculated concentrations in homes using reduced -size DDVP pest strips in closets and/or cupboards. Specifically, use of a smaller pest strip was assumed to produce a proportionately smaller air concentration. Thus, the air concentrations in this revised CRA were estimated by multiplying the measured concentration values found under a "whole-house" scenario following use of an 80 gram (as per Collins and DeVries, 1973) by either 0.26 or 0.066 to represent use of Pest Strips of 21 g or 5.25 g size.[5]

The BMR term in the above exposure equation is calculated internally by the Calendex software and represents a point estimate specific to and calculated for each individual in the CSFII based on his self-reported age, sex, and weight. Both H and VQ in the above equation are constants as described above. The

[4] Mitigation actions that are currently being negotiated do permit uses in additional unoccupied areas such as attics, basements, and garages, but for purposes of this cumulative assessment exposures through these uses were not assessed.

[5] (21g or 5.25g)/80g

MET_TIME variable is represented by an age group-specific empirical distribution and accounts for the fact that an individual's breathing rate and the specific activities an individual engages in on any given day are NOT independent. That is, this factor (or term) accounts for the interrelationship that exists between the activities that an individual engages in and the breathing rate with which that activity is connected.[6] The genesis and derivation of this MET_TIME variable is discussed in additional detail below.

The MET_TIME term: As indicated earlier, OPP in the OP Preliminary Risk Assessment assumed *independence* between a person's daily activities, the place in which these activities are conducted, and the amount of time spent in these activities. OPP has refined these assumptions in this Revised CRA by using information on each of the activities that an individual engaged in on that day; as well as the location and duration spent in each micro environment (activity-location combination). Thus, this revised CRA appropriately considers the implicit relationship between a specific activity and its and duration. Specifically, OPP obtained information on time-activity data from the US EPA ORD Consolidated Human Activity Database (CHAD) (http://www.epa.gov/chadnet1/). This is a recently constructed meta-database of time use survey data in which time and activity by each individual survey participant is recorded in a chronological diary format. The database, in total, consists of 22,968 person diary days from 10 different time use surveys; there are 875,339 records in total, with each record containing detailed information for each micro environment (activity-location). Since MET values vary by activity, it is possible to calculate breathing rates for each distinct micro environment (reading the newspaper, preparing meals, eating, cleaning the house, etc.) which are weighted by the amount of time spent in that microenvironment. Therefore, an individual who reported spending 24 hours indoors in bed (illness) will have lower indoor inhalation exposure than if that individual had spent 24 hours indoors engaged in various physical activities (8 hours sleeping, 2 hours preparing meals, 2 hours exercising, etc.). In this manner, the calculated total indoor inhalation would be consistent with the information available in the time use diaries.

OPP generated a set of random MET values for each of the 875,339activities reported by respondents in the CHAD database which were consistent with the CHAD-defined distributional form of the activity category. These distribution functions were developed based on a compilation and review of the published literature. For example, the MET value for 'Sleep or nap' (CHAD activity code 14500) follows a lognormal distribution, with mean 0.9, standard deviation 0.1; minimum 0.8 and maximum 1.1. The MET values for 'Prepare and clean-up

[6] In the preliminary OP CRA, an average daily indoor 'breathing rate' factor (MET) was assumed for each individual. This MET factor was assumed to be uniformly distributed and bounded by 1 and 2 (i.e., MET ~U(1,2)). The time spent indoors (representing the duration of exposure) was drawn *independently* using the empirical distribution published in the Exposure Factors Handbook. That time spent indoors and average breathing factors are related was not explicitly considered. As discussed in the main body of this document, OPP has refined this calculation using the time-use surveys available from CHADS/NHAPES in a more comprehensive manner.

food' (CHAD activity code 11110) are exponentially distributed, with mean 2.8, standard deviation 0.9, minimum of 1.9 and maximum of 4. [7]

OPP then multiplied each generated MET value by the corresponding duration during which that activity was undertaken to maintain any correlation between time spent indoors and corresponding activities. For each individual, this MET x Time variable was summed over all records in that individual's daily diary, in which the activity occurred indoors. This value is used in the equation above to calculate that individual's daily indoor exposure. For each age cohort (Age <1, 1-2, etc), a frequency distribution of this MET x Time variable was calculated. The table I.D-8 below presents these distributions for each of the age cohorts. There was no information on respondent age for 224 of the 22,968 person-days. Included in this distribution were individuals (n=74) who did not report spending any time indoors (perhaps camping, or on vacation). Specifically, the table below represents for each of six age groups (children 0-1 years old, children 1-3 years old, children 4-5 years old, etc.) the cumulative distribution of the MET_TIME variable (e.g., 95% of children 1-3 years old have MET_TIME values of 56 or less, 98% of children in this age group have MET_TIME values of 65 or less, etc.). It was this cumulative distribution that was used for MET_TIME variable in the above equation.

Table I.D-8. Distribution of MET Time Values, By Age Group

Cum Pct	0-1	1-3	4-6	7-12	13-17	18+
N	563	2,171	2,088	3,930	1,192	12,800
25%	26	25	19	16	15	15
50%	33	32	25	20	18	21
75%	41	41	32	25	23	29
90%	50	51	41	32	28	40
95%	54	56	47	37	33	49
98%	59	65	53	44	39	58
99%	65	69	59	49	42	67
100%	70	115	101	84	120	130

Use information for the number of households using DDVP pest strips indoors was taken from the National Home and Garden Pesticide Use Survey, 1991. The use of pest strips was assumed to occur year round with these

[7] The amount of information available for specific activities varied across the different activities. These studies also varied with regards to the methodology and instruments used to measure MET corresponding to the different activities.

replaced once every 16 weeks. Based in part on information provided in the National Home an Garden Survey, two percent of the homes were assumed to use DDVP pest strips. Further, it was assumed that in those homes that used pet strips, one 5.25 g strip was placed in a cupboard and one 21 g strip was placed in a closet.

11. Pet Uses

The Cumulative Risk assessment also considered exposures through flea and tick treatments. There are several products containing TCVP which are available in aerosol, pump spray, and powder form. TCVP is also available in impregnated form in pet collars. Exposure assessments were performed for both applicators and non-applicators (i.e., post-application exposures). For applicators, both dermal and inhalation routes were considered. For post-application exposures, only the dermal and oral (hand-to-mouth) routes were considered. Each of these routes is discussed in additional detail below.

Applicator Exposure Dermal and Inhalation: The data for the applicator assessment scenarios are based on studies submitted to the Agency which involved application of a flea and tick products to dogs. In this OP CRA, applicator exposure was calculated as the product of Unit Exposure (in mg/mg ai handled), application rate (mg ai handled/lb of animal), animal weight (in lbs of animal), and number of pets treated. Each of these terms was represented in the calculation as a distribution. Unit Exposure (in mg/mg ai handled) was represented by a cumulative distributions for powder and aerosol/pump spray formulations. This empirical cumulative distribution is presented in Table I.D-9 for powder an aerosol/pump spray applications

Table I.D-9. TCVP Applicator Unit Exposure (mg/mg ai handled) for Pets

		Powder		Aerosol & Pump Spray	
		Dermal	Inhalation	Dermal	Inhalation
Dog	Pct	(mg/mg ai handled)	(mg/mg ai handled)	(mg/mg ai handled)	(mg/mg ai handled)
1	6.7%	0.0016667	0.0000004	0.0028700	0.0000001
2	13.3%	0.0017328	0.0000005	0.0043400	0.0000080
3	20.0%	0.0021848	0.0000007	0.0050300	0.0000090
4	26.7%	0.0022796	0.0000013	0.0053300	0.0000110
5	33.3%	0.0023325	0.0000025	0.0054400	0.0000150
6	40.0%	0.0023699	0.0000028	0.0056000	0.0000150
7	46.7%	0.0024669	0.0000028	0.0058800	0.0000170
8	53.3%	0.0028417	0.0000049	0.0061700	0.0000230
9	60.0%	0.0030423	0.0000052	0.0077300	0.0000230
10	66.7%	0.0034921	0.0000068	0.0093800	0.0000280
11	73.3%	0.0040102	0.0000081	0.0098400	0.0000280
12	80.0%	0.0040917	0.0000110	0.0099600	0.0000280
13	86.7%	0.0050375	0.0000114	0.0102200	0.0000460
14	93.3%	0.0052139	0.0000220	0.0143200	0.0000470
15	100.0%	0.0149053	0.0000238	0.0270900	0.0000550

Application rate in this equation was represented by a uniform distribution depending upon the formulation, as follows:

- for powder, the application rate was represented by a uniform distribution bounded by 21 and 25 mg ai handled/lb of animal ;
- for aerosol, the application rate was represented by a uniform distribution bounded by 11 and 15 mg ai handled/lb of animal; and
- for pump spray, the application rate was represented by a uniform distribution bounded by 9 and 10 mg ai handled/lb of animal.

Animal weight and number of pets were each represented by a empirical cumulative distribution. Animal weights were drawn from an empirical distribution represented in Table I.D-10 and which ranged from 3 to 148 lbs/pet.

Table I.D-10. Pet Applicator Exposure Variable Dog Weights

Cum. PCT of Dogs	Dog Weight (lbs)
1%	3
10%	11
20%	16
30%	20
40%	23
50%	30
60%	43
70%	55
80%	70
90%	80
95%	89
99%	108
100%	148

Source: Boone, Tyler, Chambers: 1999 SoT Poster session; Carbaryl Study MRID 446584-01; and MRID 446584-01.

Pet owners were assumed to treat between one and four pets of identical size as per the information presented in Table I.D-11.

Table I.D-11. Applicator Exposure Variable Number of Dogs Treated

Cum. PCT of Dog Owner-Apps	Number of Dogs
50%	1
75%	2
90%	3
100%	4

Applicator exposures through the inhalation route were calculated in a similar manner to the applicator dermal exposures described above, except that Unit Exposure (in mg/mg ai handled) were specific to inhalation exposures. These empirical unit exposures through inhalation are also presented in Table I.D.9, above. All other terms relating to application rates, animal weights, and number of pets treated remained as described earlier.

Frequency, timing, and probability of TCVP applications to pets were also considered in the OP Cumulative Risk Assessment. Based on the US EPA Home and Garden Pesticide Use Survey, less than one percent of the homes reported using TCVP products for flea and tick treatment on pets. In addition, this survey reported that between 13 and 19 percent of all households reported using a pet collar for control of fleas and tick. This estimate, however, includes **all** pet insecticide collars, not just those that contain TCVP. These use estimates are consistent with proprietary marketing data published by Kline, Incorporated. Since recent estimates for use of TCVP pet collars are not available, the percent of households applying TCVP flea and tick treatments was set in the OP CRA at 15 percent, and was assumed to be equally split (at 5% each) between each of the three (powder, aerosol, and pump spray) TCVP formulations to account for use of both the flea and tick treatments and the TCVP impregnated collars. This is believed to be protective, since high-end exposures from flea and tick treatments are expected to be higher than high-end exposures from pet collars. The household applicators were assumed to reapply TCVP flea and tick treatments every 8 weeks, with use occurring all year in the Southern regions (A,C, E, F, and G), and between April through mid-August (three applications) in the Northern regions (B and D).

Post-Application Exposure – Dermal and Oral (Hand-to-Mouth): Dermal and oral (hand-to-mouth) post-application exposures from TCVP flea and tick treatments were also considered in the OP CRA. Dermal exposures scenarios were considered to be applicable to both adults and children while non-dietary oral exposure scenarios (oral hand-to-mouth) were assumed to apply only to infants and children ≤6 years old.

Dermal Post-Application exposure: Dermal Post-Application exposure (to adults an children) was calculated as the product of Residue concentration (mg/cm^2), the Transfer Coefficient (in cm^2/hr), and the Time spent (in hrs/day). Residue concentration values on the application day were estimated from the

Day 0 residue measurement from a study conducted by Hartz for TCVP Reregistration purposes. Residues measured on Day 0 (4 hours after treatment) ranged from 0.224 mg to 0.413 ug/cm^2 for the powder formulation, 1.1 to 1.9 ug.cm^2 for the aerosol formulation, and 1.2 to 3.5 ug/cm^2 for the pump spray formulation. This information is presented below in Table I.D.12:

Table I.D-12. Post-Application Residues on Day 0 (day=0.167), (Empirical Distribution)

Obs	Powder (ug/cm^2)	Aerosol (ug/cm^2)	Spray (ug/cm^2)
Applicator A	0.413	1.603	2.433
Applicator B	0.224	1.947	1.348
Applicator C	0.395	1.750	1.416
Applicator D	0.299	1.559	3.595
Applicator E	0.230	1.061	1.267

Memo S. Hanley to D. Fuller, March 22, 2002, Re-Issue: HED's Review of Determination of the Dislogeability of Tetrachlorvinphos (TCVP) from the Fur of Dogs Following the Application of an Insecticide Powder; Pump Spray or Aerosol; MRID 454855-01. C Code 083701; DP Barcode D277543, Submission S597121. Tables 5b, 6b, 7b; 8 and 9 (half life).

These residues were assumed in the OP CRA to persist for a period of 32 days with a half life of 3 days (both as estimated from the submitted study). Thus, residue value inputs for dermal post-application exposures were assumed to be a time-series of concentrations values represented initially by a measured Day 0 value which is dissipated over a 32 day period in a manner consistent with a half-life of 3 days.

The Transfer Coefficient used in this assessment of dermal post-application exposures to adults and children was derived from a carbaryl groomer exposure study in which sixteen different veterinary technicians treated/handled eight dogs each, over a two to five hour time period. These transfer coefficients are presented in Table I.D-13 for adults and children and were derived assuming an average transfer efficiency of 2.97% (calculated as the average transfer efficiency of powder (0.62%), aerosol (3.3%) and pump spray (5%)) and an allometric scaling factor to estimate transfer coefficients specific to children.

Table I.D-13. Post-Application Transfer Coefficients for Dermal Exposure to Pet Fur Residues (Empirical Distribution)[1]

Groomer μg exposure	Duration: hrs	μg/hr	ai deposited μg/cm²	Dislodged: 2.97 % efficiency assumed [2] ug/cm²	Transfer Coefficient (adults) Cm²/hr	Transfer Coefficient (children) Cm²/hr[3]
8796	2.88	3054	37.5	1.114	2742	1016
6199	2.58	2403	31.0	0.921	2610	967
1408	3.07	459	18.6	0.552	831	308
2914	2.48	1175	36.4	1.081	1087	403
5667	3.08	1840	32	0.950	1936	717
2527	3.18	795	19	0.564	1409	522
2,348	2.93	801	15.9	0.472	1696	628
2961	2.72	1089	7.75	0.230	4731	1752
1135	4.03	282	14.8	0.440	642	238
14872	3.88	3833	28.8	0.855	4481	1660
1026	3.17	324	16.6	0.493	657	243
13490	4.05	3331	56.98	1.692	1968	729
4275	4.92	869	25	0.743	1170	433
4461	3.45	1293	42.25	1.255	1030	382
1511	3.03	499	8.87	0.263	1894	702
777	3.00	259	48.6	1.443	179	66
				Average	1817	673

[1]Source Carbaryl Groomer Exposure Study (activity - wash/dip/groom). Each vet tech treated/handled 8 dogs: held small dogs w/arms and torso; some dogs climbed on person's shoulders while grooming etc.
[2]Average transfer efficiency 2.97% =(powder (0.62%) + aerosol (3.3%) +pump spray (5%))/3;.
[3]The transfer coefficients derived from this study were adjusted by an allometric scaling factor based on the relative size of children to adults to derive an appropriate transfer coefficient for children Adult:Child surface area ratio - 2.7:1 (avg. Adult 3169: avg child 1174)

Finally, the time spent in this activity was assumed to follow a triangular distribution with minimum value of 0.0333 hours, a most likely value of 0.108 hours, and a maximum value of 1.025 hours (as per Freeman et al, JEAEE, 2001, 11:501-509).

Oral (Hand-to-Mouth) Post-Application Exposure: Post-application exposure through the oral (hand-to-mouth) route was also assessed (for children only) in

the OP CRA. Specifically, exposures through the hand-to-mouth route were calculated as the product of the Residue value (in mg/cm^2), the surface finger area (cm^2), the frequency of events (hr-1) and the time spent (hr). The residue value was obtained from TCVP residue studies. Surface finger area (per event) was assumed to follow a uniform distribution bounded by 0 and 20 cm^2. The frequency of events was assumed to follow a triangular distribution with a minimum value of 0.4 hr-1, a most likely value of 9 hr-1, and a maximum value of 26 hr-1. The time spent with the pet was assumed to follow the same distribution described above for dermal post-application exposures.

As under the Dermal and Inhalation Exposure Scenarios discussed above, applications were assumed to re-occur every 8 weeks, with use occurring all year in the Southern regions (A,C, E, F, and G), and between April through mid-August (three applications) in the Northern regions (B and D).

12. In Summary

In summary, this assessment relied upon the best available data from all sources that could be identified. Sources included chemical specific and task force generated data, as well as data from the scientific literature. When available, regional distinct residue dissipation data were used for the lawn and garden uses. Additional Region-specific information is presented in Part II of this document.

I. Revised OP Cumulative Risk Assessment

E. Water OP Cumulative Risk

1. Introduction: Incorporating Water Exposure Into the OP Cumulative Assessment

FQPA, passed in 1996, imposed an expansion of the risk assessments for food use pesticides by requiring that the Agency perform cumulative risk assessments, i.e., that the Agency assess the risks from different pesticides having a common mechanism of action and focusing on the likelihood that a person will be concurrently exposed to multiple pesticides from multiple sources (food, drinking water, and residential uses). Ideally, data to support the water side of this exposure calculation would provide information on multiple pesticides, and their transformation products, collected from drinking water sources, both surface and ground water, throughout the U.S. at a sufficient frequency to reflect daily and seasonal patterns of pesticide occurrence in water. However, due to the great diversity of geographic-, climatic-, and time-dependent factors that affect pesticide contamination in water, this approach is not possible. For the organophosphorous (OP) pesticides cumulative assessment, the Office of Pesticide Programs (OPP) must rely on both available monitoring data and modeling to develop sufficient data for use in the exposure assessment.

Because drinking water is local, the national exposure assessment for drinking water must address localized areas of the country where exposure to OPs may occur due to drinking water contamination. The methods described in this chapter account for the fact that pesticide concentrations found in drinking water are not random, but are in large part determined by the amount, method, timing and location of pesticide application, the physical characteristics of the watersheds in which the community water systems (CWS) are located, and other environmental factors (such as rainfall) which cause the pesticide to move from the location where it was applied.

OPP is using a probabilistic, calendar-based approach to appropriately match and subsequently combine estimates of pesticide residues in food with estimates of pesticide residues in drinking water to determine reasonable approximations of the amount of OP pesticides ingested in the diet on a daily basis. This approach looks at each individual day of the year and allows appropriate temporal matching of exposures through food and drinking water on a daily basis. Each single day assessment serves as a "building block" for the construction of multiple consecutive day average exposures. This method accounts for the temporal aspect of exposure to OPs due to expected seasonal pulses and seasonal use-patterns.

To realistically estimate exposures, the assessment must take into account which OPs can and do occur together in time and place to account for co-occurrence. Only those exposures which are likely to occur in the same location, in this case a watershed, are combined. Those exposures that are likely to occur on different days and in different locations will be separated. Although multiple OP pesticides may be registered for use on the same site, they may not necessarily be used at the same time.

Risk is a function of both hazard and exposure, and estimation of the exposure portion for drinking water requires data on concentrations of the pesticides in the drinking water and consumption of drinking water for different demographic populations on a daily basis. Drinking water is locally derived and concentrations of pesticides in source water fluctuate over time and location for a variety of reasons. Pesticide residues in water fluctuate daily, seasonally, and yearly as a result of the timing of the pesticide application, the vulnerability of the watershed to pesticide runoff, spray drift and leaching, and changes in the weather. Changes in concentrations also result from the method of application, the location and characteristics of the sites where a pesticide is used, the climate, and the type and degree of pest pressure. Given the data needs and the number of variables that can affect the outcome of the predictive model, it is apparent that the development of daily distributions of concentrations of co-occurring OPs in drinking water for various regions of the US is far-reaching in scope and complexity.

The goal of the drinking water exposure assessment is to provide estimates of distributions of residues (concentrations in drinking water) for use in probabilistic exposure assessment that account for

- daily and seasonal variations in residues over time due to time of application(s) and runoff/leaching events
- year-to-year variations due to weather patterns
- variability in residues from place to place, resulting from the source and nature of drinking water and from the regional / local factors (soil, geology, hydrology, climate, crops, pest pressures, usage) that affect the vulnerability of those sources
- the potential for co-occurrence of more than one OP in location and time only when this is likely to happen

The section that follows discusses briefly what we know about OP occurrence in drinking water sources from available monitoring data and how OP residues in drinking water may be affected by conventional drinking water treatment processes. Based on the needs of the probabilistic cumulative exposure assessment and the information gained from this assessment of monitoring data, OPP designed a drinking water assessment that provides multiple years of daily residue concentrations from drinking water sources in twelve regions across the country. These methods, and a characterization of the results of this assessment, follow the monitoring assessment.

2. What We Know About OP Occurrence in Drinking Water

The drinking water exposure assessment for the OPs would ideally be performed using direct drinking water data, or at least using extensive surface- and ground-water monitoring data as a surrogate. With few exceptions, the quantity, quality and relevance of available monitoring data analyzed in each of the individual OP risk assessments were considered inadequate to support a drinking-water exposure assessment. For many of the OPs, limited or no monitoring data are available. For some OPs, no detections were reported from a limited monitoring set, but it is unclear whether these non-detects signify a lack of transport, or insufficient or non-targeted sampling.

The first part of this section briefly summarizes available surface-water and ground-water monitoring studies that included multiple OP pesticides. Additional monitoring data that focused only on a single OP pesticide are summarized in the individual chemical risk assessments (available through the Office of Pesticide Programs web site at http://www.epa.gov/pesticides/op/status.htm). This is followed by a review of published literature and registrant-submitted studies on the effects of water treatment on OP residues in drinking water. The section concludes with an evaluation of the extent to which the monitoring data fulfill the needs of the cumulative water exposure assessment.

a. Summary of Monitoring Information

Evidence from the available monitoring studies confirms that OP pesticides do occur in drinking water sources. The frequency of detections is generally low, except for chlorpyrifos, diazinon, and malathion, and the magnitude generally ranges from sub-parts per billion to a few parts per billion. Significantly greater frequencies of detection occur in the limited number of targeted monitoring studies.

These OP pesticides can occur together in the same water source at the same time. Chlorpyrifos, diazinon, and malathion are most likely to occur together. However, other OP pesticides may also occur with one or more of these three in local areas. The USGS NAWQA study detected multiple OP pesticides in the same water samples at the same time in almost all of its study units. In some instances, up to 7 of the 11 OP pesticides included in the monitoring study were detected together (see Appendix III.E.1).

In general, surface water sources are more likely to be vulnerable to OP contamination than are ground water sources. OP pesticides are found in streams draining through predominantly urban/residential as well as agricultural watersheds. Chlorpyrifos, diazinon, and malathion are frequently detected in urban streams. While the residential uses of chlorpyrifos and diazinon are being cancelled, residential uses for malathion remain.

Although monitoring for OP pesticides in treated drinking water is very limited, the weight of evidence from available studies is that chlorination may transform the OPs to oxons, sulfoxides, and sulfones, which are of toxicological concern. A few studies indicate that the oxon transformation product will be stable in chlorinated water for at least 24 to 48 hours after treatment.

b. Surface Water Monitoring

Available monitoring has shown that OP insecticides contaminate surface-water resources from both agricultural and urban use. Maximum contaminant levels (MCLs) under the Safe Drinking Water Act have not been developed for the OP pesticides, and OPs will be included on the Unregulated Contaminant Monitoring List for the first time in 2002. As a result, States and public water supplies (PWS) have not often included OPs in surface-water monitoring. Therefore, with the exception of results from the pilot USGS-EPA Reservoir Monitoring Study, few studies include analyses of OP insecticides in raw and finished drinking water.

Available surface-water monitoring for OPs represents a range of surface-water bodies, from agricultural drainage ditches to outflow samples from the largest rivers in the nation. Monitoring data from bodies such as small streams may not represent direct drinking water sources, but can give an indication of possible surface-water concentrations in high OP-use areas. Sampling from streams that are used for drinking-water supply gives an indication of possible concentrations in drinking water. Without direct data at a drinking water intake downstream, however, a risk assessor cannot assume potential exposure at concentrations above or below that detected.

i. Sources of Surface-Water Data

Although the number of "ambient" surface-water monitoring studies which have included OP pesticides as analytes is extensive, extensive monitoring data is not available for all OPs. The largest available source of surface-water monitoring for OPs, the **USGS NAWQA Program**, includes only nine active OPs: chlorpyrifos, diazinon, malathion, phorate, methyl parathion, disulfoton, terbufos, azinphos-methyl and ethoprop. Two other OPs – fonofos and parathion – included in the study have been voluntarily cancelled.

The NAWQA program includes monitoring data for 76 pesticides and covers "more than 50 major river basins and aquifers covering nearly all 50 states" (Figure I.E-1) (http://water.usgs.gov/nawqa/nawqa_home.html). Results of the individual NAWQA study units are highlighted in the appropriate regional assessments and in more detail in Appendix III.E.1.

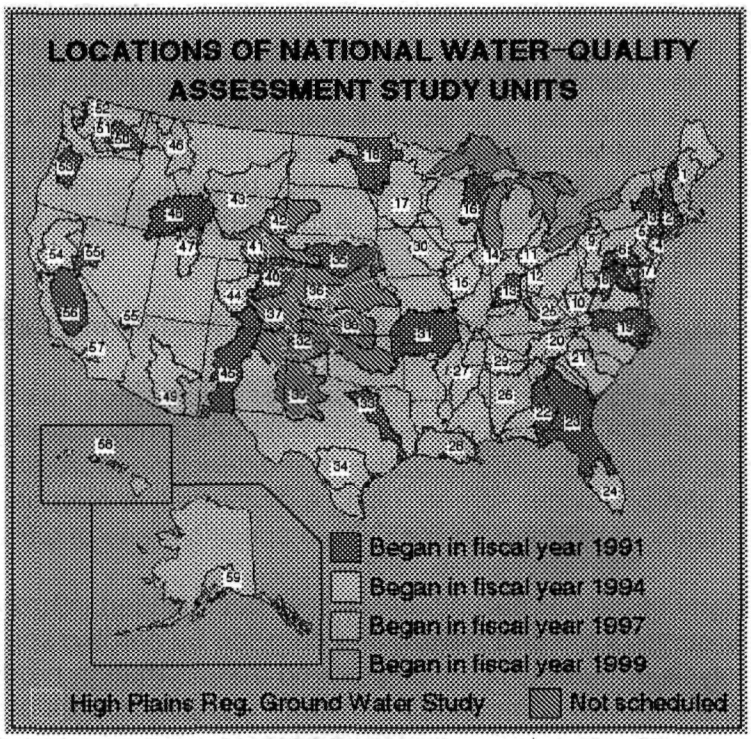


Figure I.E-1. Location of USGS NAWQA study units (Source: USGS).

The USGS **National Stream Quality Assessment Network (NASQAN)** program monitors water quality in the Rio Grande, Mississippi, Columbia, and Colorado Rivers, four of the nation's largest rivers. This study monitors for the same OPs included in NAWQA. NASQAN was designed to measure the mass flux of constituents such as pesticides and nutrients in these rivers, and so the 41 sampling stations are located at the mouths of these rivers, at the confluence of tributaries entering the

rivers, and at the intake and outflow of reservoirs along their path. Any detection of OPs in these studies is significant because detection in such large water bodies indicates that a large mass of the pesticide has run off to surface water. The relatively small number of stations and relatively infrequent sampling make it more difficult to connect detections in this study to specific OP uses.

State surface-water monitoring programs are most likely to include analytes required by the Safe Drinking Water Act, but may include OPs if consistent with budget priorities and local needs. When available, State monitoring programs are important additions to NAWQA data for a full understanding of possible OP exposure in drinking water. State programs are described in detail in Appendix III.E.2.

The USEPA Office of Pesticide Programs (OPP), USEPA Office of Ground Water and Drinking Water (OGWDW), and USGS National Water Quality Assessment (NAWQA/USGS) initiated a **reservoir monitoring project** to assess pesticide concentrations in untreated and finished drinking water derived from surface water reservoirs. Twelve drinking water reservoirs were selected from a list of candidate drinking water reservoirs which were potentially vulnerable to pesticide contamination. Vulnerable reservoirs are considered to be located in small watersheds with high pesticide use areas and high runoff potential. A summary of the results of this study occurs later in this section and in more detail in Appendix III.E.3.

ii. Completeness of the Surface-Water Monitoring Data Set

Monitoring data is most extensive for chlorpyrifos, diazinon and malathion, the three OP pesticides most frequently detected in agricultural and urban surface waters. States that did include more OPs generally did so as part of a wider screen, using a multi-analyte method, rather than specifically monitoring for the OPs in specific areas of OP use.

Many of the OP parent compounds not included in broad surface-water surveys are short-lived, and degrade by aerobic soil metabolism, photolysis or hydrolysis to longer-lived transformation products. Some of these short-lived compounds transform into degradates of toxicological concern that are more persistent and mobile than the parent compounds. The transformation of disulfoton to its sulfoxide and sulfone degradates is an example. Unfortunately, the toxic transformation products are, by and large, not included in monitoring studies.

Detection of pesticides in surface water is most likely when the sampling corresponds at least roughly to the timing and location of pesticide use. Several monitoring studies illustrate this:

- A series of studies by the California Department of Pesticide Regulation (CDPR) and the USGS investigated OP contamination from winter use as a dormant spray to tree fruits and tree nuts. The frequency and concentrations of OP detections in these studies were both relatively high. Among OPs detected in these studies were methidathion and dimethoate, which are rarely included in other monitoring programs.

- Diazinon and chlorpyrifos in urban streams represents the OP contamination most frequently detected in NAWQA surface water, followed by detection of malathion in urban streams. Since urban uses of these pesticides can occur year-round, and every NAWQA study monitored streams in watersheds dominated by urban or mixed land use, these studies were targeted to the timing and location of these uses.

- A study in the USGS San Joaquin River Basin (SJRB) further confirmed the importance of timing of sampling. Sampling three times per week in this study was more likely to detect higher concentrations than once per week. Sampling once per week was more appropriate for determining the median concentration.

iii. Effects of Study Design

In general, the surface-water studies which included OP pesticides as analytes were not specifically designed to correspond with times and locations of agricultural OP use. For instance, the same suite of nine OPs was included in NAWQA sampling programs nationwide. Azinphos-methyl was detected in surface water in the NAWQA Lower Susquehanna River Basin study unit, an area where azinphos-methyl is used in orchards. NAWQA also included azinphos-methyl as an analyte in three study units that it identified as part of the "Corn Belt." Surface-water sampling in the Lower Illinois River Basin study was specifically targeted to "two watersheds with greater than 90 percent row-crop agriculture and the basin inflow and outflow sites." Azinphos methyl is not used on corn, and it was not detected in any surface-water samples from these three study units. The USGS notes this effect of design in its analysis of OP occurrence in surface water and ground water from 1992 to 1997, reporting that azinphos methyl and ethoprop were not widely distributed in NAWQA and NASQAN studies, but that they "were detected in 43 and 69 percent, respectively, of samples from a few small agricultural watersheds in western irrigated valleys."

The design of the available programs determines their utility for the cumulative drinking water exposure assessment. While the NAWQA program samples in almost all states, a good number of the studies were designed to answer locally important questions for each river basin, and are not uniformly designed. The USGS Pesticide National Synthesis Project elaborates on why the studies are not specifically designed to produce a statistically representative analysis of national water-quality conditions (http://wwwdwatcm.wr.usgs.gov/ccpt/pns_data/data.html).

In comparison to NAWQA, NASQAN includes relatively few sites and samples each year, and is designed to allow an assessment of mass flux from some of the largest rivers. State studies were even more limited, and were most likely to include diazinon and chlorpyrifos in monitoring programs, if OPs were included at all. States that did include more OPs generally did so as part of a wider screen, using a multi-analyte method, rather than specifically monitoring for the OPs in specific areas of OP use.

iv. USGS-EPA Reservoir Monitoring Project

The USGS-EPA Reservoir Monitoring Study (Blomquist et al., 2001; available through the USGS web site at http://md.water.usgs.gov/nawqa/OFR_01-456.pdf) was designed to evaluate potential concentrations of a variety of pesticides and transformation products in untreated and treated drinking water derived from reservoirs. This study included twelve reservoirs covering a range of pesticide use areas across twelve states (Figure I.E-2). The study focused sampling during the period of the year with highest pesticide runoff vulnerability and variability in the post pesticide application season. Each reservoir was sampled quarterly for one year, as well as biweekly for a 4 month post-application period. Two sites were sampled at weekly intervals for 6 months post-application-season to improve the estimate of peak concentrations for short-lived compounds. Additional data collected for each site provided information on watershed properties, water treatment information, and reservoir characteristics.

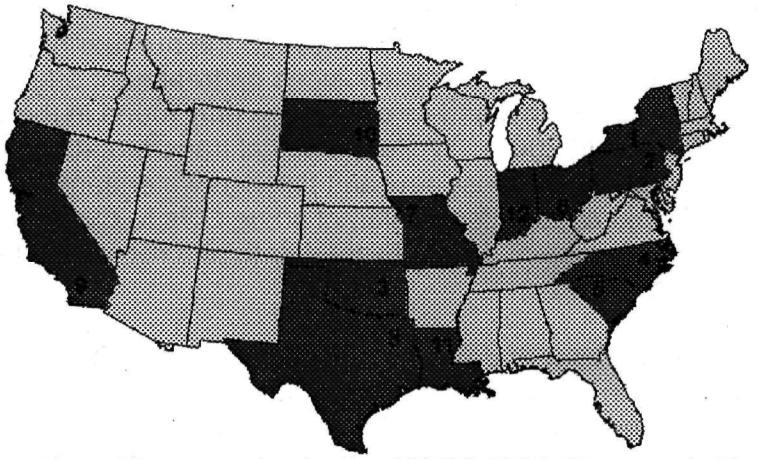


Figure I.E-2. Location of reservoirs in the USGS-EPA Reservoir Monitoring Project

While both untreated (raw) and treated (finished) water samples were taken at each sample time, the sampling scheme does not account for the travel time of the pesticide and its transformation products through the water treatment plant. Therefore, the occurrence and magnitude of pesticides in raw and finished waters cannot be directly correlated. This will likely exaggerate variability in removal efficiencies and limit direct linkage of degradation and formation patterns of pesticides during water treatment.

The pilot reservoir monitoring study provides two years of sampling, with 602 to 626 samples for each of 31 active OP parent and transformation products included in this cumulative assessment. This program included some rarely-monitored OPs, such as tribufos, phostebupirim, profenofos and dicrotofos, and rarely analyzed transformation products.

Thirteen of these 31 compounds were detected in either raw or finished drinking water samples, in spite of extreme drought conditions in 6 of the 12 watersheds in 1999 (see Appendix III.E.3 for details). Diazinon, the most frequently detected OP, was found in 35% of 323 raw water samples but in none of the 227 finished water samples. Although the lack of truly paired raw and finished water samples precludes definitive conclusions, these results suggest that diazinon may be removed by the treatment process. However, the likely transformation product, diazoxon, was not included as an analyte in the pilot program.

Results for other OPs suggest that parent OP compounds are transformed during water treatment. For instance, malathion was detected in raw water samples (2%) while malaoxon was detected in finished water samples (5%). Chlorpyrifos was detected in 5% of raw water samples; neither chlorpyrifos nor its oxygen analog were detected in

finished water. Azinphos-methyl and its oxon were both found in raw and finished water but the difference between the number of detections for each is insufficient to draw conclusions on treatment effects, especially since azinphos methyl and its oxon were only found in the same reservoir once (Missouri in 2000). While the actual transformation process is difficult to assess because raw and finished water samples were not temporally paired, the conversion of some OPs to oxon transformation products is consistent with published data and recent studies submitted by OP registrants.

A small number of detections of other transformation products are consistent with expectations based on the environmental fate properties of the parent chemicals. Fenamiphos and disulfoton were not detected in this limited sampling program, but both the longer-lived sulfoxide and sulfone transformation products were detected in one or two samples each. While their detection in raw water is an indication that drinking water contamination is possible, detections were few enough that the lack of detections in finished water is not a clear indication of removal by treatment.

Diazinon was detected in 10 of 12 reservoirs, and chlorpyrifos was detected in 6, which likely reflects their widespread use. No other OP was detected in more than three reservoirs in this limited sampling. Azinphos-methyl had the highest concentration detected of all parent products (0.114 ug/l in South Carolina raw water). Azinphos-methyl was found in 46% and 32% of samples taken in South Carolina in 1999 and 2000. Azinphos-methyl oxon was detected at a maximum concentration of 0.263 ug/l in Oklahoma, and was detected in 20% of samples in New York and Missouri in 2000. Malaoxon had the highest concentration detected of all analytes with maximum detections in Louisiana of 0.556 ug/l in 2000, and 0.204 ug/l in 1999.

Phostebupirim, which is very rarely included in any monitoring studies, was detected in 10% and 8% of 1999 raw water samples in Missouri and Pennsylvania, respectively. The concentrations were low (0.003 to 0.007 ug/l), but serve as a reminder that OPs may be transported to surface water bodies, even if few monitoring data are available to confirm this.

Although the reservoir monitoring study was not specifically targeted to high OP-use areas, it included more OPs than any previous study. Therefore, it is useful for considering the possibility of exposure to multiple OPs. Of 314 *intake samples* considered, 137 (44%) had one or more detectable OPs. Of the 137 with detectable OPs, 16 (12%) included more than one detected OP. Of 67 *outfall samples* considered, 17 (25%) had one or more detectable OPs, two of those samples (12%) having more than one OP detected. Of 218 *finished samples* considered, 24 (11%)

had one detectable OPs, and none of the finished samples considered here had more than one OP detected.

The pilot reservoir monitoring program confirmed the utility of sampling for a wide range of OPs and transformation products in drinking water, using low levels of detection. Continued and expanded monitoring should improve understanding of potential drinking water exposure, and of the effects of degradation in the field and from drinking water treatment.

c. Ground Water Monitoring

Due to the chemical properties of most of the OP insecticides, drinking-water exposure through contamination of surface-water resources is generally more likely than through contamination of ground water. However, even in regions where surface water is the predominant source of drinking water for most of the population, a significant portion of homes derives drinking water from relatively shallow domestic wells. In some areas of the country, where soils are especially permeable and depth to unconfined ground water particularly shallow, domestic wells represent some of the drinking-water sources most vulnerable to pesticide contamination.

Most OPs were described as unlikely to leach to ground water in the individual risk assessments completed over the last few years. This is due mainly to the relatively short aerobic soil-metabolism half-life of many OPs. However, there are some important exceptions. Several OPs are described as having the potential to contaminate ground water, but lack the data to sufficiently evaluate the magnitude of this risk.

Fenamiphos and its degradates, fenamiphos sulfoxide and fenamiphos sulfone, are the best examples of this problem. These chemicals have been detected at high levels in ground-water studies conducted in Florida, and to a lesser extent in California. Concentrations of fenamiphos and its transformation products detected in the Central Ridge area of Florida ranged as high as 246 ppb (204 ppb fenamiphos sulfoxide) in a retrospective ground-water study.

However, recent ground-water monitoring which includes fenamiphos is scarce. The USGS undertook a fenamiphos ground-water study at seven golf courses in Florida, and reported maximum detections of < 1.0 ug/l each for fenamiphos and its transformation products. The State of Florida reports that its database includes only two wells with detections of fenamiphos sulfoxide in its ground-water database. California collected samples from 40 drinking water wells in fenamiphos use areas during the early and mid 1990s, but did not detect fenamiphos (another round of sampling is currently underway). Hawaii, Michigan and North Carolina report that fenamiphos was not detected in a total of fewer than 100 drinking water or monitoring wells, and fenamiphos is not included among analytes in the NAWQA program.

Therefore, while fenamiphos has been detected in vulnerable to very vulnerable soils in Florida and California, sufficient data is not available which could allow a more detailed monitoring assessment for other areas of the country.

i. Sources of Recent Ground-Water Monitoring Data

The Agency contacted **pesticide lead agencies and other agencies in all 50 States** to inquire whether OPs were included in surface-water or ground-water monitoring (either ambient or drinking water) programs over the last decade. OPP requested recent data since 1) earlier data are more likely to be included in the aggregate assessments of individual OPs, 2) recent data are more likely to reflect current use rates and use areas, and 3) such data are more likely to be in electronic format, accessible either over the Internet or as an e-mail attachment. Government scientists in nearly all States offered to describe or provide summaries of current monitoring programs, or directed the Agency to data which are available online.

As a result of the relative non-persistence of most OPs in soil and the limits on funding for monitoring in State and Federal programs, few OPs are included in ground-water monitoring programs conducted over the last decade. Chlorpyrifos, diazinon and malathion are the OPs most commonly included as analytes in State ground-water monitoring programs. In some States, multiple OPs are included as part of a general screen under EPA methods 507 or 525.5. In such cases, the levels of detection are often higher than in more chemical-specific analyses.

The voluntary cancellation of non-agricultural uses of chlorpyrifos and diazinon affects the ground water assessment for these chemicals. While many of the agricultural uses remain, the Agency believes that most of the ground water monitoring detections of these chemicals are associated with uses that have been cancelled. The termiticide use of chlorpyrifos, which is currently being phased out, represents the use that has led to the highest known concentrations of any OP in ground water. The concentrations of chlorpyrifos measured in wells affected by the termiticide use ranged as high as 2090 μg/l, significantly higher than concentrations found in agricultural areas, which generally are below 1 μg/l.

The **USGS NAWQA program** is the other major source of ground-water data for the OPs. While the NAWQA program has provided a very valuable ground-water data set, it has several important limitations with respect to the cumulative OP drinking water assessment:

- Only nine OPs included in this cumulative assessment are included.

- Many NAWQA ground-water studies included only a single sample of each well in the network. Even if wells were located in OP use areas, the monitoring was not timed to correspond specifically to account for pest pressure and OP application for that particular year.

- A number of land-use studies in the program were focused on urban areas. The phase-out of homeowner uses of chlorpyrifos and diazinon renders such data less useful for our assessment.

Finally, the design of the ground-water studies differs between each study unit, reflecting the local aspect of ground-water quality that was being investigated in each monitoring program. For instance, monitoring in the Eastern Iowa Basins study unit included 65 domestic wells in order to assess the water-quality of the most heavily used aquifers in the study unit. By contrast, one of the ground-water studies in the Ozark Plateaus study unit was designed to evaluate water-quality in domestic wells in cattle and poultry-producing regions. One of the studies in the Southern Florida study unit included wells less than 15 feet deep and located in the drip line of citrus trees, where the depth to the water table was 2 to 4 feet below the land surface. In addition, a study in the Central Arizona Basins study unit included domestic, public supply, and other wells that draw older water (at least pre-1953) from a confined aquifer, which to this point is considered to have had very little hydraulic connection with potentially contaminated shallower ground-water above the confining layer. **The differing design among the different ground-water monitoring studies limits the applicability of statistical methods to the combined NAWQA ground-water dataset for a national OP drinking-water assessment.**

Some OPs are not included in any ground-water monitoring supplied to the Agency, such as phostebupirim, chlorethoxyfos and tribufos. Other OPs have only very limited monitoring data from the 1980s in which a small number of ground-water detections are reported. One example is methamidophos, which was detected in four wells near a Maine potato field in 1986 at concentrations up to 10 ug/l. Such data may not well represent current use or use rates, but may also have underpredicted possible ground-water contamination due to higher analytical detection limits. Older studies which revealed ground-water contamination indicate that exposure to rarely analyzed OPs is possible. However, the lack of extensive, recent ground-water data for some compounds makes it very difficult to quantify the potential risk nationwide.

With few exceptions, ground-water monitoring programs which include OPs are surveys which are not targeted specifically to assess the effects of OP use on ground-water quality. Examples of exceptions include chlorpyrifos termiticide use studies and fenamiphos studies near Florida golf courses. The results of survey studies give some indication of the

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possible exposure to populations as a whole. However, since survey studies usually include sampling of wells in areas where OPs are not used, they are less useful for quantifying potential drinking-water exposure in OP use areas.

Few ground-water studies include OP transformation products as analytes. The fenamiphos prospective ground-water studies and the USGS golf-course study mentioned above are rare exceptions. Lack of monitoring for transformation products might be important for other OPs which form sulfoxide and sulfone degradates, such as disulfoton, phorate and terbufos. If these OPs follow the same pattern as fenamiphos, the sulfoxide moieties of these chemicals may be a greater concern for ground-water contamination than the parent compound.

d. Effects of Drinking Water Treatment on OP Pesticides

The weight of evidence from open literature, a registrant-sponsored study, an ORD/EPA laboratory study, and the USGS-EPA reservoir monitoring program show parent OP pesticide residues in water are likely to be transformed during drinking water treatment. The most probable pathway is transformation by oxidation through chlorination and not physical removal. Oxidative transformation products of toxicological concern, such as sulfones, sulfoxides, and oxons, have been detected in finished water samples from water-treatment plants. Although not all oxons were tracked, the USGS-EPA reservoir study suggests that malathion may have been converted to malaoxon as a result of treatment.

Studies have shown oxons to be relatively stable in chlorinated drinking water for at least 48 hours. Although the detection frequencies of oxidative degradation products were low in the reservoir monitoring data, they were more frequently detected in finished water than in raw water. These data suggest oxidative degradation products such as oxons, sulfones, and sulfoxides have a high likelihood of occurrence in finished drinking water.

Appendix III.E.4 provides additional detail on removal and transformation of organophosphorus pesticides and certain degradation products through water treatment. The review extends the OPP water treatment literature review (http://www.epa.gov/scipoly/2000/September/sept-00–sap-dw-0907.pdf). Documents in this report include open literature, registrant-sponsored water treatment data, and the USGS-OPP pilot reservoir monitoring data.

Available information indicates that two common water-treatment methods lead to transformation of some OPs:

- Treatment of water by **chlorine and chlorine compounds for disinfection** can result in transformation of parent OP compounds. The P=S bond of OPs can be oxidized to a P=O bond leading to the formation of oxon transformation products. According to Magara et al (1994), several OPs are transformed to their corresponding oxons in this manner. For instance, diazinon is oxidized to diazoxon, which is relatively stable in chlorinated water for at least 48 hours. In a laboratory study at EPA-ORD's AWBERC facility in Cincinnati, Ohio, about 90% of chlorpyrifos-methyl was removed by chlorine treatment. The removal was most probably due to oxidation of the insecticide to oxons and other products.

- In areas where **water softening treatments** add lime and soda ash to reduce calcium and magnesium levels in water, the pH can increase to about 10 - 11. This high pH can lead to base-catalyzed hydrolysis of the OPs which are susceptible to hydrolysis under alkaline conditions. In the ORD treatment study, more than 99% of malathion was removed during softening treatment. The effects of softening may not be so dramatic for all OPs; although phorate has a 3-day hydrolysis half-life at pH 9, lower removal (20%) of phorate was observed.

A complete review of a registrant-sponsored jar test study on the potential effects of chlorination on six OP pesticides and four oxons (Tierney, et al., 2001) was hindered by incomplete information on the experimental procedures (particularly, water quality data, the impact of sodium thiosulfate on water chemistry, storage stability, and clarification regarding pesticide concentrations above the limit of detection and below the limit of quantification). Despite the lack of information on experimental methods, the data indicate organophosphorus pesticides (acephate, azinphos-methyl, chloropyrifos, diazinon, malathion, and methamidaphos) are transformed in chlorinated drinking water. Chemical oxidation of the organophosphorus compounds led to the formation of oxons for azinphos-methyl, chloropyrifos, diazinon, and malathion. Chloramines were formed during the experiment, and because chloramines have lower oxidizing potential than hypochlorus acid, the extent of degradation and formation of oxidative degradation products (oxons) may be different under conditions of higher free chlorine concentrations.

e. Suitability in Meeting Cumulative Assessment Needs

While the available monitoring studies provide a profile of OP occurrence in water, critical limitations preclude basing the cumulative water exposure assessment solely on monitoring. In particular, the monitoring studies were not designed to characterize daily concentration profiles and are not robust enough to provide daily distributions. Nor have the studies been conducted over a long period of time (typically less than three years) necessary to characterize year-to-year fluctuations due to weather patterns. While the NAWQA study units coincide with a number of high OP-use areas, not all of

the major OP use areas have monitoring data. Lack of monitoring for some compounds make it difficult to completely assess co-occurrence. Finally, monitoring provides a snapshot in time and does not reflect recent mitigation actions, such as lower application rates and fewer applications or cancellation of certain uses or chemicals, initiated for individual chemicals during the risk management phase.

Despite these limitations, water monitoring was used in the cumulative assessment to help identify vulnerable surface water sources, characterize OP residues in ground-water sources, compare relative impacts of OP use on water resources in different locations across the country, and provide a baseline comparison for estimated OP concentrations used in the probabilistic exposure assessment. Appendices III.E.1 and III.E.2 compare estimated OP concentrations with available local monitoring. Significant trends between estimated concentrations and monitoring are highlighted in the regional assessments in Part II.

With the publication of data from the nationwide set of NAWQA study units, more surface-water data for the OPs is available than ever before. However, the cumulative OP drinking-water exposure assessment requires the estimation of simultaneous daily drinking-water exposures to multiple pesticides, which is something that has never been attempted before. Although the available data is extensive, the cumulative drinking-water exposure assessment cannot be solely based on monitoring.

Therefore, the daily drinking water exposure estimates have been generated using the simulation models PRZM and EXAMS. A description of the use of these models for the cumulative OP drinking water exposure assessment follows. The use of models allows estimation of possible concentrations of OPs not included in monitoring programs, or in areas for which monitoring for locally important OPs was not available. As described in the Risk Characterization section, peak values from the modeling are not always as high as some seen in small streams in the NAWQA program. However, the models allow the Agency to estimate a cumulative exposure assessment for **all** OPs used in representative scenarios for each region, even if they do not consistently match all the highest detections for each individual chemical.

3. Drinking Water Assessment Methods

The goal of the cumulative assessment is to aggregate exposure from the organophosphorous (OP) pesticides over multiple routes of exposure (food, drinking water, residential) in a manner that is consistent in time (i.e., those exposure routes that are likely to occur on the same day are combined; those that are not likely to occur on the same day are not combined) and in location (i.e., only those exposures that may potentially occur in the same location are considered together). The Agency needs reasonable approximations of daily

distributions of OP residues (concentrations) in drinking water to combine with food and residential exposures using a probabilistic, calendar-based approach.

This cumulative risk assessment represents the first attempt to quantify possible drinking water exposure to multiple chemicals at the same time. Available surface-water monitoring is not sufficient to allow estimation of potential daily drinking water exposure to the OPs included in this assessment. No currently-available model is specifically designed to simulate the simultaneous application and transport of multiple pesticides in a watershed. Therefore, the Agency looked to available tools to provide these daily exposure estimates for consideration with food and residential exposures.

Because drinking water is local, the national exposure assessment for drinking water must address localized areas of the country where exposure to one or more OPs may occur due to drinking water contamination. The consideration of OP use in specific regions of the country will facilitate the assessment of potential co-occurrence of different OPs in drinking water, leading to a cumulative assessment of OPs in drinking water on a regional basis.

The sections that follow describe the steps OPP has taken to generate regional drinking water exposure assessments as a part of the cumulative OP assessment.

a. Chemicals and Uses Included in the Cumulative Assessment

Table I.E.1 lists the parent OP, transformation product(s) of toxicological concern, and approach for considering the contributions of the transformation products to the cumulative water exposure. Detailed chemical-specific inputs, based on environmental fate studies submitted by the OP registrants, are documented in Appendix III.E.5. These inputs are based on the individual chemical assessments that were published in the REDs.

Table I.E-1. OP Pesticides and Toxic Transformation Products Included in the Cumulative Water Exposure Assessment

Pesticide	Transformation Products of Toxicological Concern	Approach for Including Transformation Product
Acephate	Methamidophos	Conversion from parent to product; max rate based on fate studies
Azinphos Methyl	Oxon	Formed by treatment
Bensulide	Oxon	Formed by treatment
Chlorethoxyfos	Oxon	Formed by treatment
Chlorpyrifos	Oxon	Formed by treatment
Diazinon	Diazoxon, Hydroxy-diazinon	Formed by treatment
Dichlorvos (DDVP)	None	na
Dicrotophos	Monocrotophos	Not in field studies
Dimethoate	Oxon	Formed by treatment
Disulfoton	Sulfone, Sulfoxide	Combined residues
Ethoprop	SME, OME, M1	Not modeled; negligible residues; parent relatively stable
Malathion	Malaoxon	Formed by treatment
Methamidophos	None	na
Methidathion	None	na
Methyl Parathion	Methyl Paraoxon	Formed by treatment
Naled	Dichlorvos (DDVP)	Conversion from parent to product; max rate based on fate studies
ODM	Sulfone	Not modeled; negligible residues
Phorate	Sulfone, Sulfoxide	Combined residues
Phosmet	Phosmet Oxon	Formed by treatment
Phostebupirim (also known as Tebupirimphos)	Oxon	Formed by treatment
Profenofos	None	na
Terbufos	Sulfone, Sulfoxide	Combined residues
Tribufos	None	na

i. Parent Chemicals and Uses

The drinking water exposure assessment includes those OP pesticides with registered outdoor uses that may potentially impact surface- or ground-water sources of drinking water (Table I.E.1). Those pesticides or pesticide uses that are being cancelled and/or phased out as a result of agreements between the Agency and the specific OP registrants, and

those OPs with uses that are unlikely to reach drinking water were not included in the water exposure assessment. Those agreements in place as of May 1, 2002, were considered in this assessment. Revisions since the preliminary assessment in December 2001 include exclusion of fenamiphos and azinphos methyl use on cotton, both of which are being voluntarily cancelled.

ii. Transformation Products

Those OP transformation products identified as being of toxicological concern (Table I.E.1) were included in the cumulative drinking-water risk assessment when environmental fate studies indicate that these products may be formed in the environment or may form as a result of water treatment. Some OP risk assessments did not consider the transformation products quantitatively because no environmental fate data was available, while others assumed that the characteristics of the transformation products were equivalent to that of the parent, or combined limited data with conservative assumptions for a screening assessment.

Sulfoxide and Sulfone Products: The sulfoxide/sulfone products of disulfoton, phorate, and terbufos are often more persistent and mobile than the parent compounds. Full environmental fate profiles are not available for the sulfoxide/sulfone transformation products, requiring some assumptions to be made about their physicochemical properties. The parent OP and two transformation products were modeled as "total toxic residues". Formation and decline curves from aerobic soil-metabolism studies allowed the assessment team to fit a single modeling half-life for the combined residues. However, this required the assumption that all three chemicals were equally toxic, and that the sulfone and sulfoxide had the same soil-water partitioning coefficient as parent.

Oxon Products: Table I.E.1 identifies ten OP pesticides which form oxon transformation products. While the oxons are generally not found at significant levels in the environment, available studies suggest they are formed by water treatment – in particular, through chlorination of the parent OP, as noted earlier. Based on the available studies, OPP assumed that oxons were not formed in the environment and, for the most part, would not be found in signficant levels in untreated drinking water sources. This assumption was supported by the results of the USGS-EPA reservoir monitoring study, in which oxons were detected in the treated water samples but not in samples taken at the drinking water intake.

Transformation To Another Active OP: Acephate transforms to methamidophos and naled transforms to diclorvos (DDVP). For these pesticides, OPP assumed a conversion from one OP to the other based on the maximum percent transformation from available environmental fate studies. Thus, OPP assumed that 25% of applied acephate transformed

into methamidophos and 20% of applied naled transformed into DDVP. The transformed OP as modeled separately, with an application rate that reflected the appropriate percent conversion of the parent OP (with adjustment for differences in molecular weights). The timing of the simulated "application" was off-set by one half-life period. In the case of acephate, this amounted to two days (e.g., the timing of the formation of 25% methamidophos was simulated as occurring 2 days after acephate was applied). Because the half-life for naled was less than 1 day, the 20% DDVP load was assumed to form on the same day as application.

iii. Accounting for Water Treatment By-Products

Limited scientific evidence (section I.E.d) suggests that many parent OP pesticides may be transformed during drinking water treatment, primarily by oxidation through disinfection. The oxidative transformation products of toxicological concern – sulfones, sulfoxides, and oxons – have been detected in treated water. Limited data suggest that these treatment by-products may be stable for sufficient periods of time (for least 24 to 96 hours) to move through the distribution system.

The information is not sufficient to make quantitative adjustments to the cumulative exposure estimates. OPP estimated maximum potential impacts to determine whether additional information is needed by assuming that all OP parents that form oxons, sulfoxides, or sulfones (see Table I.E.1) are completely transformed into those products as a result of oxidation. Where the transformation is less than complete, and where non-toxic products are also formed, the such an assumption will overestimate drinking water exposure. For a preliminary evaluation, OPP did not assume removal of any of the other OP parent pesticides. OP assumed that the sulfoxide and sulfone products are equal in toxicity to the parent and that the oxon products are ten times more toxic than the parent. A comparison of the RPFs for dimethoate (0.32) and omethoate (0.96), the oxon of dimethoate, suggests that this assumption would be protective. The impacts are addressed in the risk characterization (I.G).

b. Regional Approach for the Cumulative Water Exposure Assessment

The Agency used a regional approach as a first step in addressing the impacts of regional and localized variability in site, environmental, and management practices that effect pesticide concentrations in water. The USDA Farm Resource Region map (Heimlich, 2000) provided a framework for focusing the cumulative assessment (see Appendix III.E.10). By providing general groupings according to similarities in key environmental factors affecting runoff and leaching, such as precipitation, irrigation practices, and soil types, these farm resource regions provide a framework for identifying one or more locations which represent an area of the greatest concern for

drinking water exposure in each region. In this way, the Agency chose a set of locations to represent drinking water sources throughout the US.

Within the regions, drinking water exposure will vary locally due to OP use, agricultural practices, nature and vulnerability of drinking water sources, and weather patterns. Thus, the water exposure assessment focused on one or more specific geographic areas within each region in a manner that would be realistically protective of all sites within the region. OPP selected locations where OPs in drinking water sources are likely to be of concern. If OP levels in water from these vulnerable sites are not major contributors to the total regional cumulative OP exposure, then the Agency can reasonably conclude that drinking water exposures will not be a concern in other, less vulnerable, portions of the region. If drinking water exposure from one or more of these vulnerable sites is a significant contributor to the total cumulative exposure, then additional assessments are necessary to characterize the extent of the potential exposure.

Based on results of the preliminary cumulative risk assessment, OPP has condensed the twelve farm regions into seven regions (Figure I.E-3). Table I.E-2 compares the combined regions with the original regions.

Table I.E-2. New and Old Regions and Representative Vulnerable Sites Used in the Cumulative Water Exposure Assessment

New Region	Old Region	Representative Vulnerable Site
A - Florida	Fruitful Rim, SE (12)	West Palm Beach Co (FL) *
B - Northwest	Fruitful Rim, NW (10)	Willamette Valley (OR) *
C - Arid/Semiarid West	Fruitful Rim, SW (7)	Central Valley (CA) counties of (a) Merced, San Joaquin, Stanislaus * (b) Fresno, Tulare, King, Kern
	Basin & Range (8)	none (Red R. Valley surrogate)
D - Northeast/ Northcentral	Northern Great Plains (3)	Red River Valley (ND/MN) *
	Heartland (1)	Central IL
	Northern Crescent (2)	Southcentral PA
E - Humid Southeast	Southern Seaboard (6), east	Coastal Plain, northern NC *
	Eastern Uplands (5), east section	Western NC
F - Lower Midwest	Prairie Gateway (4)	Central TX Hills *
	Fruitful Rim, TX (11)	Central TX Hills (surrogate)
G - Midsouth	Mississippi Portal (9)	Northeast LA, west-central MS *
	west sections of E. Uplands, S. Seaboard	none

* Scenario used to represent new region in revised OP cumulative risk assessment.

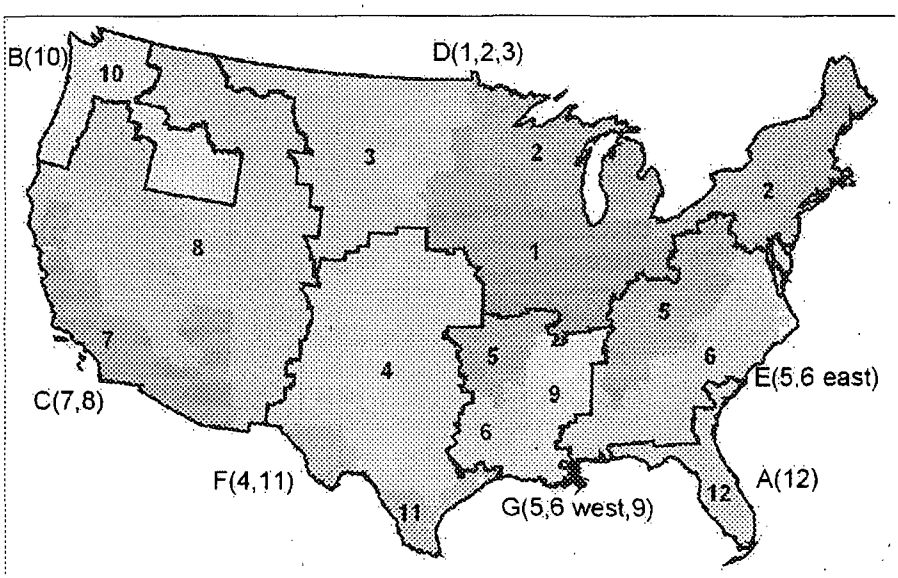


Figure I.E-3. Regions used in OP Cumulative Risk Assessment, based on USDA Farm Resource Regions

c. Selection of Regional Water Exposure Assessment Locations

The selection of a specific location for regional drinking water assessments involves several steps. First, OPP identified the high OP usage areas and high agricultural intensities within each region; these are shown on a national scale in Figure I.E-4. Next, in each high usage area within the region, OPP determined the types and locations of drinking water sources. The final step in choosing a location is to assess the vulnerability of drinking water sources within the high usage area within the region. OPP adapted vulnerability schemes proposed by Kellogg and others at USDA for this purpose. Locations of surface drinking water intakes overlain on runoff vulnerability maps (Figure I.E-5) were compared with the OP use areas to determine whether potentially vulnerable surface water sources of drinking water coincided with high use areas. For ground water, OPP compared OP use areas with a pesticide leaching vulnerability map (Figure I.E-6).

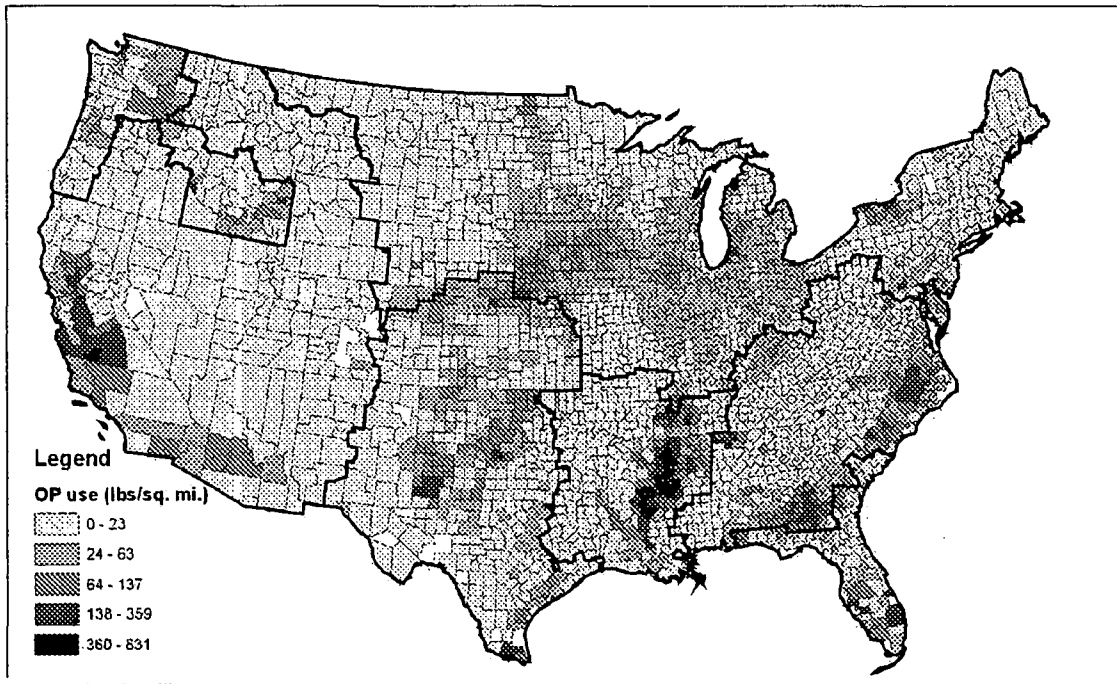


Figure I.E-4. Total organophosphorous (OP) pesticide usage on an area-weighted basis, showing high-use areas in each region.

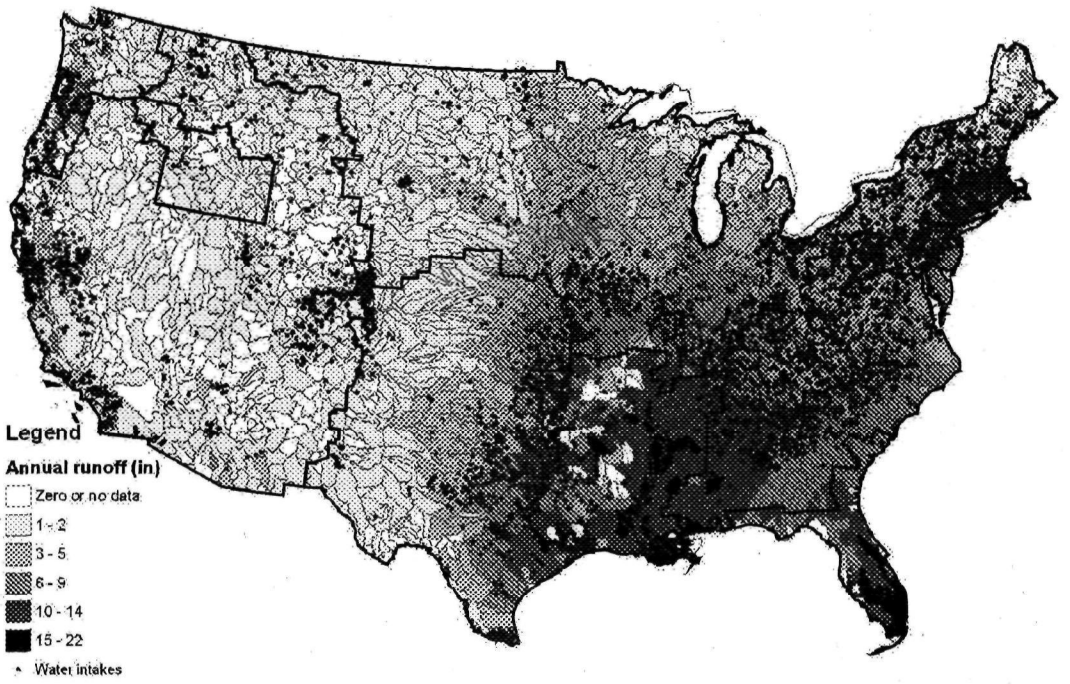


Figure I.E-5. Runoff vulnerability (in/year), adapted from USDA (Kellog, 1998)

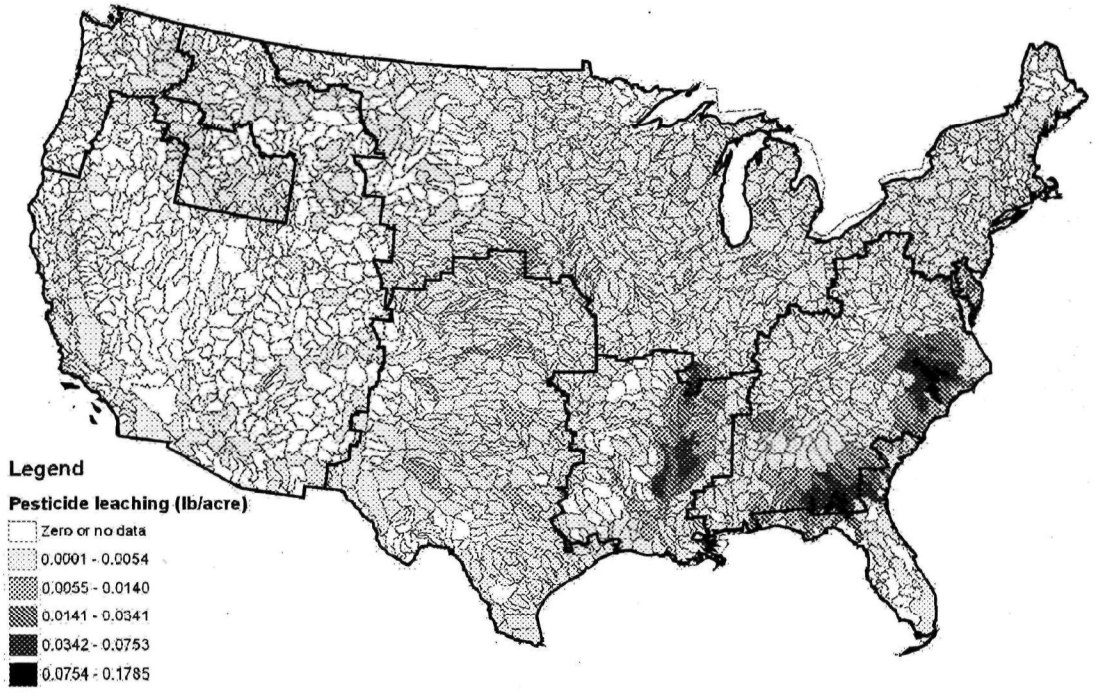


Figure I.E-6. Pesticide leaching vulnerability, adapted from USDA (Kellogg, 1998)

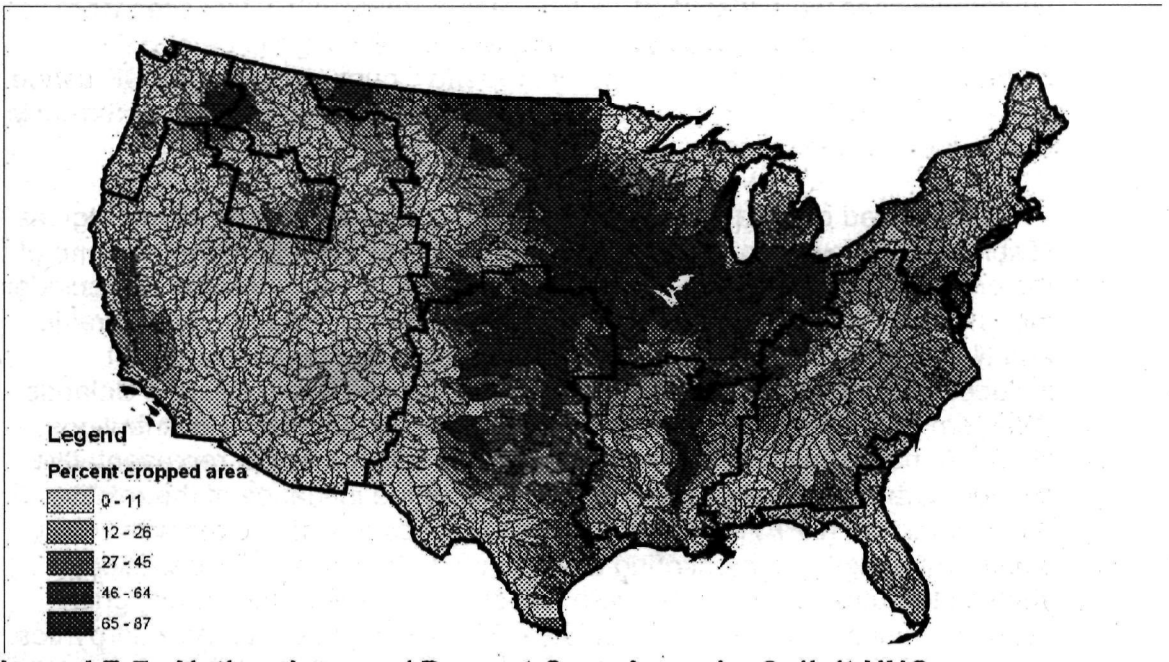


Figure I.E-7. National map w/ Percent Crop Areas by 8-digit HUC

Details of this process are provided in each regional assessment. The Northwest region (Region A) illustrates this process. Three OP-use areas stand out in the region (Figure I-E-4): Yakima County and eastern Washington are the highest OP use area (predominantly on orchards) and highest percent crop area (Figure I-E-7). The Snake River Valley in Southeast Idaho is the second highest use area (predominantly on potatoes, sugar beets). The Willamette Valley, Oregon, is the third high-use area, with a mix of OP uses. Ground water is the predominant source of drinking water in Idaho and eastern Washington, with vulnerability to leaching potentially higher in eastern Washington. A few surface-water intakes occur in the Yakima County area; the Willamette Valley has more surface water intakes and is more vulnerable to runoff. Available monitoring from NAWQA study units in Willamette Valley, Snake River Basin, and Pugett Sound suggest that Willamette Valley will be more vulnerable to OP contamination with a higher potential for co-occurrence of multiple pesticides.

OPP based its surface water assessment for the Northwest Fruitful region in the Willamette Valley in Oregon. We also looked at potential impacts of OP pesticides on ground water resources in eastern Washington and southeast Idaho, relying largely on ground-water monitoring available through the USGS NAWQA program and state monitoring programs.

In the preliminary cumulative risk assessment, OPP selected eleven vulnerable drinking water sources for the drinking water exposure assessment (Table I.E.2). Each of the 12 USDA regions had a representative vulnerable site except for the Prairie Gateway and Texas Fruitful Rim, which shared the same Central TX Hills site, and the Basin and Range, where no

vulnerable sites were identified. In the Central Valley (CA), two sites were identified: (a) Fresno County and south, where OP usage is among the highest in the country, and (b) north of Fresno County, where total OP usage is lower, but surface water sources are more vulnerable to runoff, particularly during the dormant season.

This revised cumulative risk assessment combines several of the regions (Table I.E.2). However, only two combined regions include more than one of the original vulnerable sites. The Northeast/ Northcentral Region (D) includes the original Northern Great Plains (Red River Valley), Heartland (Central IL), and Northern Crescent (Southcentral PA) sites. The Humid Southeast includes the original Southern Seaboard (Eastern NC) and Eastern Uplands (Western NC) sites. OPP compared the estimated cumulative distributions, NAWQA monitoring results, and OP usage to select a single representative site for each of these new regions. Because of the influence of the relative potency factors (RPF) in the cumulative OP loads in water, sites with significant usage and monitoring detections of the higher-RPF pesticides, such as terbufos and phorate, were selected over sites which had higher uses and monitoring detections of lower-RPF pesticides such as chlorpyrifos, diazinon, and malathion. These comparisons are discussed in the regional assessments in Part II.

d. Estimate of Pesticide Concentrations in Drinking Water Sources Within Each Region

After considering several predictive tools, the Agency adapted its paired PRZM and EXAMS models for the Index Reservoir (PRZM-EXAMS IR) to estimate a distribution of daily drinking water concentrations that could be used for multiple chemicals over several years of predictions across the country. PRZM-EXAMS IR has been modified to calculate concentrations in a small drinking water reservoir in a primarily agricultural watershed. PRZM-EXAMS has the capability of predicting water concentrations over a number of years based on collected historical weather data for the sites which are being modeled.

The PRZM component of the model is designed to predict the pesticide concentration dissolved in runoff waters and carried on entrained sediments from the field where a pesticide has been applied into an adjoining edge-of-field surface water body. The model can simulate specific site, pesticide, and management properties including soil properties (organic matter, water holding capacity, bulk density), site characteristics (slope, surface roughness, field geometry), pesticide application parameters (application rate, frequency, spray drift, application depth, application efficiency, application methods), agricultural management practices (tillage practices, irrigation, crop rotation sequences), and pesticide environmental fate and transport properties (aerobic soil metabolism half-life, soil:water partitioning coefficients, foliar degradation and dissipation, and volatilization). OPP selects a combination

of these different properties to represent a site-specific scenario for a particular pesticide-crop regime.

The EXAMS component of the model is used to simulate environmental fate and transport processes of pesticides in surface water, including: abiotic and biotic degradation, sediment:water partitioning, and volatilization. Currently, OPP is using an index reservoir as the benchmark surface water body for drinking water exposure assessments.

For each component, the values used are derived from real world data. Pesticide environmental fate properties used in the modeling come from registrant-submitted data used for pesticide registration or reregistration. The values used for soil properties and site characteristics are chosen from real world databases appropriate for the sites on which the pesticide may be used. For example, if the pesticide is approved for use on cotton, OPP uses data reflecting the soil types in the Cotton Belt. The index reservoir being modeled is based on and represents an actual, small flow-though reservoir used for drinking water. Finally, the weather inputs for the model are taken from regional specific weather data, based on the USDA Major Land Resource Areas. PRZM modeling is generally simulated for 20 to 36 years in order to calculate a return frequency of concentration in surface water body. Further information on how the Index Reservoir model is used for screening-level drinking water assessments of individual pesticides can be found in the EPA Environmental Fate and Effects Division's pesticide science policy paper, "Guidance for Use of the Index Reservoir Guidance for Use of the Index Reservoir in Drinking Water Exposure in Drinking Water Exposure Assessments."

Running the assessment with historical data for several years provides more confidence that variations due to weather have been considered in the assessment. Having the historical weather data, pertinent site information and reported use histories allows the Agency to factor regional variations into the assessment. With this method, multiple chemicals which have varying uses and application factors are assessed and co-occurrence is realistically accounted. Since the day by day component is retained, this distribution can easily be paired with residues resulting from residential applications.

The PRZM-EXAMS/IR tool has been used in many of the individual assessments to predict a reasonable high end screening concentration to factor into the aggregate assessment. However, the cumulative assessment focuses on the probability or likelihood a person will be concurrently exposed to multiple pesticides from food, water, and residential use. The method which was used in the aggregate assessments has been modified in several ways to focus on the probability of co-occurrence from the various routes.

The most significant change in terms of predicted exposure is that the entire range of PRZM-EXAMS/IR output is used for the probabilistic distribution. In other words, instead of choosing a single value at the upper end of the distribution to represent the exposure, all daily concentration values are used in the CALENDEX runs.

The cumulative assessment modeling used "typical" application rates with typical numbers of applications instead of labeled maximum rates and maximum numbers of applications which were used in the individual chemical assessments. While this is reflective of the "typical" condition, it does not reflect potential concentrations that may occur when the pesticide is used at maximum rates because of pest pressure.

The drinking water assessments for cumulative are regional in nature. This allows EPA to make informed judgements about when compounds co-occur and when they compete. Overall, the assessment is much more realistic on a regional basis. Scenarios chosen for regional assessments are reflective of regional differences in cropping and pesticide use as well as differences in run-off and leaching vulnerability.

i. Cumulative Adjustment Factors for Crop Area and OP Use

PRZM is a field-scale model, while the OP cumulative water assessment focuses on watershed-scale impacts (i.e., the contributions of multiple OP uses on multiple crops occurring in multiple fields in a watershed). In individual chemical assessments, PRZM is used to simulate a watershed. In the OP cumulative assessment, the Agency used PRZM to model multiple fields in a watershed. While this approach provides a more realistic depiction of multiple chemical usage in a watershed, it still has limitations. PRZM can simulate multiple fields, but provides no spatial context for those fields. It also assumes that the runoff from each of those fields goes into the reservoir. In other words, each field is assumed to be uniformly distributed in the watershed, with no distinction made between those fields located in the upper reaches of the watershed and those near the reservoir.

To adapt PRZM for this watershed approach, OPP must adjust the estimated pesticide concentrations to account for the portion of the watershed that is treated by a particular OP. This was done using a Cumulative Adjustment Factor (CAF), which accounts for the percentage of the watershed that is planted to a particular crop and the fraction of those acres which receive OP applications.

The CAF accounts for the percent of the location area planted to crops and treated with the corresponding OP pesticides. The CAF is based on several different data sources. The Agency used the USGS 8-digit Hydrologic Unit Codes (HUCs) to delineate watersheds, and the National

Agricultural Census for 1997, reported on a county basis, to identify areas planted to agriculture. This procedure was presented to OPP Science Advisory Panel (available through the Agency web site at http://www.epa.gov/scipoly/sap/1999/may/pca_sap.pdf) and is described in an OPP science policy paper (available through the Agency web site at http://www.epa.gov/oppfead1/trac/science/reservoir.pdf). Percent crop area values were calculated for each region. To determine the total acres planted for each crop within the selected location, the Agency used the most recent county level production statistics, generally taken from USDA publications. And finally, to calculate the area treated by the various OPs, the most recent percent of crop treated estimates, generally taken from USDA\NASS publications were applied.

In addition to primary USDA publications, various other data sources (California Department of Pesticide Regulation, Pesticide Use Reporting Data, academia publications) were used to obtain acres planted and acres treated estimates.

The following example (Table I.E-3) illustrates how CAFs are calculated and applied. Suppose, that after reviewing the various data (drinking water source, vulnerability, crop production, pesticide use, and monitoring data), a location (one or several counties) is identified around which the drinking water assessment is conducted. The total area for this location is 800,000 acres; agricultural cropland accounts for 600,000 acres of this total area, and 320,000 acres of the agricultural cropland are planted to four crops (corn, alfalfa, beans and apples) that are treated with OP pesticides:

Table I.E-3. Cumulative Adjustment Factor Illustration: Deriving Cumulative OP Percent Crop Area

		Acres	Percent of area	PCA
Total Area		800,000		
Crop Area, All Agricultural Uses:		600,000		75%
OP Uses in Region:	Corn	200,000	25%	
	Alfalfa	80,000	10%	
	Beans/legumes	16,000	2%	
	Apples/pome fruit	24,000	3%	
Total OP Use Area		320,000		40%

Further, suppose that 4 different pesticides are used on each of the 4 crops (some pesticides are used on more than one crop). Acres treated represent the total number of acres of the crop that were treated with each pesticide (may represent more than one application). Following the numerical example above, if 60,000 acres of field corn were treated with pesticide A, then the CAF for this particular use (field corn-pesticide A) is 0.075, or:

$$CAF_{Corn\text{-}OP(A)} = (Total\ Acres\ Planted_{All\ OP\ Crops} / Total\ Acres) \times (Acres\ Treated_{Corn\text{-}OP(A)} / Acres\ Planted_{All\ OP\ Crops})$$
$$= (320{,}000 / 800{,}000) \times (60{,}000 / 320{,}000) = 0.075$$

Table I.E-4. Cumulative Adjustment Factor Illustration: Individual Crop-Pesticide Factors Used for Conversions.

Crop	Pesticide	Acres Treated	Cumulative Adjustment Factor
Corn	A	60,000	.075
Corn	B	1,000	.00125
Corn	C	500	.000625
Corn	D	40,000	.05
Alfalfa	A	16,000	.02
Alfalfa	B	4,000	.005
Alfalfa	E	10,000	.0125
Alfalfa	F	8,000	.01
Apples	A	10,000	.0125
Apples	F	15,000	.01875
Apples	G	6,000	.0075
Apples	H	6,000	.0075
Beans	B	16,000	.02
Beans	E	1,000	.00125
Beans	I	16,000	.02
Beans	J	2,000	.0025

Again, these CAF are applied to the model is run for a particular chemical:crop combination. In this manner, since the use statistics come from reported data, competing and compatible uses are accounted for by summing the appropriate distributions across days after the RPFs are applied.

ii. Relative Potency and Safety Factor Adjustments

The resulting CAF-adjusted concentrations for each OP-crop combination must be converted to a concentration equivalent for an index chemical. Once this is done, the concentrations can be combined into a single set of daily distributions (spanning multiple years) for each region. The concentrations were normalized to methamidophos equivalents using the relative potency factor (RPF) and safety factor. This normalized output for each chemical:crop combination was summed day by day to give a single distribution of potential combined water residues for the region.

Factors to convert from individual to cumulative distributions:

$$Cv_{(OPx,CROPz)} = C_{(OPx,CROPz)} \times CAF_{(OPx,CROPz)} \times RPF_{(OPx)} \times SF_{(OPx)}$$

where

$Cv_{(OPx,CROPz)}$ is the converted concentration for OPx on CROPz
$C_{(OPx,CROPz)}$ is the raw PRZM/EXAM daily concentration
$CAF_{(OPx,CROPz)}$ is the cumulative adjustment factor
RPF is the Relative Potency Factor
SF is the FQPA Safety Factor

e. Pesticide Usage Information

The estimated OP cumulative distributions in each region are based on typical application rates and numbers of applications (taken as the average of rates reported in pesticide usage summaries). The timing of pesticide applications was based on label specifications (e.g., apply at plant, at harvest, at blossom) and locally-derived windows of use based on crop profiles.

USDA National Agricultural Statistics Service (NASS) and other published survey instruments provided the bases for the OP usage patterns described for all regional surface location examined. These state-level snapshots of pesticide practice are, of necessity, limited in time and scope. Usage patterns change continually to reflect OP label amendments and the availability of alternatives which include other, non-OP classes of pesticides and cultural, non-pesticidal control options. Moreover, state survey data is at a level of refinement somewhere between maximum label rates and frequencies and actual agronomic practice in specific location. And, of course, surveys are only as good as the number and quality of responses that educate the derived estimates. With these reservations in mind, this

approach was undertaken to provide transparent modeling scenarios using the best currently available data.

i. Typical Pesticide Use (Rate and Frequency)

For regions exclusive of the Arid/Semiarid West, the primary sources of information for percent crop treated, number of applications, and amount of active ingredient applied are NASS Agricultural Chemical Usage summaries. These documents provide data for selected crops in selected states; they are published annually for field crops and biennially for vegetables and for fruits and nuts. Vegetable chemical usage summaries are reported for even years; fruit and nut chemical summaries are reported for odd years. The years 1997-2000 were reviewed for field crops, 1998 and 2000 for vegetables, and 1997 and 1999 for fruits/nuts. The most recent summary data is cited for state/crop combinations appearing in the cumulative surface water assessments. Citations follow the format: "NASS, 2000 Vegetable Summary."

In a given NASS summary, specific OP pesticides may be noted, by use of an asterisk, as being applied to a crop but no usage data is provided. This situation arises where the number of individuals reporting use of the specific OP is so small (i.e., fewer than five) that respondent confidentiality could be compromised through data disclosure. In such instances, an earlier summary has been consulted.

NASS data were not available for all specific chemical/state/crop combinations examined. In some cases, additional survey instruments were consulted. All usage data sources are documented at their occurrence in the regional summaries.

OPP used the average application rate reported in the NASS summaries to represent the typical application rate for each OP-crop combination in a region. Likewise, OPP used the average number of applications to determine how many times the OP pesticide would be applied to the crop in a particular year. These rates were frequently less than the maximum allowable application rates and frequencies specified on the label. A comparison of OP cumulative distributions estimated by typical and maximum label rates in three regions found that use of all maximum rates generates concentrations that are one to four times greater than those estimated using typical rates (see I.G. and Appendix III.E.11 for detailed analysis). In reality, it is unlikely that all OP pesticides would be used on all crops at maximum rates in the same year. Thus, the difference between OP cumulative loads in a "typical" year and in a year when intense pest pressure requires maximum label rates for one or more OP pesticide on one or more crops is likely to be less than the one- to four-times estimated.

ii. Timing of Pesticide Application(s)

An application window has been established for each of the OP pesticide crop uses reported in each region. This window represents an approximate beginning and ending date for the use of the pesticide on a particular crop. Delineation of these windows was based on review of crop profiles and other relevant crop production publications; surveys such as the Doane Marketing Research, Inc. Agrotrak[tm] reports on agronomic, row and specialty crops; and on consultations with field experts. Unless otherwise noted, the default planting and harvesting dates for crops were taken from the following USDA documents:

- United States Department of Agriculture, Crop Reporting Board, Statistical reporting Service. 1977. Usual Planting and Harvesting Dates for Fresh Market and Processing Vegetables. Agriculture Handbook No. 507.

- United States Department of Agriculture, National Agricultural Statistics Service. 1997. Usual Planting and Harvesting Dates for U.S. Field Crops. Agricultural Handbook No. 628.

These USDA handbooks also provide "most active" periods during the planting and/or harvesting windows. The mid-point of the most-active period was selected as the application date for a pesticide applied at the "planting" stage of crop production. A case in point is the data input for terbufos on corn in North Carolina:

Pesticide	Stage	Application Date	Range	Most Active
Terbufos	Planting	April 17	April 1 - May 20	April 10 - April 25

When most active periods are not provided, the single application date for a pesticide is set at the beginning of the crop stage window. Multiple applications, such as OP cover sprays for tree fruits, are placed at the beginning and equidistant within the application window. The following example is for three cover sprays of phosmet on apples in the Northeast (Pennsylvania):

Pesticide	Stage	Application Dates	Range
Phosmet	Foliar	May 1 June 18 August 5	May 1 - Sep 21 May 1 - Sep 21 May 1 - Sep 21

Because the application dates are held constant through a series of years of weather patterns, variations in the selected date may affect the estimated peak concentrations. Relatively high pulse loads from runoff may occur if application events are closely followed by runoff-producing

rains. However, a comparison of OP cumulative distributions resulting from varying the application dates found that notable differences only occur at the very highest concentrations that distributions at the 99th percentile only vary by a factor of 2 or less (see I.G. and Appendix III.E.11 for discussion).

OPP assumed that the entire application of a given pesticide on a given crop occurred on the same day. Except in Region C, where detailed pesticide use reports from California Department of Pesticide Regulations were available, sufficient usage information was not available to split applications. While this is likely to result in conservative (health-protective) estimates, the assumption is not unreasonable in the smaller, more vulnerable watersheds represented by the index reservoir. A comparison of estimated OP cumulative distributions using split- and single-applications in Region C found a difference of less than a factor of two across the distribution profile (see I.G and Appendix III.E.11 for discussion).

A most likely, or predominant, application method is also designated for each pesticide. The choice is simply "air" or "ground." Review of NASS and proprietary data bases, crop production profiles, as well as consultation with field experts, informed these application method determinations.

iii. Use of CDPR Use Information in Region C

For the Central Valley (CA), used in Region C, the California Department of Pesticide Regulation, Pesticide Use Reporting (PUR) data was used to determine both the acres treated and the application dates. The PUR contains detailed information on every commercial pesticide application made within the State of California. Since the two locations identified and assessed in this region were located in the State of California, the Agency used the PUR data base to calculate the total area treated by each pesticide, on each crop for each date. For some uses, growers reporting making applications on numerous dates (>50 days) throughout the Calendar year. For data management purposes, five application dates were selected for each crop-OP use to be used in the assessment; each application date represents 20% of the total acre treatments made for that particular use.

Evaluations of CDPR and NASS usage information in California found no routine under- or over-estimation of pesticide usage from the survey methods used by NASS. A comparison of OP cumulative distributions generated using both data sources found that the distributions generated with the more complete CDPR information were greater than those generated with the NASS survey data by a factor of 3 (see Appendix III.E.11 for comparison).

f. Incorporate the Drinking Water Exposure Estimate into the Cumulative Assessment

In summary, within each region, a residue file was generated by PRZM-EXAMS/IR for each pesticide:crop combination which was reported in the county or counties selected for assessment. This day-by-day residue file was modified by the CAF specific to that pesticide:crop combination and the relative potency factor for that pesticide. Then, the modified residue files for all pesticide:crop combinations for that location were summed across days to give a distribution of combined daily residues in drinking water.

This distribution of combined daily residues can then be used as an input file for the CALENDEX model which is discussed elsewhere in this document. CALENDEX allows the Agency to combine OP concentrations from water and residential exposures which are time and location dependent with food exposures which are not time and location dependent.

The distribution of daily residues can also be compared to any water monitoring data available for the chemicals and region being examined. Plots of the daily distributions can be analyzed to ascertain which uses may be expected to contribute significant exposures. The comparison of monitoring data and the understanding of which uses contribute to exposure are important aspects of risk characterization of the water portion of the OP cumulative risk assessment.

For each vulnerable site, OPP developed a site-specific scenario for each crop group with reported OP usage (see Appendix III.E.7a and b for a description of scenario development and documentation). Thus, the site and soil characteristics are representative of those that actually occur in the region and support that particular crop growth.

I. Revised OP Cumulative Risk Assessment

F. Cumulative Assessment

1. Introduction

The previous four sections of this document have described the development of the major components of the risk assessment. They describe a highly complex process of combining multiple data sets to develop a description of the possible risks from OP pesticides by each of the pathways described. OPP has had to develop new methods for each component of the assessment in order to produce an assessment which presents as realistically as possible the potential exposure to OP pesticides. The purpose of this section is to explain the concepts used to accumulate risk from each pathway into a total risk estimate, and to provide a basis for understanding the presentations that are provided in Section III for each of the regional assessments.

2. Basic Concepts

The definition of cumulative risk developed as a result of the passage of FQPA requires OPP to conduct a risk assessment for a group of pesticides with a common mechanism of toxicity that is multi-pathway, multi-route, and multi-chemical in scope. As described in section I.B above, the RPF method was used to address the issue of combining toxic responses from OPs with varying propensities to inhibit acetylcholinesterase. Exposure to each OP was normalized to equivalent exposure to the index compound, methamidophos. The toxicity data currently available for conducting this analysis are estimates of response by route-specific dosing, and do not support estimating delivered dose to the target tissue. OPP decided to address this problem by comparing route-specific exposures to route-specific points of departure to produce unitless margins of exposure for each route. In this case, the POD was a BMD_{10}. MOEs were combined by taking the inverse for each route, adding them together, and then taking the inverse of that sum. This process was used to produce a distribution of daily estimates for the subpopulation of concern that reflects regional and seasonal variation in the patterns of exposure that are likely to occur throughout the US across the year. OPP used a probabilistic assessment to capture the full range of exposure possibilities from all sources analyzed. The intent was to produce an estimated range of risk that is as realistic as possible. The OP cumulative risk assessment is not a high end risk assessment. It attempts to reflect the full range of likely exposures for consideration in a regulatory context. However, at the same time it is designed to avoid developing extreme exposure estimates based upon the combination of exposure scenarios and assumptions that are not reasonable.

3. Framing the Population-Based Assessment

OPP focuses its risk assessment on exposure and resulting risk to the population, not to risk to an individual. This distinction is an important one with regard to defining how the components of the assessment will be combined. The current assessment focuses on highlighting inter-individual patterns of exposure instead of attempting to define intra-individual patterns of exposure. OPP made this choice because of the lack of acceptable longitudinal data defining intra-individual behavior for any component of the risk assessment. This issue has been repeatedly discussed at SAP meetings reviewing the conduct of dietary risk assessment methodology. Longitudinal data permitting modeling of the consumption of food and water by the US population is not available. The data describing the use of pesticides in a residential setting is even more uncertain. Although ranges of use parameters are available and have been used in this assessment, they are only adequate to define the behavior of the population across time, and cannot accurately reflect the day to day variability in behavior of an individual. Therefore, OPP decided to develop a series of daily exposure distributions and array them as a distribution across time.

The distribution of daily exposures and resulting MOEs are developed such that the exposures from OPs in foods, drinking water, and from residential uses are all calculated simultaneously for each hypothetical individual in the subpopulation. OPP uses the Calendex software to develop the distributions and resulting MOEs. Calendex permits incorporation of time course information with regard to residential uses of pesticides, but does not permit specific allowance for regional variability. OPP addressed this issue by running separate risk assessments for each of seven regions of the US. The regions correspond to agronomic cropping areas and reflect climatic and soil conditions that are likely to affect pest pressure and resulting pesticide use. Regional differences in pesticide use are major considerations in appropriately estimating exposure from pesticides in drinking water and residential uses.

To generate a daily distribution of exposure, consumption records are selected from the CSFII for each individual in the survey. Calendex uses this consumption record to estimate OP exposure from food by randomly assigning a residue value for each food reported consumed by that individual. After multiplying each amount of food consumed by its selected residue value, the total exposure from food for this individual is calculated by summing the exposures from the individual foods which were reported consumed. At the same time, all appropriate residential scenarios that may be encountered for the calendar day 1 (January 1) are reviewed. A probability-based decision is made as to whether or not that scenario will be encountered (e.g., a lawn treatment would probably not occur in January in the Northeast/North Central region). If the scenario is assigned a "yes" answer (i.e., treatment does occur), then the appropriate values defining the exposure are selected from the many distributions of input parameters for residential exposure scenarios. The exposures for the dermal, oral and inhalation pathways are calculated for all

selected residential scenarios. A drinking water value taken from the PRZM/EXAMS output for January 1 is selected and paired with the water consumption reported in the CSFII consumption record. These values are used to calculated exposure from drinking water for that date. All of the exposures are converted to route-specific MOEs to define the total exposure to the hypothetical individual on January 1. The process is repeated for each consumption record for the age group in the CSFII ten times (i.e., ten iterations) to build a distribution of exposures for January 1. This process is repeated for January 2, January 3 and so forth across the year.

The 365 daily exposure distributions are arrayed together in order to provide a profile of possible exposures by each route and in total as MOEs. An example of such a distribution of distributions is presented in Figure I.F.1. In this figure, each daily distribution is arrayed on the yz plane of the plot. Day 365 can be clearly seen on the right side of the plot. This distribution of total risk is expressed as a cumulative distribution function of MOEs versus percentile of exposure. Percentile of exposure refers to that portion of the population output distribution that has less than or equal exposure. For example, at the 80^{th} percentile of exposure, 20% of the output distribution has an MOE lower than the one at the 80^{th} percentile point on the distribution.

The distribution of daily distributions is used to estimate the potential risk, with accompanying distributions generated for each pathway and route. OPP acknowledges that this approach does not describe intra-individual risk. In all likelihood, the variability in an individual exposure would be much greater than in a population-based approach because of the limited likelihood of repetitive events such as residential pesticide applications. However, the population at large will experience some degree of exposure each day. This factor is a likely source of conservatism in the current assessment.

4. Interpreting the Outputs

The results of the final assessment are presented in tabular (Calendex output) form in the appendices. The reflect year-long slices across the 3-dimensional plot in Figure I.F.1. In that plot, dark lines can be seen across the total MOE surface. For instance, the top line in the 3-dimensional plot represents the 99.9^{th} percentile of exposure for the population. A slice through the surface parallel to the xy plane at the 99.9^{th} percentile would look like the plot presented in Figure I.F.2. This plot presents the potential total MOE for the exposure scenarios included in this assessment. In addition, the contributions from various pathways and routes of exposure are arrayed separately to assist the risk manager in identifying contributors to risk for further evaluation. Other age groups (or percentiles) of exposure may also be of interest. For example, Figure I.F.3 presents the results of the 99.9 percentile assessment for the age group Adults, 20-49.

5. The Rolling Time Frame Approach

One important aspect of the revised cumulative risk assessment for the organophosphate pesticides (OPs) is the manner in which estimated exposure is compared with toxicity endpoints. The above paragraphs detail and describe one "mode" or option of analysis (termed the *single consecutive day* option) in which separate, independent estimates are made for each day of the year (January 1, January 2, etc.). As discussed above, these can be arrayed into an exposure timeline for any selected percentile (and graphed, if desired). That is, for example, the estimated 99.9th (or any other percentile) percentile exposure value is calculated by DEEM/Calendex for each day of the year from January 1 through December 31. These represent independent daily estimates of the 99th percentile exposures on each day of the year and do not necessarily represent the same individual on consecutive days[1]. Thus, it is NOT possible (with this mode of analysis) to interpret an extended period (or series) of elevated exposures over time as necessarily representing extended exposures to the *same* individual, and comparison of any estimated exposure to multi-day endpoints (e.g., a multi-day BMD_{10} would be expected to provide a very conservative estimate of risk to the extent that exposures on consecutive days at any given percentile are unlikely to be the same individual.

[1] For example, biomonitoring data from CDC and others indicate that a sizeable percentage of the U. S. population has measurable levels of OP metabolites in their urine or blood.

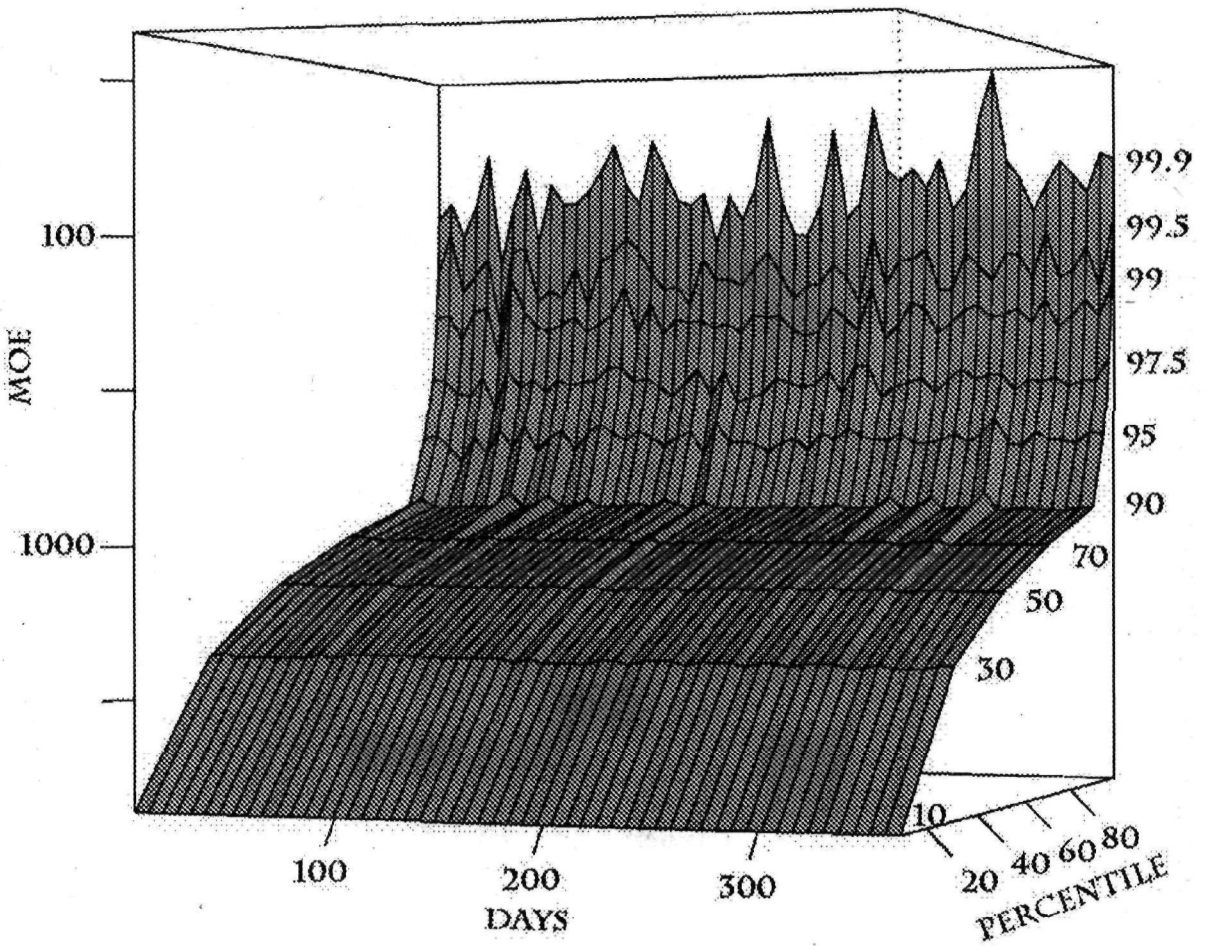


Figure I.F-1. Three-dimensional plot of the total MOE by day of the year and percentile of exposure

Figure I.F-2. Cumulative Assessment - 99.9th Percentile Estimate for Children Ages 1-2 Years for All Routes and Pathways

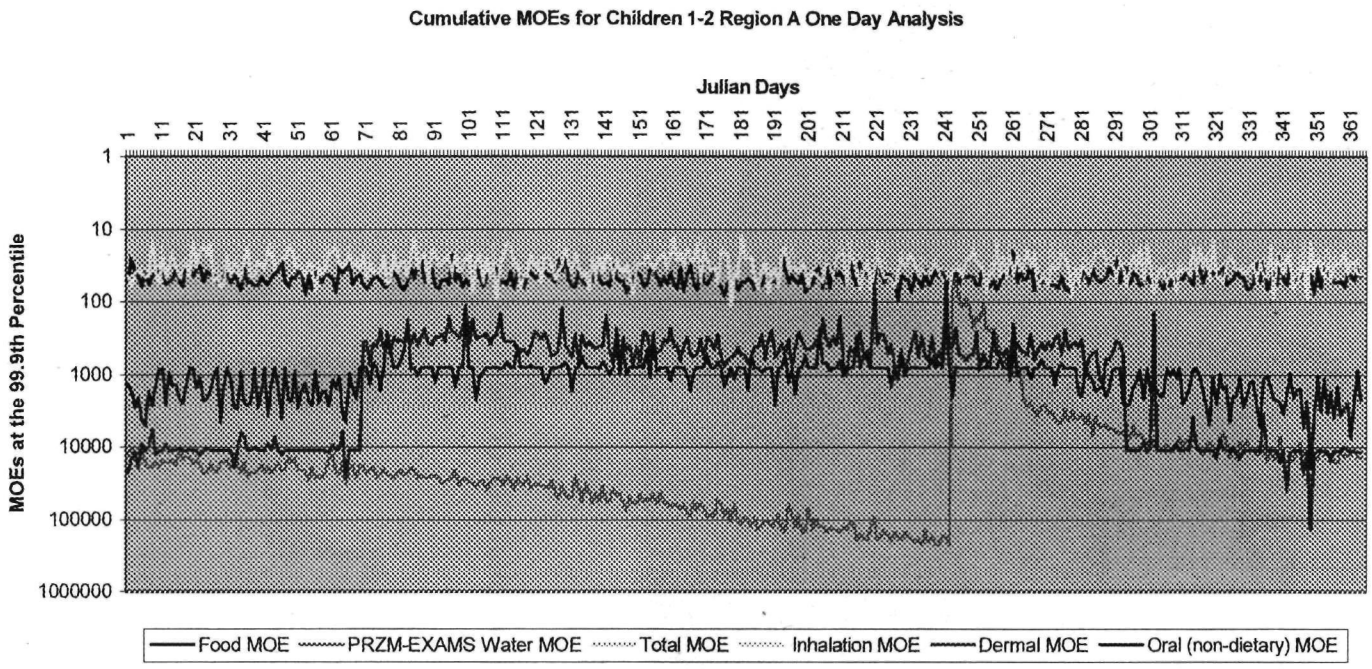
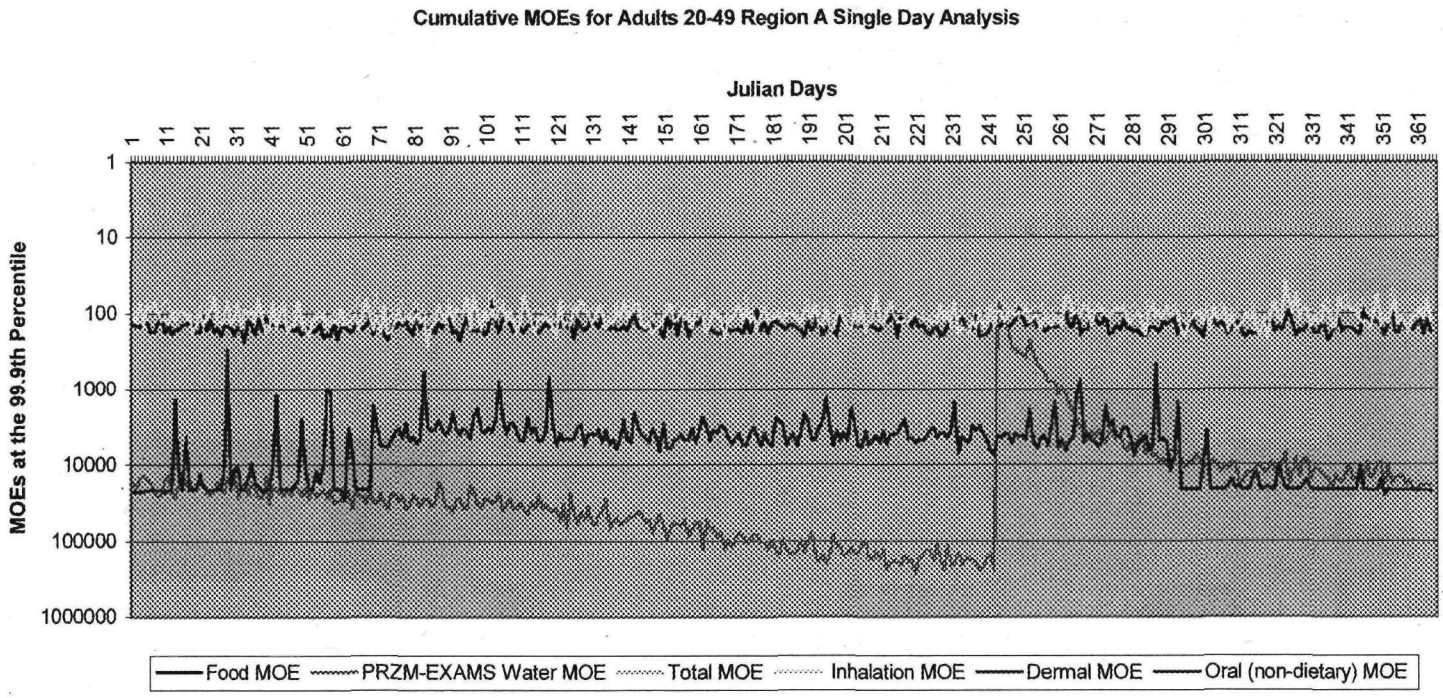


Figure I.F-3. Cumulative Assessment - 99.9th Percentile Estimate for Adults 20-49 Years for All Routes and Pathways



The DEEM/Calendex program can perform analyses under a second option. Under this second option (termed the *multiple sequential day option*), a rolling (or sliding) time frame is used and multi-day average exposures are calculated for each individual (e.g, average exposures for each individual for January 1 through January 7, January 2 through January 8, etc.). Under this mode, average exposures over multiple consecutive days (e.g., January 1 through 7, January 2 through 8, etc.) are assessed for the same individual. It is then this distribution of multi-day average exposures at any given percentile which serves as a basis of comparison with the (multi-day) BMD_{10}. An example graph of this is presented in Figure I.F-4 which shows a seven day rolling average exposure profile for Children 1-2.

In the Preliminary Cumulative Risk Assessment, exposures were estimated on a single-day basis (the first option) and a comparison made of each independent DEEM-estimated single-day exposure with the steady-state (21 day) equilibrium BMD_{10} value That is, separate exposure estimates were made for January 1, January 2, etc. for each individual in the CSFII survey *for each (single) day of the year* with exposure at a given percentile (e.g., 99th) calculated and compared to a multi-day BMD_{10}. In viewing these results, and despite their one-day exposure basis, OPP is NOT concerned with exposure spikes lasting only one or perhaps a few days since the MOE's associated with these "spikes" are based on multi-day toxicity endpoints. Rather, OPP is interested in extended periods of high exposure (or, equivalently, low MOEs) which indicate not that an *individual* is being exposed to high levels of OP pesticides over a multi-day time period, but instead that the overall level of exposure to the sub-population in the tails of the distribution has increased. This is an important distinction which brings up two issues:

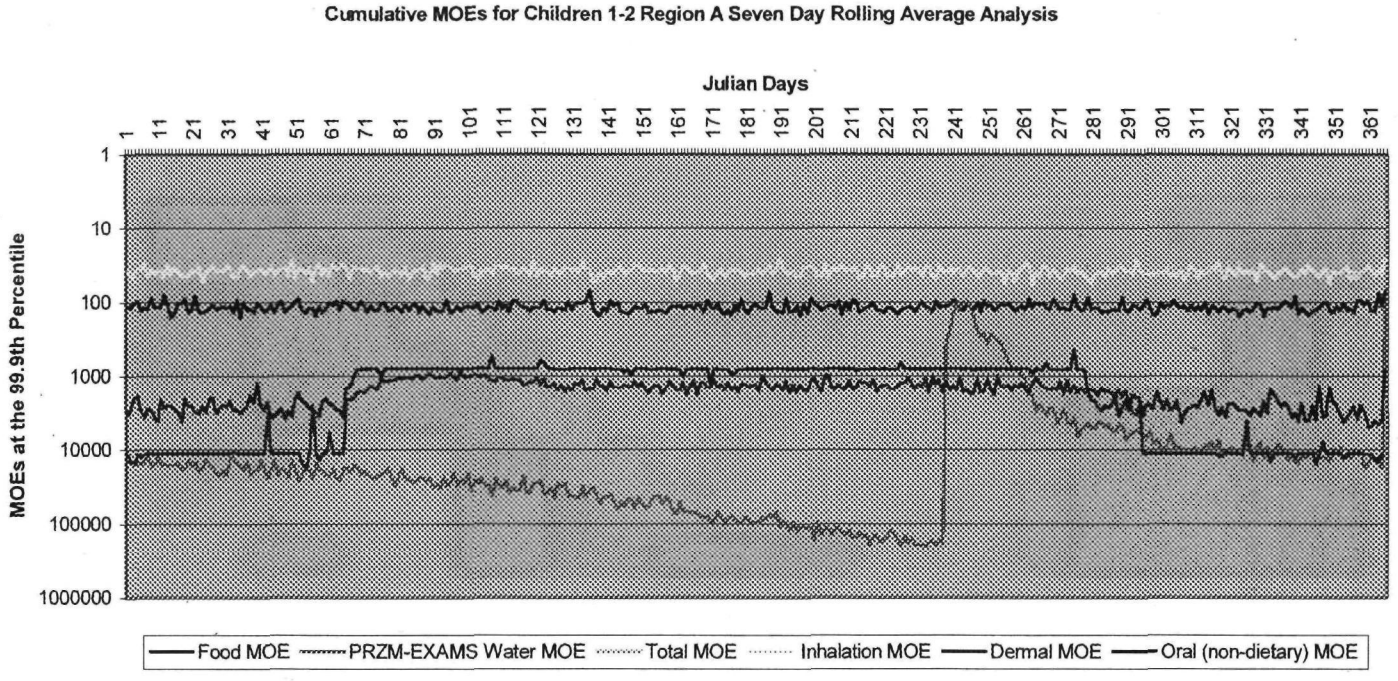
- comparing a series of elevated single-day exposures to multi-day endpoint may have less relevance than comparing a multi-day average exposure (at any given percentile) to a multi-day endpoint.

- Consecutive single-day estimates of exposure are likely to significantly overestimate multi-day exposures to an individual (at higher percentiles) e.g., the 99.9th percentile individuals are unlikely to be the same individual on consecutive days.

An alternative option – which was explored and incorporated into this revised CRA and supplements the *single consecutive day option* – is to estimate multi-day rolling average exposures in which average exposures over multiple consecutive days (e.g., January 1 through 7, January 2 through 8, etc.) are assessed for the same individual. It is this multi-day average exposure which then serves as a basis of comparison with the (multi-day) BMD_{10}. There are a number of advantages to this alternative. In addition to providing a means of estimating exposure which is more directly comparable to a multi-day endpoint, the multiple sequential day mode of analysis better incorporates variability in exposure for an individual across multiple days and is likely to provide a more

realistic estimate of exposures for individuals across multiple days. It is also flexible with respect to matching time-frame associated with BMD10 in that multi-day averages can be calculated over 7, 14, 21, or 28 days. However, as discussed in the February 2002 Scientific Advisory Panel meeting associated cholinesterase inhibition level will be underestimated if one fails to allow for the residual (or lingering) cholinesterase inhibition effect from those previous days in cases where a day's exposure is preceded by nonnegligible exposures on previous days.

Figure I.F-4. Cumulative Assessment - Seven Day Rolling Average 99.9th Percentile Estimate for Children Ages 1-2 Years for All Routes and Pathways



I. Revised OP Cumulative Risk Assessment

G. FQPA Safety Factor

1. Introduction

There is currently a significant focus on the potential susceptibility and increased sensitivity of infants and children to toxic effects of chemicals (see National Resource Council's 1993 report, *Pesticides in the Diets of Infants and Children*). The Food Quality Protection Act of 1996 (FQPA) instructs the U.S. Environmental Protection Agency (EPA or the Agency), in making its "reasonable certainty of no harm" finding, that in "the case of threshold effects, . . . **an additional tenfold margin of safety** for the pesticide chemical residue and other sources of exposure shall be applied for infants and children to take into account **potential pre- and postnatal toxicity and completeness of data with respect to exposure and toxicity to infants and children**." Section 408 (b)(2)(C) further states that "the Administrator may use a different margin of safety for the pesticide chemical residue only if, on the basis of reliable data, such margin will be safe for infants and children."

a. Guidance Used for Consideration of the FQPA Safety Factor

EPA's Office of Pesticide Programs (OPP) has recently released revised guidance addressing application of the FQPA safety factor provision in risk assessments for individual pesticide chemicals (USEPA, 2002a). Additionally, OPP has prepared a separate guidance document addressing the application of the FQPA safety factor provision in the context of cumulative risk assessments for two or more pesticides sharing a common mechanism of toxicity (USEPA, 2002b; released February 28, 2002 for a 60-day comment period). Both FQPA safety factor guidance documents (USEPA, 2002a,b) were used to provide general guidance on applying traditional uncertainty factors and on implementing the FQPA safety factor provision for the cumulative risk assessment of organophosphorus (OP) pesticides. In implementing the FQPA safety factor provision, key considerations in a cumulative risk assessment are:

- Determining the completeness of the data with respect to effects that may occur in the young due to the common mechanism of toxicity;
- Evaluating the degree of concern regarding the potential for pre- and postnatal effects associated with the common mechanism of toxicity and determining the residual uncertainties not addressed by application of traditional uncertainty factors to account for deficiencies in the toxicity data; and
- Determining the completeness of the exposure database for all pertinent pathways of exposure to OP pesticides.

b. Scope of Analysis on Sensitivity and Susceptibility

Single-chemical risk assessments should generally be conducted for each member of a common mechanism group before a cumulative assessment is attempted. Thus, previous determinations have been made whether to retain or replace the FQPA 10X safety factor for the individual pesticide members of the OP cumulative risk assessment group. These FQPA safety factor decisions should be revisited, however, in the cumulative risk assessment process because they are based on broader considerations of potential toxic effects in the young (*e.g.*, teratogenicity, carcinogenic effects) that may not relate to the common mechanism of toxicity. A cumulative risk assessment differs from the single-chemical risk assessment both in focus and purpose. The cumulative risk assessment of the OP pesticides is based on their ability to target and inhibit the enzyme acetylcholinesterase (AChE) in nerve tissue, in other words, the common mechanism of toxicity for which these pesticides are grouped. Thus, decisions on the FQPA safety factor for the cumulative assessment group (CAG) reflect considerations that pertain to the common effect and the common mechanism of toxicity.

Several years ago, the International Life Sciences Institute/Risk Sciences Institute (RSI) convened an expert panel to address whether the OP pesticides act by a common mechanism of toxicity (Mileson *et al.*, 1998). Although some OP pesticides may act by several different neurotoxic mechanisms through interaction with other esterases and nonesterase targets (for review see Pope and Liu, 2001), there are insufficient data to support subgrouping of the OP pesticides based on other actions operating instead of, or in addition to, the inhibition of AChE. It should be pointed out that these other mechanisms are considered in the individual risk assessments of the OP pesticides when there is sufficient available information. For example, in evaluating the susceptibility of the young to chlorpyrifos, OPP considered data that showed effects on the developing rat brain such as structural defects and changes in macromolecular synthesis, neurotransmitter levels, and cell signaling. Although these other neurodevelopmental mechanisms are considered in the single chemical assessment, they will only be considered in the cumulative analysis as they relate to AChE inhibition. Because AChE inhibition is the mechanism of toxicity and precursor event to toxicity, functional effects in the young that result from the inhibition of AChE activity should not occur at doses lower than those causing AChE inhibition.

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2. Hazard Assessment: Sensitivity and Susceptibility[1]

The hazard assessment, below, considers the potential pre- and postnatal developmental effects that may be associated with the inhibition of AChE, the comparative AChE inhibition between adults versus the immature animal, and the completeness of toxicity data on AChE inhibition in young animals.

a. Role of Acetylcholinesterase in Neurodevelopment

AChE is the enzyme that hydrolyzes the neurotransmitter acetylcholine at cholinergic synapses and neuromuscular junctions. The inhibition of AChE leads to accumulation of synaptic acetylcholine, overstimulation of postsynaptic cholinergic receptors and consequent signs of neurotoxicity or cholinergic toxicity. It has been suspected, however, for more than 25 years that AChE may have an extrasynaptic, noncholinergic role during development (*e.g.*, Karczmar *et al.*, 1973; Drews, 1975). Recent research indicates that the roles of AChE during development center around neurogenesis, cell adhesion and possibly stress response (*e.g.*, Layer and Willbold, 1995; Grisaru *et al.*, 1999; Bigbee *et al.*, 1999; Brimijoin and Koenigsberger, 1999). Moreover, the widespread expression of AChE is often mirrored by the expression of acetylcholine, which is involved with basic developmental processes such as mitosis, cell-to-cell contact, cell adhesion, cell differentiation, and organization of the cytoskeleton (reviewed in Wessler *et al.*, 1999; Lauder and Schambra, 1999).

Both AChE and acetylcholine are highly conserved molecules which have multiple roles in the developing nervous system as well as extraneuronal functions. Because AChE controls acetylcholine levels in neuronal as well as extraneuronal tissues and blood (*e.g.*, Wessler *et al.*, 1998; Fujii and Kawashima, 2001; Kirkpatrick *et al.*, 2001) and because AChE activity is more commonly measured as compared to acetylcholine levels, most of the work reviewed below concentrates on changes in AChE activity rather than acetylcholine levels. One may assume, however, that as mentioned above, a decrease in AChE activity should also increase acetylcholine concentration. Changes in the structure, activity or level of these neuromodulators, AChE or acetylcholine, may elicit novel effects on the developing brain. It is not known to what extent neuronal AChE needs to be altered to have adverse effects on the developing brain, nor is it known what adverse effects on neurodevelopment may result from AChE inhibition. Nevertheless, because of the potential developmental role of AChE, it is reasonable to consider the evidence for whether inhibition of AChE in the developing nervous system may affect neural development.

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[1]The term susceptibility is used qualitatively to indicate unique effects (*e.g.*, a different pattern of effects of concern) in the young. The term sensitivity is used to refer to quantitative susceptibility, or to quantitatively indicate effects of a type similar to those seen in adults, but which occur at doses lower than those causing effects in adults.

In vitro work has shown that some OP compounds can inhibit neurite outgrowth, but enzyme inhibition does not appear to correlate completely with inhibition of outgrowth (Dupree and Bigbee, 1994; Layer *et al.*, 1993, Bigbee *et al.*, 1999). Inhibition of neurite outgrowth is compound-specific, as some compounds inhibit AChE activity but do not inhibit neurite outgrowth. It is now accepted that the cell adhesive function of AChE is mediated by a peripheral anionic site located at the rim of the 20 Å gorge, a site distinct from the catalytic site located at the bottom of that gorge (Johnson and Moore, 1999; Sternfeld *et al.*, 1998). OP inhibitors bind to the catalytic site; little is known about prerequisites for binding to the peripheral anionic site mediating cell adhesiveness. Perhaps some OPs bind specifically to that site or perhaps some OPs can perturb the function of that site when bound to the catalytic site (*e.g.*, Bigbee *et al.*, 1999).

In any event, AChE inhibition does not necessarily predict perturbations of neuronal differentiation. It is possible to create fruit flies (Greenspan *et al.*, 1980) or mice (Xie *et al.*, 2000) that do not produce AChE because they have no gene for AChE. In fruit flies, this is a lethal mutation, but in mice the absence of AChE is only lethal to approximately 25% of the homozygous fetuses *in utero*. At birth, the surviving homozygous animals appear overtly normal, but fail to develop normally and usually die by day 21 unless care is taken to provide their nutritional needs, in which case they may live to adulthood. The authors speculate that the animals survive because butyrylcholinesterase assumes many of the biochemical functions of the absent AChE. As with any study with knockout mice, the phenotype must be interpreted with caution as compensation may occur during development that would not mimic AChE inhibition during development.

Is there evidence that exposure to OP pesticides pre- or postnatally perturbs neurodevelopment? Some animal studies using prenatal exposures show effects on neurodevelopment, while other studies do not show any effect. In general, the literature shows that high levels of dosing of an OP during gestation (*e.g.*, affecting maternal weight gain) will tend to be embryotoxic (*i.e.*, lethal). More subtle effects may be noted at lower doses if other neurodevelopmental specific tests are employed. For example, the offspring of mice receiving diazinon during gestation showed developmental delays and abnormal endurance and coordination at doses of 0.18 or 9 mg/kg/day (Spyker and Avery, 1977). Malathion or dicrotophos showed dose and age-related abnormalities (assessed histologically) of nervous and extranervous system development in one-, two-, and three-day-old chick embryos (Wyttenbach and Thompson, 1985; Garrison and Wyttenbach, 1985) An *in vivo* study of malathion, however, showed no teratological effects in rabbits dosed from day 7 to day 12 of gestation (100 mg/kg; Machin and McBride, 1989); note that this study did not include any detailed assessment of nervous system tissues. Fetal brains of rats given chlorpyrifos repeatedly during late gestation show abnormalities in neuronal migration and other biochemical endpoints (Lassiter *et al.*, 2002; Qiao *et al.*, 2002).

Gestational exposure (day 6 to day 15) to tribufos, oxydemeton-methyl, azinphos-methyl, fenamiphos, isofenphos or fenthion at doses that produced 20-50% maternal brain cholinesterase (ChE) (ChE is used when there was no distinction between butyryl- or acetyl-cholinesterase in the experimental procedure) inhibition showed no embryotoxicity or teratogenicity; neurodevelopment was not assessed (Astroff and Young, 1998). Although the authors conclude that gestational dosing with these compounds caused "no effect on fetal ChE," this activity was not assessed until five days after the last dose, a time that is not optimal for assessing AChE inhibition in fetal tissues (Lassiter *et al.*, 1998; Michalek *et al.*, 1985).

Rats given OP pesticides postnatally may show abnormal nervous system development. In a series of papers exploring the neurotoxicity of postnatally administered chlorpyrifos, many changes were noted (*e.g.*, RNA levels, transcription factor expression, disruption of catecholaminergic and cholinergic pathways) (Johnson *et al.*, 1998; Crumpton *et al.*, 2000; Dam *et al.*, 1999), resulting in persistent biochemical and behavioral changes long after the dosing ceased (Dam *et al.*, 2000; Slotkin *et al.*, 2001a,b; Levin *et al.*, 2001; Slotkin *et al.*, 2002). Other studies in which chlorpyrifos was administered to the dam so that the pups received their dosage only through the milk were largely negative (Breslin *et al.*, 1996; Deacon *et al.*, 1980; Maurissen *et al.*, 2000), although the endpoints examined were not as targeted and discriminating as those used by the Slotkin laboratory. The relationship of these neurodevelopmental changes to ChE inhibition is unclear because many studies are lacking correlative ChE activity, thus making it difficult to draw firm conclusions. In the few prenatal studies where ChE activity was assessed, however, few of these effects occur at dose levels that do not inhibit ChE activity in the fetal brain, and probably none of these effects occur in the absence of ChE inhibition in maternal tissues. In both the studies assessing prenatal effects of chlorpyrifos, effects on brain development were noted at dosages (1 mg/kg/day) that did not inhibit fetal brain ChE (Lassiter *et al.*, 2002; Qiao *et al.*, 2002), but would be predicted to show inhibition of maternal blood and brain ChE activity (Maurissen *et al.*, 2000). In postnatal studies, there are no reports of effects in the absence of ChE inhibition. In some cases, this assertion is made by the authors, but the authors fail to ascertain that the ChE measurements were taken at the time of peak effect. Often the measurements are taken 24 hours after the last dose, rather than assessing ChE activity during the entire dosing period. Thus, it is reasonable to assume that adverse neurodevelopmental outcomes that are a result of the inhibition of ChE should not occur at doses that do not inhibit ChE. Because, however, the cumulative risk assessment is based on adult brain ChE data, it is important to address the age-related sensitivity of ChE inhibition in the adult versus the young animal. The available studies are reviewed below.

b. Differential Sensitivity of the Young Compared to the Adult

Although reports of increased sensitivity of the young following exposure to OP pesticides date back over two decades, it is the work that has emerged recently that provides a better basis for understanding the issues concerning the sensitivity of the young to ChE inhibition. This understanding comes from recently generated chemical-specific data in young animals on ChE activity, as well as generic human and animal studies on the biological and biochemical parameters involved in age-dependent sensitivity. The current state of the knowledge is summarized and discussed below.

i. Human Incident Information

There are reports of symptoms associated with cholinergic toxicity due to accidental acute exposures. A 1999 review based on pesticide-related exposures (excluding cases of exposure to multiple products, attempted suicides, malicious intent, and confirmed non-exposure) examined Poison Control Centers Data from 1993 through 1996 (USEPA, 1999). Of the exposures that occurred in a residential setting 16% were due to OP pesticides. The review of the residential pesticide exposure concluded:

Organophosphate pesticides pose a greater hazard from accidental acute exposure than do other pesticides, especially for children under six years-of-age. Children were three times more likely to be hospitalized, five times more likely to be admitted for critical care, and four times more likely to have experienced a major medical outcome or death than if exposed to some other pesticide.

In this review of residential exposures, there were 24,889 exposures reported in children under the age of six, 5,080 exposures among children six to 19 years-old, and 32,087 exposures among adults. Of those cases with medical outcomes determined, children under age six were 22% more likely to experience a life-threatening or fatal outcome as a result of their exposure than adults or children six to 19 years-old. Additionally, based on the Centers for Disease Control mortality data (see http://wonder.cdc.gov/mortsqu.shtml), the ratio for death in young children exposed to OP pesticides was 3.3 times higher than in adults.

These data show that there is more potential for harmful exposures in young children than in older age groups, but they do not necessarily demonstrate an increase in the sensitivity of young children. There is a possibility that young children may be exposed to higher doses on a body weight basis compared to adults (from spills, ingestion, inhalation) because they are ignorant of the hazard, and not because of differences in sensitivity based on age to the effects of these pesticides. Furthermore, the human data on children come from accidental exposures to these pesticides that are associated with acute poisoning

resulting in significantly higher blood, tissue, and urine concentrations of these chemicals compared to exposures that humans would normally encounter in food or the environment.

Because of the reasons stated above, it is difficult to draw conclusions from human incident data on the sensitivity of the young compared to adults. The animal literature below allows for evaluations of age-dependent sensitivity.

ii. Laboratory Animal Studies

Some studies are available in the open literature that have evaluated ChE inhibition following *in utero* or lactational exposures to OP pesticides, as well as dosing of young animals. EPA issued a Data Call-In (DCI) on September 10, 1999 for adult and developmental neurotoxicity (DNT) studies on the OP pesticides, and as part of the DNT protocol, measures of brain, red blood cell (RBC), and plasma ChE activity in dams and pups were required to characterize comparative levels of inhibition at the time of peak effect. However, very few DNT rat studies have been submitted to the Agency.[2] In addition to studies on OP pesticides that allows a comparison of the differential in response to ChE inhibition between adult and immature rats, several recent published studies provide an important perspective on the underlying basis for observed increased sensitivity. The analyses below will focus on differences in ChE inhibition between fetal, neonates, and juvenile rats compared to adults.

Differential Sensitivity Following Gestational/Lactational Exposure

Fenamiphos, tribufos, trichlorfon, and oxydemeton-methyl were evaluated for ChE inhibition in a rat multigeneration reproductive feeding study (Astroff *et al.*, 1998; discussed in Sheets, 2000). Dams were treated with these OP pesticides via the diet during gestation and continuing throughout the lactation period. Pups are assumed to be exposed due to consumption of feed at about 14-21 days-old.

Plasma and RBC ChE activity were measured in the adults during the premating phases of both generations following eight weeks of exposure to each of the OP pesticides, and again at termination when

[2]Out of the 30 OP pesticides included in the December 2001 preliminary cumulative assessment, DNT studies have only been submitted for chlorpyrifos, dimethoate, malathion, methyl parathion, methamidophos, and tribufos. The DNT studies submitted for dimethoate, malathion, and methyl parathion also included comparative ChE activity. These studies investigated ChE activity in adult and immature rats following either acute or repeated dosing. A review of the chlorpyrifos DNT study was completed in 1999, and reviews of the dimethoate and malathion DNT studies have recently been completed. The DNT studies for tribufos, methamidophos, and methyl parathion are currently under review, although a review has been completed on the ChE data for malathion and methyl parathion. It should be pointed out that the DNT studies on methamidophos and tribufos are feeding studies in which the pups were not directly dosed, and thus the pups were presumed to be exposed only *in utero* and during lactation; no comparative ChE data have been submitted for methamidophos and tribufos.

brain ChE activities were measured. Separate contingents of postnatal rats were evaluated for plasma, RBC, and brain ChE activity on lactation day (LD) 4 and on LD21. The effects found on LD4 could be due to gestational and lactational exposure, whereas the results on LD21 may reflect exposure through the milk and some exposure through the diet as pups begin consuming feed in the late lactational period, in other words, postnatal days (PND)14-21. Each study consisted of a control and three dose groups. The highest dose level was selected based on parental toxicity.

Toxicity (reduced body weights or viability) in the young was not apparent until there were significant maternal effects (decreased body weights and food consumption) and substantial ChE inhibition in the blood and brain of the parental animals. In fact, the adult animals were more affected than the young in this study. Although young rats, when exposed to these OPs *in utero* and via lactation, do not appear to exhibit more ChE inhibition than is found in maternal tissues, the dose that may be absorbed by the fetus and adult is unknown. Thus, conclusions can not be reached about the relative sensitivity of fetuses versus dams to ChE inhibition.

Maternal and fetal ChE inhibition were evaluated following maternal exposure to **azinphos-methyl, fenamiphos, fenthion, isofenphos, tribufos, and oxydemeton-methyl** in a prenatal developmental toxicity study in rats (Astroff and Young, 1998). These pesticides were administered to the dams by gavage on gestation days (GD) 6-15. Maternal ChE activity (brain, RBC, plasma) was measured onGD16 and 20, and fetal brain ChE activity was measured on GD20. The dose levels for these studies were selected such that maternal ChE inhibition at the highest dose tested was greater than 20%. At the highest dose tested on GD16 (in plasma [except for azinphos-methyl], RBC [except for fenamiphos], and brain [except for fenamiphos], and on GD20 (in plasma [only for fenthion], RBC [except for aniphos methyl], and brain [except for fenamiphos]), maternal ChE was significantly inhibited. However, no remarkable brain ChE inhibition was observed in fetuses at any dose on GD20.

The effect of treatment with **chlorpyrifos** on ChE activity was compared in dams and fetuses by Mattsson *et al.* (1998; 2000). Pregnant Sprague-Dawley rats were administered chlorpyrifos by gavage at doses of 0, 0.3, 1.0, or 5.0 mg/kg/day on GD6-20. The magnitude of brain, plasma, and RBC ChE inhibition in the fetus on GD20 was found to be less than or equal to that observed in dams. At 5.0 mg/kg/day, ChE activity in fore- and hindbrain of the dams on GD20 was inhibited by 76.0 and 86.7%, respectively, and by 58.8% in fetuses. At 1.0 mg/kg/day, brain ChE activity in fore- and hindbrain was inhibited in dams by 7.8 and 8.0% (statistically significant at

$p \leq 0.05$ or 0.01), respectively; there was no statistically significant depression of brain ChE activity in fetuses. In another study of the comparative ChE inhibition between dam and fetus with chlorpyrifos, Lassiter *et al.* (1998) concluded that the fetal brain ChE inhibition was less than the maternal brain ChE inhibition during repeated dosing primarily because the fetal brain tended to recover more completely between doses than the maternal brain ChE. When dams were given a single dose, both maternal and fetal brain ChE appeared to be depressed to the same degree, but when subjected to a repeated dosing regimen, the fetal brain showed less inhibition probably because of the higher rates of new synthesis or more rapid turnover of inhibited molecules of ChE in the fetuses compared to the adult. In two different studies which compared the tissue burden of chlorpyrifos and metabolites in dam and fetus, one group (Mattsson *et al.*, 1998, MRID 44648102, Mattsson *et al.*, 2000) found lower blood concentrations of chlorpyrifos in the fetus as compared to the dam, whereas another group (Hunter *et al.*, 1999) found three times more trichloropyridinol (a metabolite of chlorpyrifos) in the fetal brain as compared to the maternal brain. Trichloropyridinol (TCP) can either be produced as a by-product of a toxic action (*i.e.*, TCP is the leaving group wh chlorpyrofos-oxon binds to ChE) or as a detoxification action (*e.g.*, TCP can be produced when chlorpyrifos-oxon is catalyzed by PON1).

Results of a recently submitted DNT study with **dimethoate** indicated that treatment by gavage of dams with the pesticide induces equal or less inhibition of ChE in the fetus compared with the dams (Meyers, 2001; MRID 45529702). Treatment of dams with 0.5 mg/kg/day of dimethoate during GD6-20 induced statistically significant but marginal ChE inhibition (10%) in brain tissue of both adult and fetal rats. The responses at 3 mg/kg/day (the highest dose tested) indicated less brain and RBC ChE inhibition in fetuses (33% and 31%, respectively) compared with dams (60% and 58%, respectively). Measurements of ChE inhibition were also conducted on four-day-old pups that were exposed to dimethoate *in utero* from GD6 to GD20, but not directly exposed postnatally. At 3.0 mg/kg/day, brain and RBC ChE activity was inhibited by 13% and 17% in the PND4 pups.

A DNT study performed with **malathion** (Fulcher, 2001; MRID 45566201) also showed that there was less effect on ChE activity (measured at GD20) in fetuses than in dams that had been treated by gavage with the pesticide during GD6-GD20. At the highest dose examined (150 mg/kg/day), RBC ChE was inhibited by 19% in fetuses and by 51% in the dams. No effects on brain ChE activity were observed in either the fetuses or dams at that dosage. At PND4, at which time the only exposure to malathion could be through milk, ChE activities in treated pups were comparable to controls.

ChE data that were recently submitted to the Agency (Beyrouty, 2002b; MRID 45656501), supplemental to a DNT study on **methyl parathion**, demonstrated that treatment of dams by gavage from GD6-20 induced more ChE inhibition in the brain of dams than in the fetuses. Analyses of brain tissue at GD20 showed that ChE activity was inhibited by 31% in dams at a dose of 0.60 mg/kg/day (the highest dose tested), while there was no brain ChE inhibition in their fetuses. At the same dose, RBC ChE inhibition was 58% in dams and 22% and 18% in male and female fetuses, respectively. In PND4 pups, ChE was not inhibited in any compartment.

In summary, results of studies with fenamiphos, tribufos, trichlorfon, oxydemeton-methyl, chlorpyrifos, methyl parathion, dimethoate, malathion, and azinphos-methyl show that treatment of pregnant dams with an OP pesticide during gestation induces more ChE inhibition in the dams than in the fetus. Data from these studies also show that the newborn (one- to four-day-old pups), when only exposed *in utero* or possibly through the milk, also has less inhibition of ChE than the maternal, adult rat. The lack of similar levels of ChE inhibition in fetuses or neonates relative to adults may be due to the fetuses receiving a lower dose of these OP pesticides compared to their dams because of pharmacokinetic differences, such as a lower dose being transferred to the fetus through the placenta or to the neonate through the milk than is received by the dam directly in the diet. A lower response in the immature animal may also be due to the increased synthesis or more rapid turnover of inhibited molecules of ChE in the fetal brain compared to the adult (Lassiter *et al.*, 1998; Mortensen *et al.*, 1998).

Differential Sensitivity Following Direct Postnatal Exposures

Neonatal, juvenile, and adult rats show differential sensitivity to ChE inhibition following an acute gavage treatment with **chlorpyrifos** (Pope, 2001a). When rats from each age group were administered chlorpyrifos at 0.5 times the LD_{10} (7.5 mg/kg, neonates; 23.5 mg/kg, juveniles; 68 mg/kg, adults), peak ChE inhibition in the cortex (estimated from Figure 11 of the report) was 70% (neonates), 65% (juveniles), and 68% (adults). Thus, based on similar magnitudes of peak ChE inhibition at 0.5 of a LD_{10} dose and considering the differentials in the 0.5 LD_{10} doses, neonates were shown to be about threefold more sensitive than juveniles and about ninefold more sensitive than adults. In another study by Moser *et al.* (1998) a single gavage dose of 20 mg/kg produced 89% and 91% (males and females) brain ChE inhibition in PND17 pups, compared to 39% and 36% (males and females) inhibition in adults (*i.e.*, about a twofold difference in relative sensitivity).

Chlorpyrifos produces a minimal difference in ChE inhibition in neonatal rats compared to adult rats following repeated dosing (14 treatments by gavage during PND7 to PND21). Based on ED_{50} levels (adults, 3.3 mg/kg/day and neonates, 2.2 mg/kg/day), the difference in the response of neonates to brain ChE inhibition compared to adult males is a 1.5-fold increase (Zheng *et al.*, 2000).

Similar results were reported in a recent study in which neonatal and adult rats were administered chlorpyrifos by subcutaneous injection (Liu *et al.*, 1999). Neonatal (seven-day-old) pups and adults were administered 0, 5, or 10 mg/kg/day for seven or 14 days and sacrificed for ChE measurements one day after the final dose. At seven days, inhibition of ChE activity in the cortex and striatum of the neonates was 62 and 65%, respectively, compared with 50 and 55% in adult animals. Following 14 days of treatment, ChE inhibition in the cortex and striatum of neonates was 60 and 65%, respectively and 65% in both of these tissues from adult animals.

Diazinon. A recent abstract by Moser and coworkers (Padilla *et al.*, 2002) reported an increased sensitivity to ChE inhibition for diazinon when PND17 pups were given a single oral dose (via gavage) of 75 mg/kg (75% brain ChE inhibition) compared to adult rats (38% brain ChE inhibition). This observation was correlated with detoxification by carboxylesterases and A-esterases (as discussed later in Section II.C.). There are no data available on the effects on ChE activity following repeated dosing of neonates or young adults with diazinon.

Dimethoate. In a recent DNT study (Meyers, 2001; MRID 45529702), dimethoate was evaluated for ChE activity in plasma, RBC, and brain following acute exposures and repeated dosing (subacute exposures) to 0.1, 0.5, and 3 mg/kg/day of dimethoate. Dimethoate was given by gavage to pregnant rats GD6 through LD10 (LD10; equivalent to PND10); their pups were treated by gavage from PND11 through PND21. Plasma, RBC, and brain ChE was measured at GD20 (dams and fetuses), PND4 (pups only), and PND21 (pups only). ChE activity was also measured following an acute dose of dimethoate to additional groups of young adult and PND11 rats. In general, there was no striking difference in sensitivity to dimethoate-induced brain or plasma ChE inhibition between males and females of either adults or pups following acute or repeated treatment.

Acute (single dose) treatment with dimethoate of adult male and female rats and 11-day-old offspring with 3 mg/kg/day induced statistically significant, treatment related ChE inhibition in brain or RBC. At that dose, brain ChE inhibition in adult male and female rats was 12% and 14%, respectively, and in day 11 male and female

offspring 17% and 18%, respectively. At 3 mg/kg/day, RBC ChE inhibition was greater in adult females than in adult males (26% versus 17%) and there was no statistically significant depression of RBC ChE activity in PND11 offspring.

Repeated dosing (11 doses) with 0.5 mg/kg/day dimethoate induced statistically significant but marginal brain ChE inhibition (10-13%) in both sexes of adult and 21-day-old rats. The response is likely due to treatment with the chemical because of the positive finding in both sexes of both age groups and because data from GD20 dams also showed an effect at 0.5 mg/kg/day. At the 3 mg/kg/day dose level, brain ChE inhibition was substantial in both adults (up to 58%) and 21-day-old offspring (up to 45%). In the repeated dosing study, a small, but statistically significant, difference in brain ChE inhibition was found at the low dose (0.1 mg/kg) between adults and pups (GD20, PND4 and PND21). As the dose was increased, this differential was not found at the high dose 3.0 mg/kg (see Table 1).

Because dimethoate does not show age-dependent sensitivity (discussed above), it is reasonable to assume that its oxon–omethoate–will also not show a differential toxicity in adults versus pups. Unlike acephate (discussed later), the parent compound–dimethoate–has been characterized for ChE inhibition in the young animals compared to adults.

Malathion. Recently submitted ChE data (supplemental to a DNT study) (Fulcher, 2001; MRID 45566201) clearly demonstrate a differential sensitivity to inhibition of the ChE enzyme in immature animals compared to adult rats treated with acute or repeated exposure to malathion. In this study, pregnant rats were administered malathion by gavage from GD6 through LD10; gavage dosing of their pups was then continued from PND11 through 21. Plasma, RBC, and brain ChE was measured at GD20 (dams and fetuses), PND4 (pups only), and PND21 (pups only). ChE activity was also measured in additional groups of young adult and immature (PND11) rats that had been administered a single (acute) dose of malathion. The dose levels were 5, 50, 150 mg/kg/day in the repeated dosing studies, and 5, 50, 150, and 450 mg/kg in the acute studies.

Following an acute dose of malathion, brain ChE was inhibited in PND11 pups at 150 mg/kg (44% in males and 48% in females) and at 450 mg/kg (84% in males and 81% in females), while brain ChE was not affected in young adults at either of those doses. At 450 mg/kg, however, RBC ChE was inhibited in both young adults (25% in males and 17% in females) and PND11 pups (72% in males and 61% in females).

Repeated dosing of malathion at 150 mg/kg/day from PND11 through PND21 (11 days of treatment) produced a marked inhibition of plasma (24-32%), RBC (67-68%), and brain (16%) ChE compared to controls. For dams, 14 days of treatment at 150 mg/kg/day resulted in RBC ChE inhibition (51%), but no inhibition of plasma or brain ChE. Similarly, for young adult rats that were treated for 11 days with 150 mg/kg/day malathion, RBC ChE was inhibited 43% in males and 48% in females, while plasma and brain ChE were not affected. At 50 mg/kg/day, plasma (19%) and RBC (34-39%), but not brain, ChE activity was inhibited in the PND21 offspring, while in dams and young adults, only RBC ChE (19-20%) was inhibited. No effects on ChE activity were seen at 5 mg/kg/day for dams or young adults. In PND21 offspring, however, RBC but not plasma or brain ChE was inhibited (17% in males, 15% in females).

Methamidophos was evaluated for age-related differences in ChE inhibition by Moser (1999). Comparisons for brain and blood ChE activity were made between PND17 and adult rats following acute oral doses of 1, 4, or 8 mg/kg. The dose response curves for ChE inhibition were quite similar between pups and adult rats. ED_{50} values for brain ChE inhibition in PND17 and adult rats were approximately 3.3 and 3.0 mg/kg/day, respectively. The ED_{50} values for blood ChE inhibition were 2.5 (PND17) and 2.2 (adults) mg/kg/day.

Although acephate is metabolized to methamidiphos, it is not possible to determine, based on available data, whether acephate would show comparable responses in adult and young rats. This is because acephate, the parent compound, has not been evaluated for comparative ChE activity in young versus adult animals. In rats, only a small portion of acephate is metabolized to methamidiphos (5%) (Warnock, 1973; MRID 00014219). Furthermore, it is unknown to what extent the parent chemical may induce ChE inhibition or to what extent the parent chemical may alter the effects of methamidiphos on ChE activity in the adult or young rat.

Treatment of neonatal, juvenile, and adult rats with a single gavage dose of **methyl parathion** induces a differential response among the age groups in ChE inhibition in the brain (cortex) (Pope, 2001a). Treatment with methyl parathion at doses of 1.0 mg/kg (neonates), 2.05 mg/kg (juveniles), or 7.3 mg/kg (adults) induced similar magnitudes of peak ChE inhibition (60%-70%, estimated from Figure 14 of the report). Based on a comparison of the doses that induced similar levels of ChE inhibition, neonates are 2.5-fold more sensitive than juvenile rats and about sevenfold more sensitive than adult rats to methyl parathion induced ChE inhibition.

Methyl parathion was investigated by Liu *et al.*, (1999) for ChE activity and other neurochemical effects after repeated dosing in postnatal and adult male rats. Adult and postnatal rats (eight-day-old) were treated with methyl parathion subcutaneously at 1.5 mg/kg/day or 3.0 mg/kg/day for either seven or 14 consecutive days. Brain ChE activity was measured in the cortex and in the striatum one day after seven days of dosing or eight days after 14 days of dosing. Brain ChE activity was more reduced in postnatal pups compared to adults. Following seven days of dosing at 1.5 mg/kg/day, neonates showed 62 and 75% ChE inhibition in the cortex and striatum, respectively, compared to 25 and 30% in the adult male rats. In neonates treated subcutaneously with methyl parathion for 14 days, ChE activity was inhibited in the cortex by 65% and in the striatum by 80%. ChE activity was inhibited in adult rats by 40% (cortex) and by 50% (striatum).

A recently submitted DNT study on methyl parathion with supplemental ChE data (Beyrouty, 2002b; MRID 45656501) demonstrated a differential sensitivity of immature versus adult rats to ChE inhibition following acute or repeated exposure. The protocol for this study was similar to that used for the DNT ChE studies conducted for dimethoate and malathion. Methyl parathion was administered by gavage to pregnant rats from GD6 through LD10 at doses of 0.03, 0.11, 0.3, and 0.6 mg/kg/day. Pups from these litters were then administered methyl parathion by gavage from PND11-21. Plasma, RBC, and brain ChE was measured at GD20 (dams and fetuses), PND4 (pups only), and PND21 (pups only). Additional groups of young adult and PND11 rats were dosed acutely with methyl parathion (at doses of 0.03, 0.11, 0.3, and 0.6 for adults and doses of 0.03, 0.11, 0.3, and 1.0 for pups), and ChE activity was measured. Following acute exposures of 0.3 mg/kg, ChE was inhibited in brain (15-18%), RBC (20-31%), and plasma (25%) in PND11 pups; no inhibition was observed in any compartment for adults.

Repeated dosing of PND11 to PND21 pups (which had also been exposed *in utero* and via lactation) also showed an increased sensitivity of neonates compared with adult rats to treatment with methyl parathion. At 0.3 mg/kg/day, ChE activity was inhibited in PND21 pups (brain 26-29%, RBC 62-65%, and plasma 24-31%). In dams treated with the same dosage from GD6 to GD20 (*i.e.*, 14 days of treatment), ChE inhibition was seen in brain (9%) and RBC (35%), but plasma ChE was not affected. In adult rats treated with 11 repeated doses of 0.3 mg/kg/day methyl parathion, ChE inhibition was seen in RBC (30% in males and 35% in females) and plasma (25% in males), but there was no inhibition of brain ChE. At 0.6 mg/kg/day, brain ChE was inhibited 60-62% in PND21 pups, 31% in GD20 dams, and 6-13% in adults; RBC ChE was inhibited 85-86% in PND21 pups, 58% in GD20 dams, and 40-58% in adults; and plasma ChE was

inhibited 56-61% in PND21 pups, 29% in GD20 dams, and 28-34% in adults.

Summary of Differential Sensitivity

Table 1 shows results of ChE measurements performed in acute and repeat dosing studies with OP pesticides using neonatal, juvenile, or adult rats. The information provided in Table 1 is confined to data that could be used to estimate the relative sensitivities of different age groups based on the amount of ChE inhibition reported following treatment with an OP pesticide. Estimates of relative sensitivities (4th column) were derived by either: (1) the ratio of the response *(i.e.*, percent ChE inhibition) for adults: pups at the same dose of chemical, or (2) the ratio of doses in adults: pups that induce a comparable amount of ChE inhibition. The different approaches to estimating the relative sensitivities to a ChE-inhibiting chemical were necessary because of the differences in study designs and results among the studies evaluated. For example, some studies used single doses such as a proportion of an LD whereas other studies used multiple doses that allowed calculations of an ED_{50}. It should be noted that estimates of relative sensitivities are a function of the doses or percentages of ChE reported in studies and that, depending on dose-response characteristics of ChE inhibition among different age groups, actual sensitivities may be different at doses other than those used in Table I.G-1.

[Since this section was written, preliminary BMD_{10}'s were derived for the dose-response ChE data from repeated dosing studies on pups and adults in RBC and brain for malathion (Fulcher 2001), methyl parathion (Beyrouty 2002)and chlorpyrifos (Zheng et al., 2000). These data were modeled using the EPA Benchmark Dose Software version 1.3.1 - Hill model (available at website: http://cfpub.epa.gov/ncea/cfm/bmds.cfm?ActType=default). The modeling confirmed that there was less than two-fold difference in response between adults and pups following repeated dosing with chlorypyrifos. For malathion, a difference between adults and pups up to approximately 3-fold was found for RBC ChE inhibition based on the BMD10s. For brain ChE , there was 16% inhibition in pups at the highest dose tested (150 mg/kg/day) but no inhibition in adults. Thus, relative sensitivity could be determined because of the lack of comparable dose response data in pups and adults. Although Table 1 reports a differential in brain ChE inhibition for methyl parathion up to 3.-fold (comparing percent inhibition), modeling the Beyrouty data showed differences up to approximately 4-fold based on BMD10s.]

Table I.G-1. Summary of Sensitivity to ChE Inhibition in Neonatal or Juvenile Rats Treated with Organophosphorus Pesticides

Pesticide & Reference	Treatment Groups; Doses (mg/kg/day); Route of Administration	Results	Relative Sensitivity (Fold Difference)
Chlorpyrifos			
(Pope, 2001a)	Neonates, juveniles, and adults 7.5 neonates, 23.5 juveniles, 68 adults single gavage dose	**Neonates:** 70% ChEI in cortex at 7.5 mg/kg **Juveniles:** 65% ChEI in cortex at 23.5 mg/kg **Adults:** 60% ChEI in cortex at 68 mg/kg	**ACUTE** **Juveniles/neonates:** 23.5 mg/kg/ 7.5 mg/kg = 3.1 **Adults/neonates:** 68 mg/kg/ 7.5 mg/kg = 9.1
Moser *et al.*, (1998)	Adults and PND17 pups 20 mg/kg single gavage oral doses	**Pups Brain ChEI:** 89% (♂) and 91% (♀) **Adults Brain ChEI:** 39% (♂) and 66% (♀) inhibition in adults	**ACUTE** **Pups/Adults:** 89 % ChEI/39% ChEI=2.3; 91% ChEI/36% ChEI=2.3
(Zheng *et al.*, 2000)	Repeated gavage doses of 0.15, 0.45, 0.75, 1.50, 4.50, 7.50, or 15.0	**Pups:** ED_{50} for ChEI in cortex, 2.2 mg/kg/day **Adults:** ED_{50} for ChEI in cortex, 3.3 mg/kg/day **Pups:** 54.9% RBC ChEI, 1.5 mg/kg/day **Adult:** 91% RBC ChEI, 1.5 mg/kg/day	**REPEATED** **Adults/pups:** 3.3 mg/kg/day/2.2 mg/kg/day = 1.5 (no difference) **Adult/pups:** 54.9% ChEI/91% ChEI = 0.6 (no difference)
Diazinon			
(Padilla *et al.*, 2002)	Adults and PND17 pups single gavage dose of 75	**Pups:** 75% brain ChEI **Adults:** 35% brain ChEI	**ACUTE** **Pups/Adults:** 75% ChEI/35%ChEI = 2.1
Dimethoate			
(Myers, 2001; MRID 45529702, unpublished)	Adults and PND11 pups single gavage doses of 0.1, 0.5, or 3.0	**Pups:** 18% brain ChEI at 3.0 mg/kg; 26% RBC ChEI at 3.0 mg/kg **Adults:** 14% brain ChEI at 3.0 mg/kg; 27% RBC ChEI at 3.0 mg/kg	**ACUTE** **Pups/Adults:** At 3 mg/kg 18% ChEI/14%ChEI=1.3 26% ChEI/27% ChEI=1 (no difference)

Table I.G-1. Summary of Sensitivity to ChE Inhibition in Neonatal or Juvenile Rats Treated with Organophosphorus Pesticides

Pesticide & Reference	Treatment Groups, Doses (mg/kg/day), Route of Administration	Results	Relative Sensitivity (Fold Difference)
	Adults and PND11-21 repeated gavage doses of 0.1, 0.5, or 3.0	**Pups:** 45% brain ChEI at 3.0 mg/kg/day; 13% ChEI at 0.5 mg/kg/day; 65% RBC ChEI at 3.0 mg/kg/day; no RBC ChEI at 0.5 mg/kg/day **Adults:** 60% brain ChEI at 3.0 mg/kg/day; 13% brain ChEI at 0.5 mg/kg/day; 63% RBC ChEI at 3.0 mg/kg/day; no RBC ChEI at 0.5 mg/kg/day	**REPEATED** **Pups/Adults:** At 3 mg/kg/day 45% ChEI/60% ChEI=0.8 (no difference) At 0.5 mg/kg/day 13% ChEI/13% ChEI=1 (no difference) At 3 mg/kg/day 65% ChEI/63% ChEI=1 (no difference)
Malathion			
Fulcher, 2001, MRID 45566201, unpublished)	Adults and PND11 pups single gavage doses of 5, 50, 150, or 450	**Pups:** 84% brain ChEI at 450 mg/kg; 48% brain ChEI at 150 mg/kg; 72% RBC ChEI at 450 mg/kg; 55% RBC ChEI at 150 mg/kg **Adults:** No brain ChEI at 150 or 450 mg/kg; 25% RBC ChEI at 450 mg/kg; no RBC ChEI at 150 mg/kg	**ACUTE** **Pups/Adults:** 84% brain ChEI/no brain ChEI at 450 mg/kg; fold difference uncertain **Pups/Adults:** 72% RBC ChEI/25% ChEI at 450 mg/kg = 2.9
	Adults and PND11-21 pups repeated gavage doses of 5, 50, or 150	**Pups:** 16% brain ChEI at 150 mg/kg/day; no brain ChEI at 50 mg/kg/day; 68% RBC ChEI at 150 mg/kg/day; 39% RBC at 50 mg/kg/day 17% RBC ChEI at 5 mg/kg/day **Adults:** No brain ChEI and 51% RBC ChEI at 150 mg/kg/day; 20% RBC ChEI at 50 mg/kg/day	**REPEATED** **Pups/Adults:** 16% brain CHEI/no CHEI at 150 mg/kg/day and no brain at 50 mg/kg/day in pups or adults; fold difference uncertain **Pups/Adults:** 68% RBC ChEI/51% RBC ChEI at 150 mg/kg/day =1.3; 39% RBC ChEI/20% RBC ChEI at 50 mg/kg/day =2.0
Methamidophos			
(Moser, 1999)	Adults and PND17 pups single gavage dose of 1, 4, or 8	**Pups:** ED_{50} for brain ChEI 3.0 mg/kg; ED_{50} for blood ChEI 2.3 mg/kg **Adults:** ED_{50} for brain ChEI 3.0 mg/kg; ED_{50} for blood ChEI 2.0 mg/kg	**ACUTE** **Pups/Adults:** 3 mg/kg/3 mg/kg=1 (no difference); 2.3 mg/kg/2 mg/kg=1.2 (no difference)
Methyl Parathion			

Table I.G-1. Summary of Sensitivity to ChE Inhibition in Neonatal or Juvenile Rats Treated with Organophosphorus Pesticides

Pesticide & Reference	Treatment Groups; Doses (mg/kg/day); Route of Administration	Results	Relative Sensitivity (Fold Difference)
(Pope, 2001a)	Neonates, juveniles, and adults treated with a single gavage dose neonates 1.0, juveniles 2.05, adults 7.3	**Neonates:** 60% ChEI in cortex at 1.0 mg/kg **Juveniles:** 60% ChEI in cortex at 2.05 mg/kg **Adults:** 70% ChEI in cortex at 7.3 mg/kg	**ACUTE** **Juvenile/neonate:** 2.05 mg/kg/ 1.0 mg/kg = 2.05 **Adult/neonate:** 7.3 mg/kg/1.0 mg/kg = 7.3
(Beyrouty, 2002a; MRID 45656501, unpublished)	Adults and PND11 pups single gavage doses of 0.03, 0.11, 0.3, or 1.0 pups; 0.03, 0.11, 0.3, or 0.6 adults	**Pups:** 18% brain ChEI at 0.3 mg/kg; 31% RBC ChEI at 0.3 mg/kg **Adults:** No brain or RBC ChEI at 0.3 mg/kg	**ACUTE** **Pups/Adults:** 18% brain ChEI/no brain ChEI at 0.3 mg/kg; fold difference uncertain 31% RBC ChEI/no RBC ChEI at 0.3 mg/kg; fold difference uncertain
	Adults and PND11-21 pups repeated gavage doses of 0.03, 0.11, 0.3, or 0.6	**Pups:** 62% brain ChEI at 0.6 mg/kg/day; 29% brain ChEI at 0.3 mg/kg/day; 86% RBC ChEI at 0.6 mg/kg/day; 65% RBC ChEI at 0.3 mg/kg/day **Adults:** 31% brain ChEI at 0.6 mg/kg/day; 9% brain ChEI at 0.3 mg/kg/day; 58% RBC ChEI at 0.6 mg/kg/day; 35% RBC ChEI at 0.3 mg/kg/day	**REPEATED** **Pups/Adults:** 62% brain ChEI/31% brain ChEI at 0.6 = 2.0 29% brain ChEI/9% brain ChEI at 0.3 =3.2; 86% RBC ChEI /58% RBC ChEI at 0.6=1.5; 65% RBC ChEI/35% RBC ChEI at 0.3 =1.9

iii. Recovery from ChE Inhibition in Young Rats Treated with Organophosphorus Pesticides

Studies that included analyses of recovery from ChE inhibition in young rats have been performed on chlorpyrifos, methamidiphos, methyl parathion, and parathion.

PND17 pups were reported to recover from ChE inhibition in one week after cessation of dosing with a single maximum tolerated dose (MTD) of **chlorpyrifos** of 15 mg/kg compared with a greater than two-week recovery period in adults administered a MTD dose of 80 mg/kg/day (Moser and Padilla, 1998). Pope *et al.* (1991) also reported a faster recovery in ChE activity in neonates compared to adults when treated with a MTD of chlorpyrifos. Adults treated with an acute, subcutaneous, dose of 279 mg/kg chlorpyrifos showed about a 90% inhibition of brain ChE activity seven days after dosing compared to approximately 40% inhibition in the brains of seven-day-old neonates treated with 45 mg/kg chlorpyrifos.

One day following oral treatment every other day with three doses of 3 mg/kg/day and eight doses of 6 mg/kg/day from PND1-21, brain ChE activity was inhibited by 57% (Tang *et al.*, 1999). Following a 19-day recovery period, brain ChE activity (about 20% inhibition relative to controls) was still depressed. Thus, although ChE levels in juvenile rats return to control levels after an acute treatment with chlorpyrifos, repeated treatments can lead to prolonged ChE inhibition.

PND17 and adult rats orally administered 8 mg/kg **methamidiphos** each showed about 80-85% brain ChE inhibition 1.5 hours after dosing (Moser, 1999). Twenty-four hours after dosing, more recovery was noted in the pups than adults (30-35% brain ChEI in pups versus 55% in adults). At 72 hours post dosing, ChE activity in pups had returned to normal but there was still brain ChE inhibition in adults (10-15%)

Neonatal (seven-day-old) pups and adults were found to have similar brain ChE activities (about 20% activity compared to controls) when administered a MTD of **methyl parathion** (7.8 mg/kg: neonates; 18 mg/kg: adults) but a more rapid recovery was reported for the neonates (Pope *et al.*, 1991). By seven days after treatment, neonatal ChE activity was almost completely recovered (about 90%) whereas brain ChE activity in adults was about 50% relative to controls.

Repeated treatments with methyl parathion of PND7 or 14 neonates and adults showed more inhibition initially but a faster recovery in the young rats (Liu *et al.*, 1999). On day 8, one day after seven days of subcutaneous treatment of neonates and adults, inhibition in the cortex of neonates administered 1.5 mg/kg/day was 73% (neonate) and 32% (adults). At a dose of 3.0 mg/kg/day, more inhibition was found in striatal than cortex tissues: Striatal inhibition at that dose was reported as 86% (neonate) and 64% (adult) one day following seven days treatment; seven days after cessation of dosing, brain ChE inhibition was about 45% in both age groups, indicating that more recovery had occurred in neonates (41%) than in adults (only 19%).

Liu *et al.* (1999) also investigated the effects on ChE inhibition in neonatal rats and adults following administration of MTD doses of **parathion**. As with methyl parathion, maximum brain ChE inhibition was similar (>85% on the day of dosing in neonates and 90% in adults four days after dosing), but recovery in the neonates was more rapid. Seven days after cessation of dosing, brain ChE activity had essentially returned to normal in neonates but brain ChE was inhibited by 80% in the adults.

c. Mechanisms Underlying the Differential Age-Related Sensitivity For ChE Inhibition

Age-related differences in sensitivity to pesticides can occur for a number of reasons (Pope, 2001b). Exposures to pesticides are age-related (discussed in Section D) where children may be more exposed than adults based on their diet and behaviors. Toxicodynamic and toxicokinetic differences may also contribute to the young being at a different risk to pesticide exposure. As summarized below, there are several reports in the literature investigating the basis underlying the differential sensitivity found for certain OP pesticides.

Toxicodynamic Considerations: There may be different mechanisms underlying age-related sensitivity to ChE inhibition for different OP pesticides. The exact mechanisms are not clearly understood in laboratory animals. For obvious reasons, no data are available in humans. There are studies, however, in laboratory animals that provide such information. Intrinsic differences in neuronal AChE (*i.e.*, differential inhibition of the target enzyme itself) do not appear to account for the observed age-related sensitivity found in young animals as suggested by *in vitro* studies (Benke and Murphy, 1975; Chanda *et al.*, 1995; Mortensen *et al.*, 1996; Atterberry *et al.*, 1997). Another toxicodynamic factor, the ability to restore function following exposure, does not appear to be the basis for age-related sensitivity to the OP pesticides because more rapid recovery of AChE activity in younger animals is found compared to adults (Chakraborti *et al.*, 1993; Moser, 1999; Pope *et al.*, 1991; Pope and Liu, 1997).

Other toxicodynamic differences that could affect age-related sensitivity to AChE inhibition concern the regulation of acetylcholine receptor number as well as acetylcholine release. Inhibition of ChE activity in the nervous system results in the accumulation of acetylcholine in the synapses causing hyperstimulation of the cholinergic receptors on postsynaptic cells. It is this hyperstimulation that leads to cholinergic toxicity. This hyperactivity may also lead to a decrease in the number of muscarinic receptors (*i.e.*, down-regulation). As a measure of toxicodynamic response to OP dosing, some studies have compared the degree of muscarinic down-regulation in adult and young rats. In a study of repeated, subcutaneous dosing with methyl parathion or chlorpyrifos, Liu *et al.* (1999) found that muscarinic receptor number was markedly reduced in pups compared to adult rats following repeated dosing with methyl parathion, suggesting age-dependent differences in mucarinic receptor adaptation. Interestingly, the chlorpyrifos exposure also produced more receptor down-regulation in the pup as compared to the adult, but the effect was not as pronounced as the methyl parathion effects. Moreover, using a different route, the same group showed that repeated oral dosing with chlorpyrifos caused equal down-regulation of muscarinic receptors in neonatal and adult brain (Zheng *et al.*, 2000). The effect on receptor down-regulation appears to be compound-specific, and possibly, route-specific. In the normal cholinergic synapse, it is known that feedback inhibition of acetylcholine release occurs through activation of the muscarinic acetylcholine receptors located on the presynaptic nerve terminals (see Pope, 2001b). Activation of the muscarinic acetylcholine receptors would decrease further acetylcholine release, thereby reducing the excessive stimulation of the postsynaptic receptors following AChE inhibition. A limited ability or adaptability of this presynaptic regulatory process in the young could lead to increased sensitivity to OP pesticides. There are only a few reports exploring age-related differences in muscarinic presynaptic acetylcholine receptor activity: evoked acetylcholine release was lower in brain tissues from newborn animals and aged animals compared to rats aged one to six months (Pedata *et al.*, 1983; Meyer and Crews, 1984). There is no information on the receptor response (either total muscarinic receptor number or feedback inhibition of acetylcholine release) in the developing human brain.

Toxicokinetic Considerations: Toxicokinetic differences among age groups can contribute to age-related differences in response, with the interplay of metabolic activation and detoxification processes being an important major factor, particularly in the first few months after birth (*e.g.*, see Ginsberg *et al.*, 2002). It appears from the literature that toxicokinetic differences play an important role in the differential sensitivity of the young to ChE inhibition following treatment with OP pesticides (*e.g.*, Brodeur and DuBois, 1963; Benke and Murphy, 1975; Scheidt *et al.*,1987, reviewed in Pope, 2001b). In addition to inhibiting AChE, OP pesticides also interact with other esterases, *i.e.*, carboxylesterases and/or A-esterases, an by doing so become inactivated or detoxified. A-esterases (*e.g.*, chlorpyrifos oxonase,

paraoxonase, or PON1) detoxify some OP pesticides by hydrolysis, whereas some OPs bind to carboxylesterases, a reaction which effectively lessens the amount of pesticide available for inhibiting AChE. Many investigators have noted the decreased capability of the young animal to detoxify OP pesticides by A-esterase or carboxylesterase esterases compared to adults (Mortensen *et al.,* 1996; Atterberry *et al.*, 1997; Costa *et al.*, 1990; Padilla *et al.*, 2000; Padilla *et al.,* 2002; Karanth and Pope, 2000).

Laboratory Animal Literature: The importance of A-esterase protection against the toxic effects of the anticholinesterase activity of OP pesticides has been demonstrated in several studies in which exogenous administration of A-esterase can lessen OP toxicity in rodents (Costa *et al.*, 1990; Li *et al.*, 1993; Main, 1956). Studies with an A-esterase knockout mouse reinforced the important role that A-esterases play in the detoxication of OP pesticides: knockout mice were much more sensitive to chlorpyrifos oxon or diazoxon (the active metabolites of chlorpyrifos or diazinon, respectively) than their wildtype litter mates (reviewed in Furlong *et al.*, 2000). In rats, A-esterase activity is virtually nonexistent in the fetus (Lassiter *et al.*, 1998) and increases from birth to reach adult levels around PND21 (Mortensen *et al.*, 1996; Li *et al.*, 1997). The animal data regarding the role of carboxylesterase in mediating OP toxicity are also quite extensive (*e.g.*, Clement, 1984; Fonnum *et al.*, 1985; Maxwell, 1992 a,b), but there are sparse data on the role of carboxylesterase activity mediating age-related toxicity to OP pesticides. Fetal rats possess very little carboxylesterase activity (Lassiter *et al.*, 1998) with increasing activity as the postnatal rat matures, reaching adult values after puberty (50 days-of-age) (Morgan *et al.*, 1994; Moser *et al.*, 1998; Karanth and Pope, 2000).

The temporal pattern of A-esterase activity (and carboxylesterases) correlates reasonably well with studies on OP sensitivity (see summary in Table 2). Several studies have shown an increased sensitivity of newborn rats to OP compounds which are detoxified via the A-esterase and/or carboxylesterase pathways (Gagne and Brodeur, 1972; Benke and Murphy, 1975; Pope *et al.*, 1991; Chambers and Carr, 1993; Padilla *et al.*, 2000; 2002; Karanth and Pope, 2000). For example, Padilla *et al.* (2002) and Karanth and Pope (2000) have correlated age-related sensitivity with the maturational profiles of these esterases. Using an *in vitro* assay, Padilla *et al.* (2000) showed that methamidophos, a pesticide which is not more toxic to the young rat, is not detoxified by A-esterases or carboxylesterases. These observations have been extended in a recent abstract to other OP pesticides using this *in vitro* model which measures the detoxification potential via these esterases in various tissues (*e.g.*, liver, plasma) (Padilla *et al.*, 2002). It was reported that the differential sensitivities of paraoxon (the active metabolite of parathion), malaoxon (the active metabolite of malathion), and diazoxon (the active metabolite of diazinon) were also correlated with the less efficacious detoxification by these esterases in young animals (Table 2). Karanth and Pope (2000) noted that the lower levels of esterases in neonatal and juvenile

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rats correlated with the increased *in vivo* sensitivity to ChE inhibition found for chlorpyrifos and parathion.

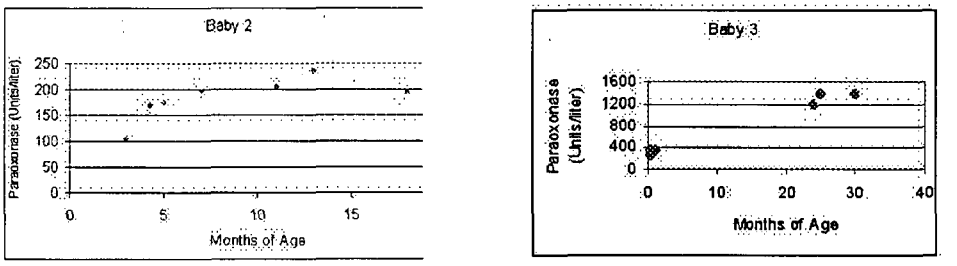
Table I.G-2. Summary of General Results for Age-Related Detoxification and Sensitivity in Rat Studies

Pesticide	Hydrolyzed by A-Esterases?	Bind to Carboxyl-esterases?	Age-Related Detoxification ?	More Sensitive to Young?	Reference
Chlorpyrifos	Yes	Yes	Yes	Yes (acute dose of PND No (repeated dosing of)	Karanth and Pope, 2000;Padilla *et al.*, 2002
Diazinon	Yes	Not Much	Yes	Yes	Padilla *et al.*, 2002
Dimethoate	Not tested	Not tested	Not tested	No	Meyers, 2001
Malathion	No	Hydrolyzed	Yes	Yes	Fulcher, 2001; Padilla *et al.*, 2002
Methamidophos	No	No	Not tested	No	Moser, 1999; Padilla *et al.*, 2000
Methyl Parathion	No	Yes (limited)	Yes	Yes	Pope, 2002a; Chambers and Carr, 1993
Parathion (not included in cumulative assessment)	No	Yes	Yes	Yes	Karanth and Pope, 2000; Padilla *et al.*, 2002

Human Literature: There are only a few studies in the older literature that have assessed A-esterase activity in children. Based on these studies, it appears that serum A-esterase levels are very low in human infants compared to adults (Augustinsson and Barr, 1963; Mueller *et al.*, 1983; Ecobichon and Stephens, 1972). After birth, there is a steady increase of this activity during the first six months to about one year (Augustinsson and Barr, 1963). In a related study of the age-dependence of total serum arylesterase activity (of which a large component is A-esterase activity), adult levels were achieved by two years-of-age (Burlina *et al.*, 1977). Although serum A-esterases are reported to achieve adult levels around six months to one year-of-age, there is uncertainty surrounding those values for the one-year-old due to the variability in the rate of maturation expected as these enzyme systems mature at different rates in a cross-section of one-year-old children. Suggestive evidence of this is the large degree of variability seen in the six-month and one-year age groups in the limited serum esterase data available for children (Augustinsson and Barr, 1983). This source of variability (maturational rate) is unique to children and is in addition to the host of factors that contribute to interindividual variability in the rest of the population and normally considered in noncancer risk assessments. Given the small number of children studied for this parameter, population distributions that reflect the central tendency and lower percentile value for A-esterase function

in one-year-olds relative to adults cannot be discerned from the data (for example see Ecobichon and Stephens, 1972; Figure 1). Moreover, these studies have only examined a few children, and given the high interindividual variability, it is very difficult to discern with confidence the maturation profile for serum A-esterases in young children. In ongoing studies in C. Furlong's laboratory, the same child is being evaluated for the appearance of serum A-esterase over time (*i.e.*, so that the high natural variation does not obscure developmental patterns) to better define the developmental profiles for serum A-esterases (See Figure 1 below). Preliminary results indicate that children reach adult levels of A-esterases around 12 to 15 months-of-age. Note that this age of maturation corresponds reasonably well with the maturation of human serum arylesterases mentioned above (Burlina *et al.*, 1977). It should also be pointed out that there is no information on the maturational profile of A-esterase in the human liver (an organ very important for detoxification), and there appears to be no information about the maturational profile of carboxylesterases in humans.

Figure I.G-1. Maturation Profile of Serum A-Esterase (Paraoxonase) Appearance in Infants and Children (Costa *et al.*, 2002).



Any anticholinesterase pesticide that is a substrate for A-esterase, the lower A-esterase levels in the blood of very young would result in more inhibitor available to reach target neuronal tissues. It should be noted that in addition to age-dependent differences in A-esterase activity, a human and animal genetic polymorphism has been well established (*e.g.*, Mackness *et al.*, 1998). Differences in observed rates of hydrolysis of paraoxon between individuals can vary by at least 20-fold (Furlong *et al.*, 2000). This large difference in A-esterase activity does not necessarily translate into equivalently large differential sensitivities to OP pesticides. There is also some recent evidence in the literature that low A-esterase activity may

predispose adult humans to a greater toxic response (Haley *et al.*, 1999; Cherry *et al.*, 2002) to nerve agents and/or pesticides.

Not only is limited detoxification a factor in increased sensitivity of the young, but another potential factor is the age-dependent ability to activate OP pesticides via oxidation by cytochrome P450s to their oxon form (*i.e.*, the active anticholinesterase metabolite). For example, oxidation by CYP3A4 plays a key role in the oxidation of OP pesticides in humans (Butler and Murray, 1997). Ginsberg *et al.* (2002) using the children's pharmacokinetic data from the therapeutic drug literature showed that compared to adults, oxidation by CYP3A4 tends to be more active in children beginning as early as two to six months-of-age with this difference lasting until at least two years-of-age. While this may increase concern for greater oxidative bioactivation in the young, the CYP-mediated oxidative dearylation pathway, which may also be more active at these ages, is involved in the detoxification of these pesticides. Therefore, it is important to compare the maturation profiles for these two CYP pathways. Based on data from rat liver microsomes (Ma and Chambers, 1994) and as modeled by Timchalk *et al.* (2002) for humans and rats, the activation step is 2.5-fold faster (based upon Vmax/Km ratios) and importantly, the activation step has a 8.4-fold lower Km than the dearylation step. The significance of this is that at relatively low, environmental exposures, OP molecules reaching the liver may be much more likely to be oxidized by the activation pathway than detoxified by the dearylation pathway. This evidence supports the potential concern that greater oxidative capacity in one- to two-year-olds may lead to more OP activation than seen in adults. The enhanced ability of the young to bioactivate OP pesticides to their oxon form, however, has not been correlated with an increased sensitivity to ChE inhibition. Nonetheless, when coupled with the potential limited ability of young children to detoxify these pesticides via the A-esterase and carboxylesterase pathways, this produces a source of uncertainty in the pesticide risk assessment for children.

d. Hazard Characterization Summary

There have been reports of signs and symptoms associated with cholinergic toxicity following high exposures to OP pesticides of adults and of young children. Common signs and symptoms of cholinergic toxicity in humans range from changes in heart rate and blood pressure, miosis, diarrhea, headaches, nausea, muscle weakness to unconsciousness, convulsions, and death. Not only can cholinergic toxicity occur in children following exposure to OP pesticides, but emerging investigations have raised concern about the effects of antiChE activity on neurodevelopment which may be a sensitive process susceptible to adverse perturbations.

As discussed in Section A, there is evidence that ChE and acetylcholine act as important neuromodulators in the developing brain. Because neurogenesis is not limited to the intrauterine period and may continue

throughout childhood, all stages of brain development are considered to be potentially susceptible to disruption by ChE inhibition. During the first few years of life, brain development is a tightly orchestrated process of migration and "pruning," which is under the influence of neuromodulators (ChE, acetylcholine, and other neurotransmitters), genetic controls, and the experiences of the child. Although OP pesticides may influence the migration of cells and the connectivity of the central nervous system (CNS) and result in consequences that could last into adulthood, it is not known how much of a perturbation (*i.e.*, degree of ChE inhibition) is needed, or how long this perturbation must be sustained, to disrupt normal development. The majority of OP pesticides included in the cumulative risk assessment have not been evaluated for neurodevelopmental effects (*e.g.*, functional, behavioral, or neuropathogical effects) or for ChE activity in immature animals.

In light of this uncertainty, it should be assumed that small perturbations resulting from either a single exposure or repeated exposure could potentially disrupt neurodevelopment. Therefore, it is important to insure that the adult brain ChE endpoints used in the cumulative risk assessment for OP pesticides are adequately protective of the young. Thus, a key issue in this assessment is whether ChE inhibition in the young will be caused at lower doses of these pesticides compared to adults or whether the young will show a higher level of ChE inhibition at comparable doses. It is the integration of the chemical-specific information along with the basic biological understanding of sensitivity and susceptibility that informs the need for the application of additional safety or uncertainty factors in the cumulative risk assessment to protect fetuses, infants, and children.

Because in humans, the process of brain development begins during gestation and continues postnatally through adolescence, it is important to identify the developmental windows of age-dependent sensitivity to ChE inhibition. In laboratory animals, ChE inhibition can be found to occur in all developmental stages of the young (*i.e.*, in fetal, neonatal, juvenile, and young adult rat tissues). In general, oral dosing of pregnant rats with OPs causes ChE inhibition in the fetus and/or neonate, but fetuses/neonates that are exposed *in utero* (and via early lactation) generally do not exhibit more ChE inhibition than is found in maternal tissues. These studies need to be interpreted with caution with respect to comparative sensitivity because the absorbed dose to the dam and fetus is typically not known. Also, the fetal rat appears to be less affected from repeated exposures to OP pesticides presumably because of the rapid recovery and resynthesis of the AChE in fetal tissue compared to the dam, making it difficult to compare relative responses in the fetus versus dam. It should be noted that rat fetal tissues and the placenta are deficient in key detoxification systems, including A-esterases and carboxylesterases. Overall, there is limited pharmacokinetic information available in fetal versus maternal tissues for OP pesticides.

Continued treatment following birth is important to ensure that critical periods of sensitivity are evaluated. Direct dosing of the postnatal rat may be necessary, however, because of the possibility of limited exposure through the milk via lactational transfer of OP pesticides. Although direct dosing of the pups (typically via oral gavage) maximizes and allows for quantification of exposure to the pups, it does not necessarily mimic the dietary intake exposure patterns in children. Furthermore, certain stages of brain development in the early postnatal rat are equivalent to the third trimester human fetus, and thus direct dosing of very young postnatal rats would not represent the pharmacokinetics of the chemical in the mother. Nonetheless, direct dosing experiments do provide a better basis to determine the comparative sensitivity of the pups and adult animals. Some direct dosing studies of postnatal rats are available on OP pesticides; however, these few studies have shown that acute postnatal exposures via direct dosing to young rats results in an increased sensitivity to ChE inhibition for certain OP pesticides (*e.g.*, malathion, methyl parathion, chlorpyrifos, diazinon), but not all (*e.g.*, methamidophos, dimethoate and by extension, its metabolite omethoate).

Age-dependent sensitivity to ChE inhibition by OP pesticides can sometimes also be found following repeated dosing studies in laboratory animals. An important issue with repeated dosing is the more rapid recovery (synthesis of new ChE enzyme) in postnatal (and fetal) rat tissues. In most repeated dosing studies comparing the responses of adults to postnatal animals dosed at the same frequency, this faster recovery in the young animals may result in less inhibition as compared to the adults, which is interpreted by some as lower sensitivity of the young. The results of such studies are critically dependent on the time interval between the doses and also the time (in relation to the last dose) at which the ChE inhibition is sampled in both age groups. As acute studies have shown, age-related sensitivity differences in rodents depend on the age at dosing, since the detoxification pathways are rapidly maturing. Therefore, in repeated dose studies, the fact that the animals are probably becoming less sensitive over time by virtue of this changing toxicokinetic pattern is an additional confounding factor. For all these reasons, a smaller differential for ChE inhibition has often been found between the pups and adults following repeated dosing when compared to acute exposure.

Although age-dependent sensitivity is found in some animal experiments, a key question is whether this sensitivity will occur in children. Children may respond to toxicity at lower doses than adults because infants and very young children may be less able than adults to metabolize and excrete toxic substances (Ginsberg *et al.*, 2002). Animal studies have shown a correlation of age-dependent sensitivity to certain OP pesticides with the developmental profiles of the A-esterases and/or carboxylesterases (enzymes that detoxify OP pesticides). As described in Section C, based on limited data, young children may have lower levels of these detoxification pathways. The most

highly exposed age group in the OP cumulative risk assessment was identified as the one- to two-year-olds. Although after birth there is a steady increase of A-esterase activity during the first six months to one year, these maturation profiles may vary among children (due to interindividual variability) and may vary among different tissues. Maturation profiles are not available for the carboxyesterases, and the developmental profile for either A-esterases or carboxylesterase has not been delineated in liver (a major detoxication organ). Furthermore, young children may also have an increased ability to activate OP pesticides to the oxon form as compared to the adult. Therefore, given the uncertainty surrounding the maturation profiles of young children for A-esterases and carboxylesterase, their potential to be more active than adults at bioactivating OP pesticides to their oxon form, as well as their rapidly developing nervous system, infants and very young children (including children in the one- to two-year age group) would potentially be vulnerable to chemical interference due to OP pesticide exposure.

Because some OP pesticides do show age-dependent sensitivity, and there are missing ChE data in young animals for many of the OP pesticides in this cumulative risk assessment, there is a degree of uncertainty regarding the estimation of risk. Under the children's safety factor provision a default safety factor of 10X is required to address this database deficiency unless there are reliable data to support a conclusion that a different safety factor would be safe for infants and children. As the following discussion indicates, OPP has concluded that reliable data do exist to support use of a database uncertainty factor to address this data deficiency. To determine whether a database uncertainty factor could protect infants and children, the degree of difference between the doses needed to cause a certain level of ChE inhibition between the young and adult was evaluated. As shown in Table 1, the differential between adults and immature animals following repeated dosing (typically 11 consecutive days) is at most approximately threefold. A single acute dose is found to cause differences ranging from about twofold up to approximately ninefold.

The relative sensitivities of immature animals found in repeated dosing studies are considered more appropriate than the results of the acute dosing studies for the cumulative risk assessment of OP pesticides for several reasons. Acute dosing studies were done with PND11 pups, which are more like the human newborn with limited detoxification ability. Repeated dosing studies of OP pesticides usually started treatment at PND11 and continued to PND21. As the immature animal ages, it rapidly reaches adult levels of A-esterases around PND21. Thus, evaluation of ChE activity in repeated dosing studies more closely mimics the maturation of A-esterase activity in children around one year-of-age when children are reaching adult levels of A-esterases. Thus, the use of repeated dosing studies better approximates the maturation profile of the age group that is significantly exposed to OP pesticides in the cumulative risk assessment. Children generally do not begin

to consume fresh (uncooked) fruits and vegetables until after six months-of-age or more. The highly exposed group in the cumulative risk assessment is the one- and two-year-olds, not the infants. Repeated dosing studies were also used to determine relative sensitivity because people are exposed every day to an OP pesticide through food, and thus an animal study using repeat exposures is considered appropriate. Also, following exposure to an OP, regeneration of ChEs to preexposure levels does not occur for days or weeks, making the exposed individual potentially more vulnerable to subsequent exposures during that period.

Repeated dosing studies are now available on six of the 22 OPs in the cumulative risk assessment. For three of these OP pesticides, the repeated dosing studies showed no increased sensitivity in the young, whereas increased sensitivity was seen in the other three. The differential sensitivity between adult and immature animals ranged from 1X (*i.e.*, no differential) up to a 3X difference. These studies are considered to provide a reasonable basis on which to establish the size of a database uncertainty factor for the following reasons. Although these six OP pesticides do not represent every structural and pharmacokinetic characteristic of the large class of OP pesticides included in the cumulative risk assessment, they are nonetheless a reasonable subset of different structural and pharmacokinetic characteristics. For example, methamidophos is a phosphoramidothioate of small molecular weight with no ring structure, does not require metabolic activation to generate an oxon form, and is not detoxified by esterases. On the other hand, methyl parathion is a phosphorothioate of larger molecular weight with a ring structure, hepatically bioactivated to its oxon form, and detoxified by esterases. In addition to the observed differential between adult and young animals following repeated dosing, it must also be kept in mind that the differential between the adult and young animal decreases as the animal ages and reaches adult levels of the detoxification enzymes. For these reasons, there are sufficient data to conclude that a 3X database uncertainty factor should be applied, and that the 3X UF_{Db} should be sufficient to account for potential age-dependent sensitivity to ChE inhibition. It should be noted that the application of a 3X UF_{Db} is in addition to the application of the customary intra- and interspecies uncertainty factors, which takes into account variability among the human population.

The question remains as to how such a database uncertainty factor should be incorporated into the cumulative risk assessment. In the cumulative risk assessment process, uncertainty or safety factors can be either applied to estimates of individual member's toxic potencies (*i.e.*, relative potency factors or RPFs) or applied as a group factor on the index chemical's point of departure.[3] Because age-dependent sensitivity to ChE

[3]In the cumulative risk assessment, the RPF approach is used to determine the joint risk of the OP pesticides, which applies dose addition. The RPF approach uses an index chemical as the point of reference for standardizing the common toxicity of the chemical members of the (CAG). Relative

inhibition is not common to all OP pesticides, application of a database uncertainty factor would be more appropriately applied as chemical-specific adjustments to the RPFs to account for ChE inhibition potentially occurring at lower doses in the young than in the adult or resulting in a more potent response at the same dose compared to the adult. These chemical-specific adjustments should be made on the RPFs for those OP pesticides that lack ChE data in the young. There are ChE data for a few OP pesticides that show age-dependent sensitivity. However, RPFs are based on a uniform measure of toxic potency using the same species, sex, endpoint, and age group from studies of comparable methodology. Given that there are too few data in young animals to determine RPFs for the OP Cumulative Assessment Group (CAG), the RPFs for those chemicals showing age-dependent sensitivity should also be adjusted to account for sensitive effects in the young. The RPFs of those OP pesticides that do not cause age-dependent sensitivity after brief periods of repeated exposure (dimethoate and by extension omethoate, methamidophos, chlorpyrifos) should not be adjusted.

In conclusion, the limited animal data on the relative sensitivity of young animals to cholinesterase inhibition (ChEI) caused by OP pesticides has raised uncertainty about the adequacy of the adult RPFs to be protective of the young and should be addressed by application of the traditional database uncertainty factor (UF_{Db}). Application of this UF_{Db} should be protective of potential age-dependent sensitivity to ChE inhibition and of potential adverse neurodevelopmental outcomes that are a result of the inhibition of ChE. Thus, there are reliable data to assign an additional factor (a database uncertainty factor of 3X) other than the default 10X additional safety factory. Further, because the database uncertainty factor addresses potential age-dependent sensitivity there is no a need to retain an additional special FQPA safety factor for potential pre- or postnatal toxicities associated with inhibition of ChE.

3. Cumulative Exposure Assessment

Another important consideration for the FQPA safety factor is the completeness of the exposure database. Whenever appropriate data are available, OPP estimates exposure using reliable empirical data on specific pesticides. In other cases, exposure estimates may be based on models and assumptions (which in themselves are based on other reliable empirical data). This section explains how the safety of the exposure estimates to infants and children were estimated.

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potency factors (*i.e.*, the ratio of the toxic potency of a given chemical to that of the index chemical) are then used to convert exposures of all chemicals in the CAG into exposure equivalents of the index chemical.

EPA identified and included three exposure pathways for the OP Pesticide cumulative risk assessment: food, drinking water, and residential/nonoccupational. Each of these pathways was evaluated separately, and, in doing this step of the analysis, EPA determined which of the OP pesticides were appropriately included for a particular pathway. The cumulative assessment of potential exposure to OP pesticides in food includes: 22 OP pesticides that are currently registered in the U.S. or have import tolerances; residential or nonoccupational pesticide uses included 11 OP pesticides (Note: many residential uses have been canceled as a result of risk mitigation efforts or are not expected to result in any significant exposure); and 24 OP pesticides (as well as several toxic transformation products) were considered in the cumulative water exposure assessment. Calendex™ software was used to determine the distribution of exposures and resulting Margins-of-Exposure (MOEs) from OPs in foods, drinking water and from residential uses.

Up until this time, OPP has performed its risk assessments using several different age groups for children including nursing infants less than one year, non-nursing infants less than one year, children one to six years-old, children seven to 12 years-old, and children 13 to 19 years-old. Because of the availability of more extensive data on children's food consumption, EPA was able to subdivide the children's age group one through six years-of-age into two different age groups: children one through two years-old and children aged three through five years-old. EPA also made some other slight adjustments to the age breaks defining groups for older children. As explained below, EPA analyzed all of the different children's age groups, but did not analyze every age group for every scenario. The children's age groups that were analyzed for all of the exposure scenarios in the revised OP cumulative risk assessment were one through two years-of-age and three through five years-of-age. EPA selected these two age groups because in single chemical risk assessments (including for the individual OPs) they most frequently reflect the highest levels of exposure. Thus, a narrow range of ages were used to capture the finer details associated with major contributors to risk under the premise that they reflect the exposure scenarios most likely to be emphasized in risk management activities.

In addition, EPA produced exposure estimates for all of the other children's age groups (children less than one year, children six through 10 years and children 11 through 19 years) for the Florida region. Florida was selected because it appears to have the highest level of exposure from all sources of pesticides combined. As expected, the exposures estimated for children less than one year-old or six and older were consistently lower than the exposures estimated for one- to two- and three- to five-year-old children. Based on this analysis, EPA concludes that, by focusing on two age groups of children (one- to two-year-olds and three- to five-year-olds), its risk assessment does not underestimate potential exposure to any age group of children.

a. Food Pathway

Exposure to foodborne pesticides is an important factor in evaluating the susceptibility of the young. Young children tend to eat more food in proportion to their body size and they tend to eat more frequently than adults. As discussed below, these characteristics are incorporated in the assessment of exposure to OP pesticides via food.

The food component of the cumulative risk assessment has been highly refined to reduce OPP's Tier 1 default assumptions (all foods contain residues at the maximum amount allowed under tolerance) to more realistic estimates of actual human exposure. It is based on residue monitoring data from U.S. Department of Agriculture (USDA) Pesticide Data Program (PDP), supplemented with information from the U.S. Food and Drug Administration (FDA) Surveillance Monitoring Programs and Total Diet Study. The PDP data provide a very reliable estimate of pesticide residues in the major children's foods. They also provide direct measures of co-occurrence of OP pesticide residues in the same sample, alleviating much of the uncertainty about co-occurrence in foods that are monitored in the program.

Another important aspect of the food exposure assessment is that it is based on actual consumption data from the USDA's Continuing Survey of Food Intakes by Individuals (CSFII). The CSFII provides a detailed representation of the food consumption patterns of the U.S. public across all age groups, during all times of the year, and across the 48 contiguous states. Additionally, OPP used a more recent CSFII in the OP cumulative assessment (the 1994-96 CSFII) that was supplemented in 1998 by the Supplemental Children's Survey. This 1998 survey focused on children from birth to nine years-old and greatly expanded (by several fold) the number of birth to four-year-old children in the survey database. OPP believes that the food consumption information used provides a very realistic estimate of potential risk concerns because it reflects the current eating habits of the U.S. public, including those of children. The use of the newer CSFII and the finer age breakouts should increase the accuracy and utility of the risk assessment overall by making it more descriptive of the anticipated exposures and risks for children.

A large percentage of the foods consumed in children's diet is addressed in this assessment. Only about 3% of the foods consumed by children still remained unaccounted for after using PDP and the FDA Total Diet Study and FDA monitoring data.

OPP is aware that some or all baby food manufacturers have adopted policies that restrict the use of OPs on fruits and vegetables that will be used in their products. As a result, children consuming commercially prepared baby food may not be exposed to OPs in their diet. OPP has investigated the impact of this assumption for children one through two years-of-age, and for

children less than one year-old. The residues in commercially prepared baby foods were assumed in the first case to be equivalent to those found in an adult diet. They were also set to zero to bound the lower limit and determine the extent of the impact on any risk assessment. Setting all residues in commercial baby food to zero had little impact on the magnitude of risk estimated for children one through two years-of-age. This observation is consistent with the very small amounts of baby food consumed by this age group. However, a substantial impact was observed for the age group of children less than one year-of-age because of the relatively large proportion of baby food in their diets. OPP believes that estimating exposure to pesticides from baby food as containing residues comparable to those in adult diets will not impact regulatory decision-making because the overall exposure to children less than one year-of-age is less than exposure to children one through two years-of-age.

Two exposure issues unique to children are not directly addressed in the current assessment. OP exposure from breast milk is not incorporated quantitatively. A review of the literature to identify any potential pesticide transfer from breast milk to children indicated no evidence that this pathway would represent a significant source of exposure (ILSI, 1998). However, further analysis has identified a study that demonstrated the presence of chlorpyrifos and chlorpyrifos-oxon in the milk of rats (Mattsson *et al.*, 1998, 2000). The results of studies generated by the regulated community in support of pesticide registration indicate no significant transfer of OPs to milk. OP pesticides are not found to transfer into cow's milk when cattle are fed a diet containing OPs. This finding is uniform across the entire class of OP pesticides. As a result, OPP believes that breast milk is not likely to be an important contributor of OPs to the diets of infants and children, especially at environmentally relevant levels of exposure. Baby formula is included in the current assessment with its consumption reflected in the FCID (Food Commodity Intake Database) translation of CSFII food consumption survey, and residue data available for all of its components.

OPP's dietary assessment also captures the metabolites of OPs that are known to occur at significant levels in food commodities (*e.g.*, omethoate–metabolite of dimethoate; methamidophos–metabolite of acephate; and, dichlorvos–metabolite of naled and trichlorfon). Although there is not extensive analytical data on other OP metabolites, there is adequate data (*e.g.*, from metabolism studies, FDA monitoring data) to indicate that the food assessment is not missing significant residues in food (such as for malaoxon– metabolite of malathion).

In summary, given the comprehensive data on potential exposure to OP pesticide residues through the food, OPP is confident that exposure to all age groups, including children via the food dietary pathway has been well characterized.

b. Drinking Water Pathway

Daily drinking water exposure estimates were generated using the simulation models PRZM and EXAMS (a description of the use of these models can be found http://www.epa.gov/oppefed1/models/water/index.htm). The use of these models allows estimation of concentrations of OP pesticides. OPP used these models to provide daily distributions of OP pesticide levels in water for incorporation into the probabilistic cumulative exposure assessment. Twelve regional water exposure assessments were conducted that were designed to represent exposures from typical OP usage conditions at one of the more vulnerable surface watersheds in the region. Each regional assessment focused on areas where combined OP pesticide exposure is likely to be among the highest within the region as a result of total OP usage and vulnerability of the drinking water sources. These methods have provided OP pesticide distributions that are, in many cases, reasonably comparable with available monitoring data in the same or nearby locations. There are too little data to quantify OP degradates that may result in drinking water. These metabolites, however, have been qualitatively assessed in the revised cumulative risk assessment by assuming complete oxon conversion with a 10-fold increase in toxicity compared to the parent compound: it was found that this assumption did not have an impact on the upper percentile distributions. In summary, OPP believes that the current cumulative assessment represents a reasonable, health protective estimate of likely exposure to OP pesticides from water to all age groups, including children.

c. Residential or Nonoccupational Exposure Pathway

The residential/nonoccupational exposure analysis includes the exposure from home lawn and garden treatments, pesticides used on golf courses, and applications made by governmental entities for the control of public health pests such as wide area mosquito sprays. The oral, dermal, and inhalation routes are considered. This analysis has incorporated activity patterns of children and the major sources of exposure to young children (*e.g.*, nondietary ingestion and hand-to-mouth behavior as established by video tapes of children). Furthermore, pet uses have been incorporated in the revised assessment. For the first time, the residential analysis used distributions of data and exposure elements instead of point values. In most cases, these data and exposure elements were chemical-specific. The analysis reflects all remaining residential uses of OP pesticides, consideration of both homeowner and professional applications, and postapplication exposures resulting from these applications. The analysis also employed the most recent survey data of residential uses and use information. Exposure due to activity in and around schools and parks is not addressed directly, because there does not appear to be any remaining OP pesticide uses for school structures and grounds. Nonetheless, the possibility of exposures encountered away from the home has been indirectly built into the

assessment by conservatively extending the duration of residential exposure beyond the two hours spent on grass to 3.5 hours spent outdoors.

The calendar-based model (Calendex™) that was used in the preliminary OP cumulative risk assessment allowed for the temporal aspects of the residential use of pesticides in twelve distinct geographic regions to be accounted for; these regions not only represent major crop growing areas and their influence on residues of OP pesticides in surface and ground water, but also present an opportunity to consider the unique climate patterns, pest patterns and potential socioeconomic patterns that influence residential pesticide use and expected exposure to OP insecticides. Furthermore, Calendex™ allows one to delineate the critical timing aspects of seasonal uses of OP insecticides that result in exposure, as well as to identify potential co-occurrences from multiple sources. Again, it cannot be emphasized too strongly that the exposure, monitoring, and residue studies that were used as input parameters in the modeling of residential/nonoccupational exposures represent the best available data on these pesticides (*i.e.*, the input parameters for residue levels and dissipation rates based on actual measurements).

d. Biological Monitoring Studies of Children

Biomarkers can serve as a useful measure of direct exposure aggregated over all sources and pathways by measuring integrated exposure from all routes. Biomarkers can be used to characterize the relative magnitude of exposure within population subgroups. In addition, biomonitoring can be used to verify predictions of exposure models.

Urinary biomarkers of OP pesticides and their metabolites have been used to characterize reference body burden levels for adult and children populations in the U.S. and Europe (Murphy *et al.*, 1983; Kutz *et al.*, 1992; Hill *et al.*,1995; Aprea *et al.*, 1996, 1999, 2000; Macintosh *et al.*, 1999; Fenske *et al.*, 2000; Quackenboss *et al.*, 2000; Adgate *et al.*, 2001; Heudorf and Angerer 2001; Krieger *et al.*, 2001). Most of this research has been designed to determine if children have higher exposures to OP pesticides than adults, and, if so, what are the differences in these exposures and what are the factors that influence these higher exposures.

Several researchers have conducted monitoring studies that have collected environmental and/or biological samples to assess the potential aggregate (inhalation, dermal, ingestion (dietary and indirect)) exposure to OPs by adults in their everyday environments. Hill *et al.* (1995) analyzed single spot urine samples from approximately 1000 adults (20-59 years-of-age) living in the U.S. to establish reference range concentrations for OP pesticide residues. Chlorpyrifos exposure was indicated by TCPY concentrations of 13 µg/L (95^{th} percentile value) and 77 µg/L (maximum value observed). Macintosh *et al.* (1999) reported on the relationship between

short-term and long-term average levels of OP biomarkers for 80 adults living in Maryland. First-morning void urine samples were collected at up to six different time periods equally spaced over a one-year period, with the range of urinary OP metabolite values being similar to the levels reported by Hill *et al.* (1995).

Only a handful of studies have been published in the literature that were specifically focused on biomonitoring of children for OP pesticides and their metabolites. These researchers noted that young children may be more highly exposed and are more susceptible to health risks from exposures to OP pesticides than adults because they are undergoing rapid physiological and behavioral development. Furthermore, in comparison to adults, young children: have a larger surface area to volume ratio; have a relatively large brain size as compared to total body mass; take in more air, food, and water on a per unit body weight; and, absorb, distribute, metabolize, and eliminate pesticides differently than adults (Guzelian *et al.,* 1992). Children also engage in specific activities in which they may more likely come into direct contact with contaminated surfaces and objects (Hubal *et al.,* 2000). These child-type activities include: sitting, playing on the floor; eating while roaming around the house; putting hands, objects, toys into the mouth; licking the furniture, pet, floor; etc.

The Minnesota Children's Pesticide Exposure Study (MNCPES) was the first published study to report multipathway pesticide exposures in a population-based sample children (Quackenboss *et al.,* 2000; Lioy *et al.,* 2000; Adgate *et al.,* 2001). Personal (hand rinse, duplicate diet, time activity diaries and questionnaires, videotape segment), biological (urine), and environmental (indoor/outdoor air, residential surfaces, soil, drinking water) samples were collected to assess children's aggregate pesticide exposure and attempt to identify the critical pathways of exposure. Three first-morning void urine samples were collected on three separate days during the study. The urine samples were then analyzed for metabolites of commonly used OP pesticides (Adgate *et al.*, 2001). Analysis of these urine samples for OP pesticides and their metabolites have shown that children do have a body burden level of OP metabolites (Quackenboss *et al.*, 2000; Lioy *et al.*, 2000; Adgate *et al.*, 2001). While the MNCPES study didn't assess adult exposures, Adgate *et al.* (2001) compared these urinary biomarker levels of OPs for children with the reference levels reported by Hill *et al.* (1995) and found similar ranges for both children and adults.

Fenske *et al.* (2000) collected and analyzed single void urine samples for OP metabolites from 109 children (up to six years-of-age) who lived in an agricultural community in the State of Washington. The children's urine samples were collected at the convenience of the child and parent. From the children's OP pesticide doses derived from this biologic monitoring study, the authors suggested that residents of agricultural communities may be more exposed to pesticides than the general population.

Two studies have compared urinary metabolite levels for all members of a household (Heudorf and Angerer 2001; Krieger *et al.*, 2001). Heudorf and Angerer (2001) examined urinary metabolite concentrations for children and adults living in dwellings that had not been recently treated with OPs (most recent treatment was four years prior). These investigators suggested that urinary OP metabolite concentrations in children and adults were not different. Krieger *et al.* (2001) assessed the extent of exposures for family members (adults and children) residing in homes where pesticides have been used. Chlorpyrifos was applied in this study by three different methods: fogger, broadcast, and crack and crevice. Analysis of the family urine samples for OP metabolites showed no significant difference between children and adult exposures for those family members living in the same households. However, both studies only examined the sample results without considering the factors associated with the physiological and behavioral differences between adults and children, a step needed to better describe and understand the real potential for exposure.

Interpreting the results of these published studies presents several challenges. First, only a few studies have been conducted and the results published in the literature. Secondly, the methodologies employed in each study have varied. Only spot urine samples have been collected, and, more importantly, the sample collection times for these spot urine samples have differed for many of the studies, ranging from first-morning voids to convenience samples collected during the morning hours. In the few studies that have collected both the environmental and biological samples, the levels of the OP pesticides and urinary metabolites have not correlated with any of the OP concentrations in the other environmental samples analyzed (Lioy *et al.*, 2000). Some investigators have tried to compare the children's and adult's OP pesticide and metabolite levels without correcting these data for the differences found in children associated with their differences in metabolic rates, muscle mass, creatinine production, and urinary output.

Although the available biological monitoring studies generally indicate children do have a body burden level of OP pesticides, based on the limited number of published studies and the inconsistencies noted above, it is difficult to make any general statements concerning the study population, much less the general population. Equally important, from these limited sets of published data, it is difficult to assess whether children's exposures to OP pesticides are the same, higher, or lower than corresponding adult exposures.

Several relatively large-scale children's aggregate pesticide exposure studies which include OP pesticides are ongoing or near completion by the U.S. EPA National Exposure Research Laboratory (NERL) scientists and academicians. However, the analyzed and published results of this research will not be available for several years. Without these additional data, questions regarding whether children's exposures to pesticides are higher

than adults or the validity of the cumulative exposure estimates can not be readily answered.

e. Exposure Characterization Summary

The cumulative exposure assessment of OP pesticides represents the first probabilistic assessment of multichemical and multipathway exposures to pesticides. Estimates of residues in food are based on actual monitoring and consumption data that capture the major food groups consumed by children. Several age groups are defined such that they reflect an adequate number of individuals in each age group and are based on real differences in age-related eating patterns. Estimates from food dietary intake are considered to confidently approximate dietary food exposure of children to OP pesticides. There is also confidence that the dietary drinking water exposure assessment for OP pesticides does not understate potential exposure to children (or any age group) given that regional water exposure assessments were conducted that were designed to focus on areas where combined OP exposure is likely to be among the highest within the region as a result of total OP usage and vulnerability of the drinking water sources. Furthermore, the cross check of PRZM and EXAMS predicted estimates with actual drinking water monitoring data gives confidence in the drinking exposure assessment. Finally, the residential and nonoccupational exposure estimates are also considered to provide protective estimates of children's exposures given the quality of the data and the conservative assumptions used. In summary, there is a high degree of confidence in the exposure data and methodologies used when assessing cumulative risk to children, that are considered to be protective of children without understating risk. Thus, for the exposure assessment, reliable data show that it is not necessary to retain the default 10X special FQPA safety factor.

4. Integrative Analysis of Hazard and Exposure

A weight-of-evidence analysis has been conducted to determine the completeness of the toxicity and exposure databases, and the degree of concern for pre- and postnatal toxicity associated with the common mechanism of toxicity, AChE inhibition. It was determined in the hazard assessment that there are reliable data to support application of a 3X database uncertainty factor (which is used to address the FQPA safety factor provision's expressed concern as to the "completeness of the data with respect to... toxicity to infants and children....") to address the limited data on ChE inhibition in immature animals and evidence that supports the potential for OP pesticides to show ChE inhibitory effects at lower doses in young animal compared to adults (*i.e.*, the age group on which the relative potencies values are based). There is no need for an additional special FQPA safety factor to address potential pre- and postnatal toxicity associated with ChE inhibition because application of the database uncertainty factor to the RPFs for the OP accounts for age-dependent sensitivity in the young and potential neurodevelopmental effects associated with ChE inhibition.

The revised cumulative risk assessment for OP pesticides is based upon the most comprehensive and data-specific exposure assessment ever performed by OPP. This statement is true for all aspects of the exposure estimates including pesticide sources from food, drinking water and residential uses. Each aspect of the assessment relied upon the use of the best available data for input parameters. The data were introduced into the assessment in large part in the form of distributions, permitting the assessment to reflect the full range of variability in each input parameter. This approach deviates from the past practice used particularly for drinking water and residential exposure estimates that relied upon high endpoint estimates. In this assessment, drinking water and residential estimates have been refined in much the same manner previously established for food assessments. The comprehensiveness and thoroughness of this exposure assessment allows OPP to conclude that an additional safety factor is not needed to address the completeness of the exposure database.

While the available data and methodologies used by OPP to estimate exposures cannot be used to precisely define an exact exposure for any given percentile of the population, OPP can bracket or otherwise define the range within which exposures are expected to fall. Specifically, OPP believes that the traditional single-day analysis in which individual days are assessed in isolation reflects a likely upper-bound of exposures. OPP also believes that the actual upper-bound of exposure is lower than the high-end estimated by the rolling average exposure (discussed in the Risk Characterization Section of the OP cumulative risk assessment). Additionally, the cumulative assessment was conducted in a way that does not intrinsically bias the analysis toward over estimation or under estimation of exposures, but instead reflects exposures anticipated to be experienced by the public. Accordingly, OPP believes that the analysis captures the highly exposed groups (including children) and represents exposures reasonably likely to occur and that the above-mentioned "bracketing" represents realistic expected upper and lower bounds on the estimated exposure. Final determinations regarding which predicted exposures will be considered in making a regulatory decision will depend on sensitivity analyses of predicted high-end exposures. These determinations could also play a role in a final conclusion about whether OPP remains confident that the analysis adequately captures the upper-bound of estimated exposures and, therefore, whether there is continuing support for the conclusion that an additional FQPA safety factor is not needed to address the completeness of the exposure database.

In summary, given the highly refined nature of estimates for all pathways of exposure, the use of bounding estimates to reflect the potential issues associated with timing and repeated exposures, and the application of the database uncertainty factor of 3X, the presumptive 10X safety factor can be removed.

I. Revised OP Cumulative Risk Assessment

H. Risk Characterization

1. Introduction

Risk characterization is the interpretation phase of the assessment process. Appropriate interpretation of results is particularly important for an assessment as complex as the OP cumulative risk assessment. Many types of data, derived from a variety of sources, have been combined to produce highly detailed estimates of risk from multiple OPs in food, drinking water or from residential use. The outputs of the assessment should be evaluated in a variety of ways. Potential biases in input parameters, the direction of the bias, and the uncertainty surrounding the inputs and the exposure model must be considered with regard to their potential impact on the results of the assessment.

OPP has attempted to reflect the completed risk mitigation measures from the single-chemical assessments. OPP will continue to make risk decisions about individual pesticides over the next months. Changes resulting from risk mitigation measures completed through March 2002 have been included in this assessment. Modifications in OP use patterns made after that date can be incorporated after they occur. The current document presents the estimates of risk associated with exposures to OPs in food, drinking water and from residential uses of OPs. The current assessment has used two modes of analysis (single-day and 7-day)to provide bounding estimates of potential exposures, and also reflects the risk estimates at a variety of percentiles of exposure. In addition, analyses were performed for periods of 14 days and 21 days to demonstrate that extending the averaging time for the risk assessment has little impact on the results obtained. The detailed results of this assessment are presented as a plot of MOEs over a period of 365 days. Contributions from various pathways and routes of exposure are arrayed separately. The results are presented graphically for the seven Regions, for the 1-2 year old and 3-5 year old age groups (Appendix III.J.2 to III.P.2). Data output tables for the 20 to 49 year old and 50+ groups are presented as spreadsheets (Appendix III.J.3) The results presented are based on a one day and seven day rolling average. For Region A the assessment also presents the 14 and 21 day rolling average results for the 1-2 and 3-5 year old groups. **No single value in the assessment should be used to independently arrive at the interpretation of the results.** As discussed below, interpretation of the assessment depends upon the synthesis of a vast body of information about the input data and the processing of that data to determine whether an acceptable risk has been achieved. A number of crop/chemical combinations in the food assessment and one chemical/use combination in the residential risk assessment warrant additional scrutiny in determining any future activities arising from this assessment.

2. Hazard and Dose-Response Assessment

The hazard and dose-response assessment is presented in detail in section I.B. That section outlines the steps in developing the dose-response relationships for each pesticide and its capacity to inhibit acetylcholinesterase in the brain of female rats. It includes a description of all of the data used in the dose-response analyses. Reasons for the selection of methamidophos as the index chemical for the OP cumulative risk assessment are also discussed. Finally, section I.B. describes the exponential dose-response model used to develop the dose response curves that provided the basis for developing the relative potency factors (RPF) for each chemical and the points of departure (POD) for the index chemical for each route of exposure (i.e., oral, dermal, and inhalation).

a. Acetylcholinesterase Inhibition: Data Quality & Common Effect

The first step in deciding that a cumulative risk assessment was needed was the determination that the OPs were toxic by a common mechanism, i.e., cholinesterase inhibition. This determination was made and subjected to peer review by the Scientific Advisory Panel in 1998 (http://www.epa.gov/scipoly/sap/1998/march/comec.htm). Once a common mechanism was identified, the next step in the process was to select an appropriate method for combining the risks from exposures to several pesticides from more than one source/route. A large body of data describing the inhibition of acetylcholinesterase in plasma, red blood cells and brain has been generated for each registered OP. OPP has elected to use the brain acetylcholinesterase data from female rats as the basis for developing RPFs and PODs for use in the assessment. The choice addressed a number of the concerns raised by the SAP and the public. Brain acetylcholinesterase inhibition is the endpoint used because it reflects a response in a target tissue of concern that is relevant to humans. Although RBC and plasma cholinesterase inhibition do reflect exposure to OPs and, therefore, the potential for adverse effects, brain acetylcholinesterase inhibition is an indication of direct effects upon the brain itself. Error due to the extrapolation between the response in a surrogate tissue (i.e., red blood cell and plasma) and a target tissue itself (brain) is eliminated. In addition, the data for the brain compartment have very narrow confidence limits when compared to those from the plasma and RBC compartments, suggesting that there is much less variability in this compartment across the data base.

This assessment uses the Relative Potency Factor (RPF) approach which applies dose addition. Briefly, the RPF approach uses an index chemical as the point of reference for standardizing the common toxicity of the chemical members of the cumulative assessment group (CAG). Relative potency factors (i.e., the ratio of the toxic potency of a given chemical to that of the index chemical) are then used to convert exposures of all chemicals in the CAG into exposure equivalents of the index chemical. The RPF approach

utilizes dose-response information to provide an estimate of each OP's potency for the common toxicity, and thus allows for the quantification of exposure as it relates to the joint risk of the CAG. OPP selected the relative potency factor approach based upon the relatively rich oral toxicity data base on cholinesterase inhibition available for the OPs which permitted consideration of the entire dose-response curve for each pesticide rather than only focusing on NOAELs that are a function of study design. Although a biological or pharmacokinetic modeling approach would have advantages in determining the cumulative risk for these OPs, the input parameters for such an approach are not available. Thus, the pharmacokinetic (PK) characteristics of the OPs could not be incorporated in the dose-response assessment which would allow for a more refined estimate of the combined risk to humans. Therefore, OPP has applied simple dose addition and used an empirical curve fitting model (i.e., the exponential model described below) to determine RPFs and PODs.

b. Exponential Dose-Response Model

OPP, in collaboration with ORD, developed an exponential model to describe the oral dose response curves for each OP that permitted fitting of a combination of cholinesterase (ChE) activity data from different studies. This model has been subjected to public comment and peer review by the SAP (http://www.epa.gov/scipoly/sap/2001/september/finalreport.htm). Although a PK model is the ideal approach, the SAP regarded the exponential model (with their recommended improvements) to be appropriate for the data being analyzed for derivation of relative potency factors and points of departure. OPP has responded to the SAP recommendations on the exponential model by making modifications to address the issues raised. One issue was that the original model did not appropriately reflect cholinesterase inhibition at very low doses. The revised statistical model now incorporates, to the extent supported by the data, a flat region at the low dose portion of the dose response curve. Another issue raised by the SAP concerned the derivation of the factor "B". The B value is the limiting value for the maximum cholinesterase inhibition (called the horizontal asymptote). The SAP raised the issue that the weighting strategy used for calculating the "B" which assumed 100% cholinesterase inhibition (i.e., 0% ChE activity) did not adequately reflect the actual B value for each OP (the B value was often less than 100% inhibition at the asymptote). The revised approach has been modified in order to generate B values for each OP reflective of its dose-response data.

OPP assumed dose additivity by application of a single model to all of the OP's dose-response curves. There is some uncertainty surrounding the assumption of dose additivity given that the B values (horizontal asymptotes) are heterogeneous among the OPs analyzed. This heterogeneity is indicative that the dose-response curves are not parallel and, therefore the application of simple dose addition is only an approximation of joint risk and may not be

precise. Dose additivity assumes that the common mechanism chemicals behave in a similar fashion (i.e., same pharmacokinetics and pharmacodynamics) and that their dose response curves will be parallel (i.e., the ratio of their relative toxic potencies remain the same throughout their dose range). The underlying biological processes that determine the toxic potency of each OP are extremely complex and involve several metabolic systems in different organs as well as re-synthesis rates of the different cholinesterases. The activation and/or deactivation rates differ for some of these OPs. However, because of insufficient data, these pesticides can not be separated into subgroups based on pharmacokinetic and pharmacodynamic characteristics. Thus, current information on OP pharmacokinetics and pharmacodynamics cannot provide a sufficient basis to depart from the assumption of dose additivity. Also, available studies on OP mixture interactions do not provide a sufficient basis for departure from dose additivity.

In summary, OPP believes that the model fitting procedure used in this assessment provides reliable estimates of relative potency and points of departure. The cholinesterase data used for the oral route of exposure was quite extensive and, in general, of good quality for dose-response modeling. The data for the inhalation and dermal routes tended to be less extensive and not as robust for dose response modeling. OPP has refined the dose response modeling for the oral dose by incorporating the SAP recommendations in its dose response assessment of these OPs. OPP has attempted to address uncertainty in extrapolating to lower human exposures by the revised model and by using a low model estimate (BMD10) to develop OP relative potency factors. OPP acknowledges that there is uncertainty that dose addition applies to all of these OPs at human exposure levels. In the absence of data to the contrary, however, dose additivity is assumed. OPP realizes that the assumptions of additivity and the dose response modeling used in this assessment may slightly overestimate response due to the assumption that response will be uniform regardless of the underlying background exposure level.

A BMD10 was selected as the basis for comparison of the dose-response curves for the OPs. OPP's goals in selecting a point of comparison were to choose a point in the observed response range, but low enough on the curve to reduce the impact of any lack of proportionality between response that might result from deviation from the assumption of proportionate dose response between OPs. In addition, OPP was concerned that the magnitude of the response (cholinesterase inhibition) be sufficient to ensure that it was reliably distinguishable from background. A power analysis of the data used in deriving the 21-day steady state determination indicated that there was insufficient power to distinguish the change in cholinesterase inhibition reliably below 10% inhibition. In addition, OPP has used the central estimate of the BMD10 instead of the BMDL generally used for single chemical assessment. This decision reflects the complexity brought to the analysis by the joint

consideration of multiple studies for multiple chemicals. The use of the BMDL has been suggested for those instances in which single studies are modeled to provide an indication of a reasonable lower limit on response. In the OP cumulative risk assessment, the results of several studies were combined, introducing the potential for inappropriately broadening the confidence limits about the BMD10 and making the BMDL a likely underestimate of the POD for each chemical. These considerations strengthened the case for selection of methamidaphos as the index chemical because the BMD10 and the BMDL were very similar suggesting a very good fit of the data to the model.

c. Selecting the Index Chemical

OPP selected methamidophos as the index chemical for the current assessment. Methamidophos has sufficient data for cholinesterase inhibition to support modeling of a BMD10 by all three routes of exposure. The high quality dose response data for methamidophos permits reliable estimates of PODs for all routes without resorting to the use of the less precise NOAELs. Certainty in the PODs was considered to be of great importance in as much as they will impact the outcome of the assessment to a greater extent than any other aspect of the toxicity data base.

d. Use of Steady State

During the data evaluation phase, OPP elected to use only those data points that resulted from exposure of rats for 21 days or longer. This choice was made for a number of reasons. First, because of the many agricultural uses of OPs and the resulting residues that occur in food and water, and also the application of OPs in homes across the US (as reflected in the assessment), the likelihood of encountering an exposure to OPs with no prior recent exposure was considered to be small. Therefore, the use of single-day toxicity data was considered inappropriate. Further, following exposure to an OP, regeneration of cholinesterases to pre-exposure levels occurs in the time scale of days to weeks, not a single day, making the exposed individual potentially more vulnerable to subsequent exposures during that period. Examination of the rat data suggested that for most pesticides, cholinesterase inhibition reached steady state approximately by 21 to 30 days after the start of dosing. After that point, little change occurred in the degree of inhibition resulting from continued administration of the dose for a longer period. OPP selected 21 days as a reasonable time point to assume that steady state had been achieved. For the purposes of this discussion, steady state is defined as the point at which further inhibition of the enzyme is offset by regeneration of the enzyme and equilibrium has been achieved. All of the pesticides considered have very stable, reproducible levels of cholinesterase inhibition in all compartments measured.

The selection of the data set to support the steady state decision hinged upon two determinations about the data available. The first was the

evaluation of rate of change in cholinesterase inhibition as discussed above. The second was the decision that a 10% inhibition of brain cholinesterase was a tolerable level of inhibition that was unlikely to result in an unacceptable adverse outcome for the exposed individual. This decision is the more critical in determining the application of the hazard data to the running time frame approach than the actual selection of the time point of determining the extent of inhibition. The application of a steady state approach is predicated on the assumption that the extent of cholinesterase inhibition on any given day reflects the balance between prior exposures and the extent of recovery experienced. The processes of inhibition and recovery are balanced in the rat data as they are in exposed human populations. The major distinction between the steady state data from the rat studies and the likely inhibition in the exposed population is that the actual dose to the rat on any day and on preceding days is known. In the human population, the prior exposures can not be known with certainty. However, as demonstrated by the current exposure assessment, the prior exposures may be either higher or lower than for the current day. OPP believes that the use of steady state data is consistent with the results of biomonitoring data available in the literature. There is a body of evidence that indicates a sizeable proportion of the US population has a fairly constant background exposure to OPs. This is evident from the results of the NHANES III in which 82% of people who provided urine samples for analysis were found to be positive for trichloropyridinol, a metabolite of the OPs chlorpyrifos and chlorpyrifos-methyl (Hill et al., 1995). Further examination of the NHANES III data indicate that a sizeable proportion of the population have metabolites in their urine that are not compound specific, but are associated with other OPs. Preliminary analyses of data collected under the auspices of NHEXAS also indicate that metabolites from a variety of OPs are found in urine from populations of adults and children sampled around the US.

The use of 21-day steady state data in rats may over- or understate the potential for cholinesterase inhibition based upon exposure in the current day combined with residual effects from the preceding day(s). The extent and direction of the error can not be known, however, data pertaining to prior exposure to OPs such as those cited above reflect a pattern of exposure to humans that is qualitatively different from the repeated daily dosing used in rat feeding studies and therefore there is a possibility that risk is overstated. The use of the 21-day steady state data fixes the estimate of dose relating to a 10% cholinesterase decrement and permits a reasonable estimate of risk from exposure to OPs.

This finding was important in determining the appropriate manner in which to incorporate the available acetylcholinesterase inhibition data into the hazard assessment. In conjunction with the understanding that the period of reversibility for OP-induced cholinesterase inhibition is on the order of several days to weeks, it provides a reasonable basis for the decision to use steady state measures of cholinesterase inhibition as the basis for OPs RPFs and

the PODs for methamidophos. It also supports the need to consider multiple modes of exposure, focusing on both more extreme episodic exposures as well as longer term average exposures. These two modes of analysis when used together acknowledge the potential for continuous exposure over an extended period of time while allowing an evaluation of the potential impact of periods of elevated OP exposure.

In summary, OPP has taken steps to address the most significant methodological issues raised concerning the dose response assessment developed in support of the OP cumulative risk assessment. OPP is confident that the assessment as performed is scientifically and statistically sound and based upon a reliable data set.

3. Use of Calendex and the Mode of Analysis

The use of Calendex in conducting the current assessment is described in section I.F of this document. Calendex permits the simultaneous evaluation of more than one pathway of exposure. It also permits the evaluation of exposure on a calendar basis, considering changes in exposure patterns with season as pest pressures change. In the December 3 Preliminary OP Cumulative Risk Assessment, OPP demonstrated the use of Calendex to develop a distribution of linked single-day exposures. This approach to estimating an annualized distribution of exposures for use in risk assessment received numerous public comments and reviews from the FIFRA Scientific Advisory Panel.

The single day analysis approximates an analysis similar to that performed for acute dietary evaluations in single-chemical assessments. As in the acute dietary analyses, a full range of inputs for dietary residues is paired with the individual consumption records from the CSFII. In addition, a water concentration value is paired with the water consumption value developed as described in section I.E. Finally, an estimate of exposure from residential sources is calculated and combined to develop an estimate of the total MOE. A distribution of total MOEs is generated for each day of the year. A series of percentiles are then selected for each day to evaluate potential risk concern for the combined uses of the OPs. This analysis assumes that the potential exists to experience a high-end exposure on every day of the year. In the current assessment, values are presented for the 99.9th, 99.5th, 99th, and 95th percentiles of exposure.

OPP developed a second assessment considering the potential risk from a series of 7-day rolling averages across the year. This process is described in section I.F. This analysis is an attempt to better match the time frames for the toxicity data with the consumption data which are not directly comparable. The toxicity data used in the assessment are based upon 21 days of exposure to rats in feed. This data reflects steady state measures of cholinesterase inhibition and is readily available for all OPs. Food consumption data are available only on a single-day basis. The 7-day average allows for consideration of the variable

nature of likely exposures to an individual across time. It permits consideration of the impact of varying exposure in the diet and from residential uses of OPs from day to day. OPP also investigated the potential impact of longer averaging times (14 and 21 days) on the results of the risk assessment. The longer averaging times resulted in incrementally small decreases in the estimated risk, with the effect of duration decreasing with increasing time. This behavior is not unexpected in that with longer averaging time, the exposure will approach the mean exposure for the output distribution. However, the longer time frames will further obscure any time-related variability in exposure. The use of the 7-day rolling average provides a more realistic profile of exposure across a series of multi-day exposures while maintaining some sense of anticipated variability.

OPP believes that the results of the single day and 7-day analyses successfully bound the anticipated exposures resulting from residues of multiple OPs in food. The one-day analysis assumes that an individual is exposed to OP exposures from the tail of the distribution every day. This assumption overestimates risk. The seven-day analysis incorporates day-to-day variability in exposure and is more representative of anticipated exposures. The major sources of difference in the results of the two analyses arise from differences in how the data is incorporated into the analyses and the ability to reflect day to day variability. The differences are: the selection process for the two days of CSFII data, the assumption of independence of residue data inherent in the use of the PDP data in the assessment, and the inability of the approaches to allow for carryover cholinesterase inhibition from prior exposures.

a. Use of CSFII Data

In the single day analysis, one diary for each individual in the CSFII is selected to be paired with a randomly selected set of residue values for each food consumed. A set of exposures from OPs in foods is developed and arrayed as a distribution from high to low exposures. This type of assessment assumes that the consumption of foods from one day to another is independent, with no consideration of the potential for eating leftovers or consuming foods purchased in bulk such as juices or potatoes. As a result, the assessment over emphasizes variability in the diet. This factor may bias the exposure assessment up or down depending the food/pesticide combination that is not repeated appropriately. The magnitude of the effect also will vary depending upon the specific food/pesticide combination.

The use of the CSFII data in the 7-day rolling average consists of a random redraw of the two available days of consumption data for each person in the data base. This process is intended to maintain the integrity of the data for individuals, including to the extent possible, any information defining patterns of diet peculiar to them. However, the redraw process results in the implicit assumption that every individual in the CSFII consumes a diet that is limited to the records in the diaries repeated randomly across the year. As a result, the variability likely to occur in the diet is not fully expressed in the

current risk assessment. This factor is expected to reduce the range of exposures to which any particular individual can be exposed by limiting the number of commodities and pesticides possible to those reported in the two daily diaries. This factor is anticipated to introduce a downward bias into the exposure assessment. However, the impact on the assessment is anticipated to be small because all possible combinations of exposures are still available. The shape of the final distribution may be modestly affected by the difference in averaging that occurs due to the reduction in combinations available, but the exposure estimates at the upper percentiles of exposure should not be significantly affected.

b. Use of PDP Data

PDP data are used for most of the pesticide residues in food assessment. These data are introduced into the assessment in a manner that imposes the assumption that all eating days are independent with regard to the source of food consumed. In fact, consumption on any given day may not be independent of preceding days to the extent that individuals consume bulk items such as juice, bunches of grapes, or bags of produce or left-overs that have the same level of residues on multiple days. As a result, exposure from items of these types may be under represented in the single day and 7-day rolling analyses to the extent that a high end residue may be selected on one day, but not resampled on the subsequent days. As result, these assessments may be biased downward with respect to the exposure estimates developed, although the magnitude of the error is not known.

c. Impact of Residual Cholinesterase Inhibition

Cholinesterase inhibition resulting from OP exposure is not immediately reversible. OPs bind covalently to the active site of the enzyme. Recovery is largely due to regeneration of the enzyme rather than dissociation. As a result, the recovery time (time required for cholinesterase levels to return to pre-exposure levels) is extended, requiring on average 1 to 2 weeks in humans. As a result, the cholinesterase inhibition experienced on any given day is the sum of inhibition from that day's exposure combined with residual inhibition due to exposure on the preceding several days. As each day passes, the importance of inhibition from any given preceding day declines until it is fully reversed. The single day analysis does not incorporate an estimate of the phenomenon. This results in a downward bias of unknown magnitude. The magnitude of the bias will be dependent on the likelihood of exposures on previous days. The Calendex model attempts to incorporate some aspect of the prior exposure in the 7-day rolling average approach by allowing for the combined exposure over a 7-day period of time. To this extent, Calendex captures the carryover aspect of **exposure** to pesticides. However, this approach can not account for the biological aspect of declining importance of an exposure with the passage of time. It also de-emphasizes the impact of intermittent high exposures as they are averaged into the

background. To the extent that Calendex can not reflect this aspect of the impact of exposure to OPs, the 7-day rolling average will tend to be biased downward with regard to the estimate of risk from exposure to OPs.

4. Food Assessment

The food component of the OP cumulative risk assessment is based primarily upon two extensive, reliable data sets: 1) USDA's Pesticide Data Program, and 2) USDA's Continuing Survey of Food Intakes by Individuals, 1994 -1996 + 1998 (CSFII). The PDP data provide a very reliable estimate of pesticide residues in the major children's foods. They also provide an indication of the co-occurrence of OPs in the same sample, alleviating much of the uncertainty about co-occurrence in foods that are monitored in the program. The CSFII provides a detailed representation of the food consumption patterns of the US public across all age groups, during all times of the year and across the 48 contiguous states. These two data components provide a firm foundation upon which to assemble other data to develop the OP cumulative risk assessment.

a. Consumption Data

Up until this time, OPP has performed its risk assessments using the 1989-91Continuing Survey of Food Intakes by Individuals (CSFII). This survey was conducted by USDA and was based on responses over three consecutive days. A more recent CSFII was performed (the 1994-96 CSFII) which was supplemented in 1998 by the Supplemental Children's Survey. This 1998 survey focused on children from birth to 9 years old and greatly expanded the number of birth to 4 year old children in the survey data base. Importantly, the Supplemental survey was designed in a manner such that the results from the 1998 CSFII survey could be combined with the 1994-96 survey. OPP believes that the newer survey information provides a more realistic estimate of potential risk concerns because it reflects the current eating habits of the US public. Based in part on past recommendations of the FIFRA Scientific Advisory Panel and other advisory bodies, based in part on OPP analyses of dietary and behavioral patterns, and based in part on a minimum number of individuals needed to provide a good representation of eating patterns, OPP has determined that the following age groupings are appropriate for the cumulative assessment: birth to 1 year of age (i.e., 0 - 11 months); 1 to 2 year of age (i.e., 12 - 36 months); 3 through 5 years of age; 6 through 12 years of age; 13 through19 years of age; 20 through 49 years of age; and 50 years of age and greater.

For this assessment, the following age groups were analyzed for all regions: 1 to 2 years of age; 3 through 5 years of age; 20 through 49 years of age; and 50 years of age and greater. These age groups were selected because the other age groups are rarely the most highly exposed in the single-chemical assessments. For Region A, all subpopulations were evaluated to confirm this assertion. Region A was selected as an appropriate

analysis to demonstrate the impact of a variety of parameters within the assessment because it consistently demonstrates the highest exposures and risks estimated for regions across the US. The change to the more refined age groupings should improve our ability to identify age-related differences in food consumption (especially among young children). The use of the newer CSFII and the finer age breakouts should increase the accuracy and utility of the risk assessment overall by making it more descriptive of the anticipated exposures and risks for each age group.

OPP is confident that the consumption data available from the CSFII permit a reasonable basis for estimating exposure to OPs in foods. The data are used empirically in combination with residue values to estimate exposure. As a result, no issues relating to the appropriateness of curve fitting procedures have been introduced into the assessment. OPP also believes that an adequate number of samples are available to support estimation of exposure. Approximately 4000 consumption days for 2000 individuals are available for each subpopulation. This body of data is sufficient to support simulation well out into the tails of the exposure distribution with little concern for overestimation of consumption. However, as is the case with all sampling protocols, the proportion of samples available declines toward the extremes of the output distribution. As a result, extreme output distribution values are less well represented than those reflecting the central tendency for the output distribution. OPP acknowledges that the use of CSFII in this assessment may not fully reflect the eating habits of high end eaters, introducing some uncertainty with respect to the tails of the distribution of estimated exposures in the assessment.

b. PDP Monitoring Data in the Assessment

The use of PDP as a source of residue data has a number of inherent benefits that preclude the need for the use of conservative assumptions in the assessment. PDP provides a direct measure of the occurrence of more than one OP in any sample analyzed. OPP can use these data as an indication of pesticide co-occurrence likely to be encountered in foods. OPP assumes that co-occurrence mirrors the PDP values; in fact PDP composites contain multiple individual units which may have different profiles of co-occurrence. Therefore, use of PDP data in this manner may overstate potential risk. PDP implicitly reflects the percent of a crop that has been treated with any given OP by measurement of the residues.

Samples with non-detectable residues are assumed to be "zero" values in this assessment. The impact of this assumption was tested in the OP Cumulative Risk Case Study (USEPA, 2000c) that was presented to the SAP in December 2000. In the Case Study, a similar use of PDP data as the residue data source in this assessment was demonstrated for 24 OPs. The resulting data set had characteristics very similar to the one used in the current assessment. The analysis performed demonstrated that the use of

the "zero" values had only negligible impact on the MOEs developed at the upper percentiles of exposure.

Although the result of replacing all non-detectable residues with "zero" values would intuitively suggest an under-estimation bias, OPP has demonstrated through its case study that this change has little impact at all on the portion of the exposure curve likely to be used for regulatory purposes. This result is not surprising for a multiple chemical assessment addressing the number of chemicals under evaluation here. This assessment combines many data elements, with no single chemical or commodity dominating the exposure. The residue data used in this assessment include highly consumed foods, and several of these have large numbers of detects as well as a few high detects of OPs. There are detectable residues of at least one OP on 25% of the samples used in this assessment with a high of 66% on one commodity. Generally, the LODs for PDP data are very low (the average LOD for the entire data base is about 0.01 ppm). Therefore, it seems reasonable that the effect of assumptions related to estimation of values below the LOD would not significantly influence exposures at the highest percentiles of exposure. This result may not be the case for other assessments containing fewer foods or lower levels of detectable residues and should be evaluated for each subsequent case.

c. Data Translation from PDP

Not all foods to which OPs are applied are monitored in PDP. OPP has developed a scheme by which commodities that are measured by PDP serve as surrogate data sources for commodities that are not. This approach is outlined in OPP/HED SOP 99.3 (USEPA, 1999b). It is based upon the concept that families of commodities with similar cultural practices and insect pests are likely to have similar pesticide use patterns. Although this approach is generally sound, it introduces uncertainty with regard to how similar the use patterns for a given pesticide are to those for even closely related commodities.

For example, the same OP may be applied on a similar time schedule. However, the rates of application may differ between the crops treated. The number of treatments may also differ for application to the two crops. This issue is of importance to consider when conducting sensitivity analyses of the results of the risk assessment. When the data are adapted for the use of several chemicals simultaneously, and estimates of co-occurrence are derived from that data, the likelihood of an inappropriately assigned residue becomes greater. Although the commodities may have similar cultural practices, they may differ in the number of OPs registered for these uses. In addition, the translation from one commodity to another implicitly assigns the inherent percent crop treated information from one commodity to another. The direction and magnitude of this error will differ from one commodity to another.

OPP believes that this potential source of error in its assessment will most likely result in over-estimation bias. However, the magnitude of the error is probably not great in that the commodities for which PDP data was translated represent only ~1% of a child's diet.

d. Other Sources of Residue Data

PDP data and surrogate PDP data do not cover all commodities of interest. For meats, seafood and eggs, FDA's Total Diet Study and FDA Monitoring data provided residue estimates. These data suggest that eggs and seafood contain negligible residues. For most meats (beef, pork, sheep and goat), the maximum residue from the Total Diet Study was used. Although the use of the maximum residue as a single data point for meats is an overestimate, OPP has conducted a sensitivity analysis making all residues for meats zero and found that there was no change in the outcome of the risk assessment at the upper percentiles of exposure. This is not surprising in that the highest residue observed is itself very low. Therefore, OPP considers these factors neutral with regard to their impact on the results of the assessment.

Approximately 3% of the foods consumed by children 1 - 2 years of age still remained unaccounted for after using FDA Total Diet Study and FDA Monitoring data. Sugar, molasses and syrups were assigned a residue value of zero. These products are highly processed commodities that are unlikely to retain any significant residues following the processing steps. The limited data from the Total Diet Study found no residues in pancake syrup or sugar. No data are available for field corn or dried beans. However, these commodities are also blended and highly processed before consumption. OPP believes that omission of these foods from the assessment will not result in any change in the results of the assessment.

e. Impact of Regulatory Actions

Inherent in the use of monitoring data to estimate future residues is the concern that any changes in use patterns will not be reflected in the data. The OPs are currently undergoing use changes as a result of the individual chemical decisions. In most cases for which legal agreements have been signed, the uses have been removed from the assessment. For other pesticides, pre-harvest intervals have been extended or rates have already been reduced. These changes are not reflected in the assessment as they are not yet apparent in the monitoring data available. A specific example of this issue is the rate reductions agreed upon for azinphos-methyl on apples in 1999. Although the rate reductions have been implemented, they will not be reflected in monitoring data until the 2002 PDP data become available. This delay reflects the year lag in affecting a new growing season following implementation as well as the long period during which treated apples can remain in the chain of commerce following harvest.

Decisions have not been completed for all OPs included in this assessment. Completion of the regulatory process for these pesticides could result in additional exposure and risk reduction measures. These changes could result in further reductions in exposure in the food portion of the assessment. The magnitude of that change is uncertain.

f. Model Outputs

The single-day food component of the OP cumulative risk assessment was conducted using the DEEM software. This program evaluates the full range of dietary exposures across a single day. It permits a detailed evaluation of the source of exposures with regard to which foods and pesticides are the likely sources of the exposure. This analysis served as the basis for determining which commodity/pesticide combinations warrant further scrutiny in the event that further regulatory action is determined to be needed. The use of the single day assessment was considered to be appropriate because exposure to OPs in foods is uniform nationally, and it has no significant seasonal variations. OPP has extensive experience with the two data bases that confirm this assumption as reasonable. OPP has conducted a large number of seasonal assessments of exposure to individual pesticides in foods. These assessments show virtually no differences in exposures across seasons. This finding is not surprising in light of the widespread distribution of foods across the United States, and the proportion of foods that are imported. Lack of seasonal consumption patterns is also not unexpected given the ability to preserve and store foods for delayed consumption, and the import of seasonal foods to bridge gaps in domestic production periods. Similarly, PDP does not suggest any significant alteration in the types of pesticides encountered or the magnitude of residues across the year. The assumption of nationally uniform distribution of foods does not reflect highly localized consumption events that may be encountered by individuals who obtain foods at road side stands and consume it closer to the time of harvest than the foods available in larger grocery stores. OPP does not have reliable data on either consumption or anticipated pesticide residues to permit evaluation of this type of exposure, however we anticipate that only a small percentage of food consumed would be affected.

The results of the food portion of the revised OP cumulative risk assessment are summarized in Table I.H-1. The results are presented in the form of MOE for children 1 - 2 years of age, 3 - 5, adults 20 - 49, and adults 50+, at the 95th, 99th, 99.5th and 99.9th percentiles of exposure. The percentile of exposure as used in this document indicates the percent of the output distribution that is predicted to experience exposure less than or equal to the exposure at that point on the exposure distribution curve. In other words, at the 95th percentile of exposure, 95% of the output distribution is likely to have the exposure indicated or less. Five percent are likely to be exposed to higher amounts of OPs. The 1 - 2 year age group is consistently the most highly exposed subgroup in the analysis. This is due to a higher consumption

to body weight ratio for this age group. Results are presented for both single-day and 7-day analyses for all regions, with 14-day and 21-day analyses included for Region A. The FQPA Safety Factor was incorporated into the RPFs to permit modification of the assessment on a chemical-specific basis as appropriate based upon our current understanding of age-related sensitivity. The toxicity endpoints for this assessment were developed in consideration of a 10X uncertainty factor to account for interspecies variability and a 10X uncertainty factor to account for intraspecies variability. As discussed fully in section I. G., because some OP pesticides show age-dependent sensitivity and there are missing comparative ChE inhibition data in young animals for many of the OP's, the magnitude of the FQPA Safety Factor was set at 3X for most of the OP pesticides. Age-dependent susceptibility data are available for seven of the OP's. The data for dimethoate, omethoate (a metabolite of dimethoate), chlorpyrifos, and methamidophos support reducing the FQPA Safety Factor to 1X.

MOEs from the 7-day analysis exceeded 100 with all remaining uses (Table I.H-1). The MOE for children 1 - 2 years was 119 at the 99.9th percentile of exposure. As discussed above, OPP believes that this estimate is a reasonable approximation of the risk anticipated from consumption of OPs in foods.

MOEs for the single-day assessment do not reach the target value of 100 at the 99.9th percentile (Table I.H-1). The MOE for children 1 - 2 years was 45 at the 99.9th percentile of exposure. An MOE of 100 was reached at the 99.4th percentile of exposure. OPP believes that the 99.9th percentile of exposure in the single-day assessment is an overestimate of anticipated exposure, especially when considered as occurring over more than one day at a time. In addition, there is an overestimation of exposure resulting from the inability to reflect changes in residues due to recently implemented mitigation activities such as application rate changes and extended pre-harvest intervals increases. This value may be biased toward overstating the risk from OPs in food. However, bias reflected in this particular point estimate is anticipated to diminish at lower percentiles of exposure. OPP can not determine at what point in the exposure distribution the exposure estimate begins to be biased toward understating the exposure anticipated.

The decision as to whether additional mitigation activities are needed can not be made by looking at any single value in the results. Many factors must be weighed in determining the extent to which any particular value over- or understates the need for additional action. OPP believes that the actual exposures to the US public fall somewhere between the results of the two analyses presented. In addition, the application of hazard values results in offsetting issues with regard to the direction of change in the MOEs calculated.

OPP has identified commodity/pesticide combinations that appear at the upper end of the distribution and may warrant further study. These include: acephate on green peppers and succulent beans; azinphos methyl on apples and pears; dimethoate on apples, grapes, green peppers, pears, spinach, succulent beans, and tomatoes,; methamidaphos on potatoes and tomatoes; mevinphos on grapes and spinach; phorate on potatoes; and phosmet on apples, grapes, and pears. Until the individual assessments for DDVP and dimethoate are complete, it is premature to attach significance to these commodity/pesticide combinations. The significance of these commodity/pesticide combinations cannot be fully understood without taking into account all other relevant information, such as the results of the sensitivity analyses.

OPP has evaluated the consumption records occurring in the tail of the distribution to ensure that they reflect reasonable consumption patterns. Analysis of the tail of the distribution (>99th percentile) indicates that no small subset of consumption records dominates the outcome. This observation increases OPP's confidence that the food and water components of the assessment are not unduly influenced by unusual consumption patterns and reflect the consumption habits of the public at large.

Table I.H-1. Summary of the OP Cumulative Food Assessment

Children 1-2 Route: Food*	Percentile	Exposure Period Single Day Analysis MOE**	Exposure Period 7-day Analysis Mean MOE	Exposure Period 14-day Analysis Mean MOE	Exposure Period 21-day Analysis Mean MOE
	95	353	475	517	539
	99	128	249	295	320
	99.5	91	197	239	262
	99.9	45	119	151	166

*The additional FQPA Safety Factor is included as an adjustment to the chemical-specific Relative Potency Factors
**For the single day analysis for food, MOEs were calculated using DEEM software rather than Calendex software and thus no mean is applicable

Children 3-5 Route: Food*	Percentile	Exposure Period Single Day Analysis MOE**	Exposure Period 7-day Analysis Mean MOE	Exposure Period 14-day Analysis Mean MOE	Exposure Period 21-day Analysis Mean MOE
	95	437	570	616	634
	99	158	290	340	364
	99.5	111	225	271	295
	99.9	53	131	165	184

*The additional FQPA Safety Factor is included as an adjustment to the chemical-specific Relative Potency Factors
**For the single day analysis for food, MOEs were calculated using DEEM software rather than Calendex software and thus no mean is applicable

Adults 20-49 Route: Food*	Percentile	Exposure Period Single Day Analysis MOE**	Exposure Period 7-day Analysis Mean MOE
	95	1286	826
	99	439	784
	99.5	304	622
	99.9	146	364

*The additional FQPA Safety Factor is included as an adjustment to the chemical-specific Relative Potency Factors
**For the single day analysis for food, MOEs were calculated using DEEM software rather than Calendex software and thus no mean is applicable

Adults 50+ Route: Food*	Percentile	Exposure Period Single Day Analysis MOE**	Exposure Period 7-day Analysis Mean MOE
	95	1136	824
	99	403	735
	99.5	282	537
	99.9	139	340

*The additional FQPA Safety Factor is included as an adjustment to the chemical-specific Relative Potency Factors
**For the single day analysis for food, MOEs were calculated using DEEM software rather than Calendex software and thus no mean is applicable

5. Residential Assessment

The residential component of the preliminary OP cumulative risk assessment is the most sophisticated analysis of its type that OPP has ever conducted. It is the first application of distributional analysis to residential exposure assessments. It also factors in the seasonal and regional aspects of pesticide use. Three types of data are used in the residential assessment: pesticide use; pesticide residue dissipation; and exposure contact and exposure factors. Pesticide use data are utilized to determine the percent of households using a pesticide, the timing of the pesticide treatments, frequency and duration of exposure. Use data are also important in identifying geographic regions where the pesticide will be applied. In the current assessment, use data are specific to the region under evaluation and vary according to the specific aspects of that region. Pesticide residue dissipation data address the fate of the pesticides once applied to an environment (e.g., lawns). Exposure contact data are exposure-specific metrics that relate human exposure to pesticide residues. Humans come in contact with the residues by contacting the product directly or by contacting the residues left after the pesticide applications are made. Distributions of human exposure factors, such as breathing rates, body weight and surface areas used in this assessment come from the Agency Exposure Factors Handbook. These will not be discussed in the risk characterization of the document because the values are established and used throughout the Agency.

OPP has used all of the known available data to assess the significant residential uses of the OP pesticides. The residential uses not covered by this assessment are pet collars (DDVP and tetrachlorvinphos), crack and crevice uses (DDVP) and pest strips (DDVP) used in attics, basements and other areas with limited human access. Use of DDVP pest strips in closets and cupboards were included. It should be noted that the DDVP pet collars are currently not being marketed. While the tetrachlorvinphos pet collars have not been assessed, the CRA does address the use of tetrachlorvinphos pet shampoos , sponge-on treatments and powders. Exposure from the shampoo, sponge-on and powder treatments is likely to be higher than from pet collar use. This is because greater amounts of active ingredient are applied and larger areas of the pet are being treated. Although tetrachlorvinphos treated pet collars represent the largest usage of the product, the number of people treating pets with the liquid and powder products were adjusted upwards to reflect the collar use in addition to the use of the other products. The usage data was taken from NHGPUS.

Each data set used in the assessment introduces some potential bias in the outcome of the exposure assessment. A summary of these biases, their direction and magnitude, is presented in Table I.H-2.

EPA recently funded a study assessing adult and children's exposure to insecticides in flea collars. Preliminary results show that the use of pet collars does not result in significant exposure to pesticides (Boone et al., 2001). Spot urine analysis of 110 pre-school children in the Seattle Metropolitan area monitored for dialkylphosphate (DAP) metabolites suggested that DAP concentrations were not significantly higher in children whose parents reportedly used pet care products (Lu et al., 2002).

a. Exposure Contact and Pesticide Residue Dissipation Data

Exposure contact data used to assess exposures experienced by the applicator of consumer oriented pesticides are by far the most robust information used in the residential portion of this assessment. In addition, the application of pesticides is one of the more straight-forward activity patterns to measure since it represents easily defined activities. Recent data generated by the Outdoor Residential Exposure Task Force (ORETF) have been used to assess the use of hose-end sprayers (lawn care products), rotary granular spreaders (lawn care products), hand-pump sprayers (home gardens and orchards) and hand held dusters (home vegetable gardens). Another study, submitted by a registrant, was also used to assess residential applicator exposure using granular shaker cans to apply disulfoton. All studies meet or exceed current Agency guideline requirements (in particular regarding the number of replicates) and can be extrapolated to include clothing scenarios ranging from short-sleeved shirts and short pants to long-sleeved shirts and long pants. OPP has high confidence in the use of these data. Exposure contact data used to address the pet scenarios include chemical specific handler exposure

There are two post-application dermal exposure scenarios addressed in this assessment. These are: post application dermal exposure to lawn care products, and post-application exposure to vegetable and home orchard pesticide applications. Like the applicator scenarios, the post application garden and home orchard exposure scenarios are easily defined activities. For harvesting vegetables or weeding, there is a substantial amount of data based on farm worker exposure performing similar activities in crops requiring substantial hand labor. These contact values have the potential to overestimate exposure since they are based on individuals working for profit based largely on their productivity. Such workers are likely to be more efficient and therefore exposed to a larger amount of treated surface than most home gardeners. A uniform distribution of values representing hoeing and harvesting may overestimate early season activities that consist of potential exposure to small plants.

Dermal exposure from post-application contact with the lawn chemicals is equally varied. Contact data, representative of the range of human activities has been difficult to model. Dermal contact exposure values were identified in data described in Vaccaro et al., 1996, for adults who performed scripted

activities and contact values for children performing non scripted activities on lawns treated with a non-toxic substance were described by Black in 1993. Rates of pesticide transfer in the studies with surrogate compounds were similar to those observed in the chemical specific dissipation data available to OPP.

Turf transferable residue data are available for all turf chemicals. For malathion, these studies were conducted at multiple locations. Studies conducted in Missouri, North Carolina and Pennsylvania were used for the eastern regions and the study conducted in California was used for the western regions. Similar regional residue data were available for the use of malathion on home gardens and orchards and were used accordingly in this assessment. These data are of good quality and provide accurate estimates for this parameter.

There are no chemical specific data that measure the influence of wet hands and the mouthing behavior of young children on the efficiency of residue transfer. OPP considered a study performed by Clothier et al. (2000) in which he observed an increase in transfer efficiency (1.5- to 3-fold) when comparing a turf residue collection method to volunteers pressing dry hands or hands wetted with saliva. He observed a higher transfer rate for the compound with the lowest application rate. This may suggest that the hand surface becomes saturated and thus results in a lower transfer rate at higher application rates. The factor of from 1.5- to 3-fold was used in the assessment. The factor may overestimate the transfer of residues at higher application rates.

Estimates of exposure to pet care products were developed using an approach similar to the one taken with the turf care products. For applicator exposure, the Agency used dermal and inhalation unit exposures coupled with important statistics that influence exposure such as animal weights and number of animals treated. The latter two variables were gleaned from proprietary sources and an EPA funded study (Boone et al., 2001). For post application exposure, surrogate dermal exposure data of individuals exposed to treated animals were used to generate transfer coefficients, based on the transfer efficiency of the available dislodgeable residue data for tetrachlorvinphos on fur.

Tetrachlorvinphos specific data addressing exposure of individuals while treating pets and post application pet fur measurements were recently submitted to the Agency. The unit exposures from pet care product applicator data (n-15) were expressed as an empirical distribution. Dog weights (n-176) were expressed as a cumulative distribution. To assess post application dermal exposure, an exposure study of 16 pet groomers, each exposed to 8 dogs treated with carbaryl, was used. Dermal transfer coefficients were generated based on the transfer efficiencies of the tetrachlorvinphos pet fur data and the measured exposure of the groomers. These data were also

treated as an empirical distribution. Duration of exposure was based on video analysis of children (n-3) playing with pets (Freeman et al., 2001). At this time the method OPP is using in this assessment is the best available as it uses chemical specific data (applicator and fur residue), real world contact data (groomers and video analysis of children).

b. Pesticide Use Data

Accurate pesticide use data are key to the residential risk assessment. Useful information include regional site/pest markets, timing of application and the percent of households using their products. In the absence of specific pesticide use information, OPP developed exposure scenarios based on timing aspects found in regional Cooperative Extension Service publications and surveys such as the National Home and Garden Pesticide Use Survey (NHGPUS), the National Garden Survey, and Doane's GolfTrak. The Cooperative Extension Service publications were useful for establishing the timing of various turf chemicals. The survey data were used to establish the number of households that may use a given pesticide. For some regions, these application windows were expanded to account for the differences in length of growing season. This is particularly important when regions consist of several USDA Plant Hardiness Zones (e.g., Region 8). The NHGPUS delineates percent of households using pesticides based on a large national survey. These values consider users and non-users as well as homes having lawns and those that do not. The use of this survey introduces uncertainty into the analysis because of the age of the survey (1989-90). The data may not reflect reductions in current OP use patterns and therefore overestimate exposure. Doane's GolfTrak was used to identify the percent of golf courses treated with pesticides and is more timely (1998-99). OPP believes this is a robust data source. The National Garden Survey has been tracking percent of households employing lawn care applicators and is considered very robust. In addition, variables such as vegetable garden size are well characterized since these gardens are easy for survey respondents to define.

c. Use of Calendex

OPP believes using a calendar-based model is justified in order to manage the timing of pesticide applications and delineating subsequent exposures in the general population. Models that can employ distributions of the available residue and contact exposure data are needed to capture the inherent variability in the exposed population and can be used to provide justification regarding co-occurrence of pesticide exposure events. This method is preferable to relying solely on point estimates and combining "what if" scenarios which only adds uncertainty, while providing little information to risk managers regarding the potential numbers of exposed individuals and their ranges of exposure. Calendex provides the ability to evaluate route specific pathways which are defined by the model user so that appropriate residue and residue contact data can be used.

d. Non-dietary ingestion

Non-dietary ingestion is an important exposure pathway in the residential assessment in the southern regions. Frequencies of hand to mouth events used in the assessment are based on real world observations of children in homes and day care centers enumerated on video tape. However, a number of issues surround the estimation of the impact of this activity. The number of hand-to-mouth events occurring in a given time frame was developed by observing children's behavior during quiet play. Video tape data are based on children situated indoors and not outdoors. Hand to mouth frequency may be higher when children are engaged in "quiet play" (e.g., listening to stories) than when engaged in active play (running, tag, etc.). Children playing on lawns are likely to be engaged in active play. Therefore, the frequency of hand-to-mouth events used in the current assessment may be an overestimate.

The variety of hand-to-mouth events (such as the hand being near the mouth rather than in it) makes the enumeration of events difficult. Further, video tape values provide no information on rate of transfer from treated surfaces to hands. Transfer estimates in the assessment were based on studies measuring wet hand transfer efficiency with wet hands using surrogate compounds. No chemical specific data are available. For each hand-to-mouth event, the hand is assumed to have residue when data indicates a child may touch other things (e.g., clothing, non-treated surfaces or nothing).

e. Results

The results of the residential portion of the cumulative risk assessment are relatively straight-forward to interpret. The results of the individual regional assessments can be found in section II of this document. Inhalation exposures to DDVP from No-Pest strips are the major contributor to residential exposures. This determination is relatively obvious because this is the only remaining indoor use for OPs. Removal of DDVP from the assessment resulted in MOEs that were essentially the same as those deriving from food alone. Some of the regional assessments from the southern regions also indicate hand-to-mouth activities by children in conjunction with lawn scenarios as an important contributor to exposure. Some uncertainty surrounds the estimate of exposure from hand-to-mouth behaviors in the assessment. Any bias from this uncertainty is anticipated to overestimate exposure. The magnitude of overestimation is uncertain. OPP believes that the current OP cumulative risk assessment represents a reasonable, health protective estimate of likely exposure to OPs from residential uses.

Table I.H-2. Input Parameters Used in the Exposure Models: Bias, Assumptions, Uncertainties, and Strengths

Model	Input Parameter	Bias*	Assumptions, Uncertainties, or Strengths and Other Comments
Exposure Model for Residential Pathway (Rex)	Human Activity Pattern	+ = upward ~ = neutral - = downward	
Lawn Exposure	**Unit Exposure:push-type rotary spreader** (mg exposure per amount of active ingredient applied)	~	**Assumptions/Uncertainties** 1. This unit exposure is based on 30 replicates consisting of individuals using a push-type rotary spreader. A number of clothing scenarios are possible to be generated from these data. In this assessment short-sleeved shirt and short pants were assumed. This may overestimate exposure as large portion of exposure is to the lower legs. Although a surrogate compound was used, exposure is believed to be more influenced by the type of equipment used rather being chemical specific. OPP has high confidence in these data. 2. A lognormal distribution was selected. 3. Assumed gloves are not worn. Survey data do indicate that some residential handlers use gloves. Because consumers are unlikely to use, remove and care for PPE in the manner of professionals, it is unclear what impact this may have on actual use. 4. The surrogate compound (dacthal) used in the exposure study may be dustier than the granular formulations of the OP compounds assessed. This factor increases confidence that this variable will not underestimate exposure.
	Area treated (square feet)	- to ~	**Assumptions/Uncertainties** 5. A difficult variable to estimate. However, the assumption is reasonable given the application equipment used. Although, may underestimate areas that have larger lawns (midwest), margins of exposure are large.

Model	Input Parameter	Bias*	Assumptions, Uncertainties, or Strengths and Other Comments
Exposure Model for Residential Pathway (Rex)	Human Activity Pattern	+ = upward ~ = neutral - = downward	
	Dermal Contact Transfer	**~ to +**	6. Adults: activities performed with tank tops and short pants, lognormal distributions may be reflective of study design rather than actual activities (choreographed) 7. Children: Includes above scripted activities and a range of non scripted activities. Non-scripted activities lognormal distribution may be influenced by use of a non-toxic substance (not a pesticide) 8. Assumes all adults and children living in households being treated with lawn care products are exposed (enter treated area).
	Turf Residues: dermal	**~**	9. Chemical specific data reflect a range of high values (e.g., immediately after application) and influenced by watering-in and rainfall.
	Turf Residues: hand-to-mouth	**~ to +**	10. Based on surrogate data. Lone OP in surrogate data had the lowest transfer.
	Frequency of hand-to-mouth events	**~ to +**	11. Based on video-observations of children situated indoors. Active play outdoors may result in lower hand-to-mouth frequencies.
	Duration on lawn	**~ to +**	12. For children, the value is time spent outdoors in addition to time spent on lawns. Does not account for survey responses of individuals that did not play on lawns or go outside.
Public Health	**Drift**	**~**	13. Distribution of aerial and ground equipment values
	Population Exposed	**~ to +**	14. Assumes a large percentage of the population being exposed (based on those having lawns).

Model	Input Parameter	Bias*	Assumptions, Uncertainties, or Strengths and Other Comments
Exposure Model for Residential Pathway (Rex)	Human Activity Pattern	+ = upward ~ = neutral - = downward	
Home Garden	**Applicator: Small Tank Sprayer**	**~ to +**	15. This unit exposure is based on 20 replicates. individuals using a push-type rotary spreader. A number of clothing scenarios are possible to be generated from these data. In this assessment short-sleeved shirt and short pants were assumed. This may overestimate exposure as large portion of exposure is to the lower legs and upper arms. Although a surrogate compound was used, exposure is believed to be more influenced by the type of equipment used rather being chemical specific. OPP has high confidence in these data. 16. A lognormal distribution was selected. 17. Assumed gloves are not worn. Survey data do indicate that some residential handlers use gloves. Because consumers are unlikely to use, remove and care for PPE in the manner of professionals, it is unclear what impact this may have on actual use. confidence in these data
	Applicator: Granular	**~ to +**	18. This unit exposure is based on 15 replicates. Chemical specific data. Used study assessing exposure while treating shrubs which had higher unit exposures than for flowers. 19. A lognormal distribution was selected.
	Area treated: ornamentals	**~ to +**	20. Assumes all plants are treated.
	Area treated: vegetables/fruits	**~**	21. A lognormal distribution of a well studied variable.
	***Postapplication*: vegetables/fruits**	**~ to +**	22. *Contact values represent a wide range of activities.* All plants are assumed to be treated.
	Frequency of applications	**- to +**	23. Based on survey responses to use of insecticides. Not chemical specific.

Model	Input Parameter	Bias*	Assumptions, Uncertainties, or Strengths and Other Comments
Exposure Model for Residential Pathway (Rex)	Human Activity Pattern	+ = upward ~ = neutral - = downward	
	Plant residues	~	24. Regional and chemical specific
Indoor Air	**Residues**	~	25. Chemical specific
	Reduction in air concentration based on presumed use of smaller strips than in above residue study	**- to ~**	26. Proportional reduction is an assumption
	Duration	~	27. Use of CHAD consisting of several time activity surveys.
	Population Exposed	**~ to +**	28. Values based on use of all pest strips, not just those containing specific active ingredient.
Pet Treatments	**Applicator**	~	29. Chemical/formulation specific data. Number of pets and pet weights reasonable based on an "n" of 148 pets.
	Postapplication	~	30. dermal contact value, from studies in which there was substantial contact 31. Chemical specific fur residue data 32. video-analysis of children in contact with pets. However small n (3). 33. Best available at this time
Calendex	**Input parameter are describe above**		34. confidence in these data

6. Regional Water Exposure Assessments

The regional water exposure assessments are designed to represent exposures from typical OP usage conditions at one of the more vulnerable surface watersheds in the region. Regions were selected to reflect the climate and soil conditions causing increased pest pressure and resulting OP use. Each regional assessment focuses on areas where combined OP residues in drinking water is likely to be among the highest within the region as a result of total OP usage and vulnerability of the drinking water sources. In this manner, OPP is confident that if the regional cumulative risk assessment finds that exposure in water is not a significant contributor to the overall OP exposure from a vulnerable area, it will not be a significant contributor in other areas in the region. However, because the assessment is based on typical usage, it is not a high-end estimate of pesticide exposure via drinking water at that vulnerable site. A comparison of the estimated concentrations from individual OPs with available monitoring indicates that this assessment is by no means worst case or unrealistic. In each region, levels of one or more OP pesticides detected in monitoring studies exist that are greater than that estimated by the cumulative water assessment; in some cases, the estimates are off by an order of magnitude or more. However, in that same region, estimates of other OP pesticides are similar to or greater than detections found in monitoring studies (see Appendices III.E.1 and III.E.3, as well as the regional assessments in II.A through II.G, for detailed comparisons). Although the potential exists that peak water concentrations for one or more OP pesticides may not be captured in this approach, the impact on the contribution from water to the overall risk assessment is anticipated to be small.

The discussion that follows characterizes the results of the regional water exposure distributions, and identifies assumptions and approaches to the assessment that might impact the level of certainty in the results.

a. What Each Regional Assessment Represents

Each region in the assessment is represented by a geographic area with the highest apparent potential for cumulative exposure to OPs in drinking water. The vulnerable drinking water source in each geographic area represents an area with relatively high usage of multiple OP pesticides in relation to other parts of the region and coincides with surface water sources of drinking water that are vulnerable to potential contamination by these OPs. The focus on surface water sources of drinking water is a likely source of overestimation bias inasmuch as ground water sources generally have lower OP residues than are found in surface water.

Because OP usage varies within the region, the initial evaluation focused on the areas of highest use, based upon the crops grown, which OP(s) are used on these crops, how much OP pesticides are applied and when they are used. Because the relative potency factors (RPF) have a large impact on the

overall OP cumulative distribution, site selection tended to favor high-RPF OPs such as disulfoton, dicrotophos, and terbufos. Since the purpose of the assessment is to identify the impact from multiple OPs occurring in water in the same area, the area(s) selected for the assessment do not necessarily represent the highest exposure of a single chemical, but rather the highest multiple OP exposure within the region. Since OP use may vary from year to year and cropping and usage patterns may change, some areas in other parts of the region may have greater water exposure in a given year.

Because OPP considers both total OP usage and vulnerability of the drinking water sources, the site selected may not necessarily coincide with the highest OP use area in the region or the area where runoff alone is greatest. For instance, the highest OP use areas in the Northwest region (Region B) are in Yakima County and eastern Washington and in southeast Idaho. However, because of low rainfall, few surface-water intakes, and irrigation-dominated agriculture, OP use in this area did not necessarily pose the greatest risk to drinking water sources. Instead, the surface-water sources of drinking water in the Willamette Valley were potentially more vulnerable, despite lower OP usage.

Comparisons of the estimated pesticide concentrations with available monitoring in each region indicate that, in almost every region, a few known detections of one or more OP pesticides occur at higher levels than are being predicted for the cumulative assessment. As noted, because the estimate focuses on the cumulative impact from multiple OP pesticides, it doesn't necessarily focus on the conditions that lead to the highest concentration of one particular OP. In addition, some of the monitoring data may come from water bodies that are not representative of drinking water sources. In some instances, the higher monitoring levels may reflect uses that are being cancelled, such as the residential uses of chlorpyrifos and diazinon. In the case of azinphos methyl, in which upper percentile regional distributions were consistently one to three orders of magnitude less than monitoring detections, the underestimates may be due to inadequate or missing data on pesticide fate and transport properties or usage.

b. What PRZM-EXAMS and the Index Reservoir Represent

OPP adapted available tools to provide daily distributions of OP levels in water for incorporation into the probabilistic cumulative exposure assessment. While these tools have provided OP distributions that are, in many cases, comparable with available monitoring data in the same or nearby locations, assumptions regarding the nature of the drinking water source and watershed influence the estimated distributions.

i. Nature of the Drinking Water Source

The Index Reservoir is based on the specific geometry (watershed and reservoir size) of an actual reservoir (Shipman City) in the midwest. As such, it may best represent potential transport to similar drinking-water sources in high rainfall areas such as the eastern US. It may not so well represent reservoirs in drier parts of the west, where inflow and outflow are artificially managed. In addition, while the Index Reservoir scenario will not necessarily reflect short pulses of higher concentrations found in flowing rivers and streams, long-term average concentrations in a reservoir may be greater than in streams because of differences in the residence time for water in these water bodies.

The Index Reservoir is adapted to the runoff and stream inflow calculated from local soil and weather data. OPP used the PRZM runoff data for the cropping scenario that generated the lowest total runoff volume in the region to derive the inflow and outflow of the Index Reservoir. This introduces a small additional error into the concentrations calculated for the other chemical-crop simulations in each region.

ii. Nature of the Watershed

PRZM is not a basin-scale model, but a field-scale model which provides an edge-of-field estimate of pesticide loads in runoff to the 5.3-hectare reservoir simulated by EXAMS from a 172.8-hectare watershed. PRZM does not explicitly account for the relative contributions of each field to the Index Reservoir. OPP used a cumulative adjustment factor (a combination of the regional percentage of the total watershed area in crops with OP uses and the percentage of acres treated by each OP on each crop) to adjust the resulting reservoir concentrations calculated by EXAMS. Further information on the assumptions involved in applying Percent Crop Area (PCA) factors for drinking water assessments of individual pesticides can be found in the science policy paper, "Applying a Percent Crop Area Adjustment to Tier 2 Surface Water Model Estimates for Pesticide Drinking Water Exposure Estimates" (USEPA, 2000e).

PRZM does not account for location in the watershed: all fields are assumed to be uniformly distributed within the watershed, with runoff going directly into the reservoir. The simulation of multiple chemicals to multiple crops grown in different soils represents a significant adaptation of PRZM-EXAMS. Ideally, the cumulative drinking-water exposure assessment for a region would allow separating the different crop-soil regions within a watershed, and could simulate the different path lengths through runoff and stream-flow to the Index Reservoir. However, since PRZM is an edge-of-field model, runoff from fields representing the application of each OP to a different crop follows the same path length in the treated field and empties directly to the reservoir. In other words, this

simulation assumes that the treated fields with their individual soils are uniformly distributed throughout the watershed and essentially ring the index reservoir for direct deposition of the edge-of-field load.

Each crop use simulated in PRZM assumes that the entire area of the watershed planted in the crop consists of a single soil. In each of the regions, OPP used actual soil data from local soils on which the crops are grown. When possible, the soil selected for each scenario was a benchmark soil that was prone to runoff (classified as hydrologic group "C" or "D" soils). While OPP attempted to simulate soils that might be prone to runoff, the emphasis in developing the scenarios was to choose important local soils for which sufficient data are available, and which are known to be used to grow the crops of interest. These soils may not represent those most prone to runoff, but afford reasonable certainty that the simulation represents local soil conditions. While an assessment using a single soil assumes that each part of the watershed will be equally vulnerable to runoff, areas of higher and lower runoff vulnerability will exist in an actual watershed.

iii. Multiple Years of Local Weather Data

Because the application rates, frequencies, and timing are held constant, the PRZM/ EXAMS Index Reservoir simulations over multiple years evaluate the impact of the variability in precipitation on the amount of pesticide that reaches surface water. Because weather data spanning 24 to 36 years is available for many locations across the country, PRZM and EXAMS can account for OP runoff from a wide range of weather patterns not otherwise possible with monitoring studies that span relatively few years. The age of the data (collected through 1983) limits OPP's ability to compare of the modeling output to more recent monitoring data.

Weather data files for PRZM are available for weather stations across the country. The weather station nearest to the county or counties used for the simulations was chosen for the cumulative assessment. To the extent that precipitation in these counties over the period of record might have been greater or less than that recorded at the nearest weather station, runoff for that area may have been over- or underestimated by PRZM.

Additional uncertainty in the modeling results is associated with application of OPs to irrigated crops. PRZM has a relatively simple irrigation subroutine, applying a user-specified amount of irrigation to the simulated field when the moisture content of the top soil layer drops to some fraction of field capacity. Actual irrigation in the field follows a more complicated formula, with irrigation timing dependent on the grower's professional judgement of crop needs. In addition, PRZM has a limited ability to distinguish between various irrigation methods.

c. What the Usage, Cropping Areas, and Acre Treatments Represent

Typical application rates and frequencies for each OP pesticide on each crop were generated by taking the average reported in the USDA NASS (National Agricultural Statistics Service) Agricultural Chemical Usage summaries. This assumes that all applications were made at this typical or average rate and that frequencies of applications were constant year to year. The assessment considered only yearly variations in weather, and not variations in application rates. Thus, using these typical application rates and frequencies may underestimate water concentrations in years when pest pressure is higher than in our reported years and may overestimate in years when lower amounts of pesticide is used. The usage data was generally not sufficient to conduct a probabilistic assessment over a distribution of actual application rates.

In some instances, the typical and maximum label application rates were identical. For instance, the typical rate for phorate application on sugarcane in Florida was at the maximum label rate. In many cases the maximum label rates were one to eight times greater than the typical rates (see Appendix III.E.11). The extent to which the differences in rates would be reflected in the OP cumulative distribution depends on a number of factors, including timing of application relative to runoff events and relative potency of the pesticide. As a result, the net difference in estimated cumulative distributions between all typical and all maximum rates ranges from no difference in all but the lowest percentiles in Region A to a factor of 2 to 4 times greater at the higher percentiles (95^{th} and above) in Regions E and G (Appendix III.E.11).

Those comparisons reflect the maximum potential difference between typical and maximum application rates by assuming that all OP pesticides would be applied at the maximum rates to all crops. In reality, given the range in crops and pests treated by OP pesticides, it is more likely that only some of the OP pesticides might be applied at maximum rates in a given year and, thus, the difference would be less than that found in the comparison.

The regional percent crop area (PCA) factors are based on a large area: the size of the hydrologic units (average > 1000 square miles) used generally span multiple counties and may contain several watersheds that supply drinking water intakes. These regional PCAs represent the aggregation of crop areas from county-level NASS data and assume that the cropping area is uniformly distributed. However, cropping intensity is variable and smaller watersheds, including those capable of supporting drinking water supplies, may have a much different (higher or lower) percentage of crop land than the rest of the large basin. An example is Zollner Creek in the Willamette River Valley. This watershed had the highest concentrations and frequencies of detection of OPs among all of the NAWQA monitoring sites in the Willamette Valley. This stream drained a watershed that was 99% agriculture, much greater than the regional PCA of 60%.

The regional assessment areas coincided with the area with the highest PCA in all of the regions except the Northwest. In the Northwest, the regional assessment focused in the Willamette River Valley, a generally lower-intensity agricultural area which was otherwise more vulnerable because of OP usage and/or the nature of the drinking water source. However, as already noted, portions of the Willamette Valley had higher percentages in agriculture than reflected by the PCAs generated using the larger hydrologic units.

The typical application rates and percent acres treated are derived from state-level data (or NASS reporting districts) and assume uniform use practices across the state. Indeed, an uneven distribution of application rates and percent acres treated is expected in response to differing pest pressures. This assumption will underestimate areas where pest pressures may dictate a higher percentage of acres treated in a given year; similarly, it will overestimate areas where low pest pressures will require fewer acre treatments. In the Red River Valley (Northeast/North Central region), differences in percent acres treated and application rates between the Minnesota counties and the North Dakota counties located within the Red River Valley are more likely due to differences in the state-level data than in actual differences between the adjacent counties.

d. Timing of Application

OPP used crop profiles and other relative crop production publications to establish a time frame for making the applications of the pesticide on a particular crop (application window). The length of the window doesn't necessarily reflect the range over which a pesticide will be applied in a particular year, but the year-to-year variation in the application dates over time. Thus, in any given year, the timing of application may be clustered within a shorter time-frame than suggested by the application window. However, because of weather and other environmental factors, the timing of intensive pest pressure and/or OP application may vary across the window.

The date of application can have an effect on the predicted concentrations generated by PRZM/EXAMS, depending on how close the pesticide application coincides with rainfall events in any given year. To evaluate how this may impact on the OP cumulative distribution, where multiple pesticides are applied at different dates, OPP varied dates of application across the active window for each OP-crop combination in Regions A and D (see Appendix III.E.11 for details). The impact of varying dates of application was most evident at the extremes in the distributions. The ratio in maximum concentrations between the lowest and highest estimates was a factor of 5 to 6. For 99th and lower percentiles of exposure to OPs, the differences were not as dramatic, with the ratio between lowest and highest values generally two or less. This analysis only looked at the cumulative OP distribution and did not evaluate variations in individual chemical distributions. In both regions, the cumulative distribution generated at the beginning of the

application window and used for the regional assessment was less than the maximum estimated distribution. The ratio between the highest estimated concentration distributions and that used for the regional assessment was between 2 to 4 for the maximum estimated concentrations, but less than 2 for 99th and lower distributions.

In the absence of data to show otherwise, OPP assumed that all of the pesticide applied on a particular crop is done on the same date. While this may be an unreasonable assumption for a large watershed, it is not unrealistic for the size of the watershed used in this assessment. This assumption may result in higher peaks, but similar overall average concentrations than if applications are spread out over time. The resulting estimate of exposure may result in a small overestimation bias in the results that will be greater in large than in small watersheds.

In California (Region C - Arid/Semiarid West), OPP used California Department of Pesticide Regulations (CDPR) census data for its regional assessment. This information provided a distribution of applications by actual date of application. For that regional assessment, OPP split the total application into 5 applications, with each application representing 20% of the total amount applied on that particular chemical. The absence of information on application dates in NASS precludes OPP from taking a similar approach in other regions. OPP also generated an estimated cumulative OP distribution by using a single application at the beginning of the application window, as was done in other regions. The cumulative OP concentration distribution estimated using a single application was greater than that estimated using 5 split applications by a factor of two or less (see Appendix III.E.11 for details). While splitting the application over multiple days is expected to result in lower peaks than a single application, the degree to which a difference is seen depends on a number of factors, including the mobility and persistence of the pesticide and the timing of applications in relation to runoff-producing rainfalls.

e. Water Treatment Effects

Although not extensive, scientific evidence suggests that many of the parent OP pesticide residues in water are likely to be transformation by oxidation during water treatment, through chlorination or similar disinfection treatments. These oxidative transformation products, such as sulfones, sulfoxides, and oxons, are still of toxicological concern, have been detected in treated water from water treatment plants. Limited data suggest that these treatment by-products may be stable for sufficient periods of time (for least 24 to 96 hours) to move through the distribution system.

The information is not sufficient to make quantitative adjustments to the cumulative exposure estimates. To estimate potential impacts and to determine whether additional information is needed, OPP assumed that any transformation due to chlorination results in the conversion to a product of toxicological concern. Thus, all OP parents that form oxons, sulfoxides, or sulfones (see Table I.E-1) were assumed to be transformed into those products as a result of oxidation. Where the transformation is less than complete, and where non-toxic products are also formed, the such an assumption will overestimate the ultimate drinking water exposure. While limited information suggests that the other OP parent would be transformed and removed from treated drinking water, sufficient information is not available to quantify this for all OP pesticides. Thus, OPP did not assume that any of the other OP parent pesticides would be removed. OPP assumed that the sulfoxide and sulfone products are equal in toxicity to the parent and that the oxon products are ten times more toxic than the parent. A comparison of the RPFs for dimethoate (0.32) and omethoate (0.96), the oxon of dimethoate, suggests that this assumption would be protective.

Table I.H-3 compares the cumulative OP distribution used in the risk assessment (labeled "No treatment effects") with an estimated distribution using the assumptions of treatment impacts described above (labeled "oxon conversion w/ 10X increase in RPF"). In each region, the main cumulative OP "pulse" in any given year is dominated by an OP which transforms into sulfoxide and sulfone products (terbufos, phorate, or disulfoton). Since the estimated distributions for those OP pesticides reflect the combined parent plus sulfoxide/sulfone residues, any potential treatment effects from oxidation of these chemicals is covered in the assessment. Conversion of OP parents to oxons would not add significantly to the cumulative OP load in these regions because (a) those OP pesticides which form oxons are not contributing significantly to the cumulative "pulse" for the region, and/or (b) those oxon-forming OP pesticides that are frequently detected in water (chlorpyrifos, diazinon, malathion) have very low RPFs in comparison to other OP pesticides (such as dicrotophos, terbufos, and phorate).

Table I.H-3. Comparison of OP cumulative distribution (ppm, methamidophos equivalents) assuming no drinking water treatment effects to distribution assuming oxon conversion with increase in toxicity

	Cumulative OP Distribution, ppm		Ratio no treat: 10X oxon	Cumulative OP Distribution, ppm		Ratio no treat: 10X oxon	Cumulative OP Distribution, ppm		Ratio no treat: 10X oxon
	No treatment effects	Convert to oxon w/ 10X increase in RPF		No treatment effects	Convert to oxon w/ 10X increase in RPF		No treatment effects	Convert to oxon w/ 10X increase in RPF	
Region	**A (Florida)**			**B (Northwest)**			**C (Arid/Semiarid West)**		
Max	1.4E-02	1.4E-02	1.0	1.4E-04	2.6E-04	1.8	7.6E-04	9.9E-04	1.3
99th	9.0E-04	9.0E-04	1.0	1.2E-04	1.4E-04	1.1	2.2E-04	2.7E-04	1.2
95th	7.8E-05	1.0E-04	1.3	9.2E-05	1.0E-04	1.1	1.6E-04	2.0E-04	1.2
90th	3.6E-05	5.8E-05	1.6	7.5E-05	8.1E-05	1.1	1.4E-04	1.7E-04	1.2
80th	2.0E-05	3.5E-05	1.7	5.1E-05	5.7E-05	1.1	1.2E-04	1.4E-04	1.2
75th	1.7E-05	2.9E-05	1.7	4.6E-05	5.3E-05	1.1	1.1E-04	1.3E-04	1.2
50th	8.1E-06	1.6E-05	2.0	3.0E-05	3.6E-05	1.2	7.6E-05	1.1E-04	1.4
25th	3.4E-06	8.3E-06	2.4	2.0E-05	2.6E-05	1.3	4.6E-05	7.8E-05	1.7
10th	1.5E-06	4.5E-06	3.1	1.5E-05	2.0E-05	1.3	3.0E-05	5.4E-05	1.8
Min	4.1E-07	1.1E-06	2.6	8.3E-06	9.5E-06	1.1	1.7E-05	2.4E-05	1.4
Mean	4.6E-05	5.5E-05	1.2	3.7E-05	4.4E-05	1.2	8.3E-05	1.1E-04	1.4
Contributors to cumul. OP pulses	Phorate + sulfoxide/ sulfone; ethoprop			Ethoprop; azinphos methyl; chlorpyrifos			Disulfoton + sulfoxide/ sulfone, Phorate + sulfoxide/ sulfone		
Oxon-formers	Chlorpyrifos, diazinon			AzM, bensulide, chlorpyrifos, diazinon, dimethoate, malathion, MePara, Phosmet			AzM, chlorpyrifos, diazinon, dimethoate, malathion, MePara, Phosmet		
Region	**D (Northeast/ North Central)**			**E (Humid Southeast)**			**F (Lower Midwest)**		
Max	4.9E-03	4.9E-03	1.0	3.7E-03	3.8E-03	1.0	3.7E-03	3.9E-03	1.1
99th	1.5E-03	1.5E-03	1.0	1.1E-03	1.1E-03	1.0	1.3E-03	1.4E-03	1.1
95th	4.8E-04	4.9E-04	1.0	3.6E-04	3.9E-04	1.1	4.7E-04	5.7E-04	1.2
90th	2.0E-04	2.2E-04	1.1	1.6E-04	1.9E-04	1.2	2.3E-04	3.1E-04	1.4
80th	5.5E-05	8.5E-05	1.5	6.5E-05	8.3E-05	1.3	5.7E-05	1.2E-04	2.1
75th	3.1E-05	6.0E-05	2.0	4.9E-05	6.4E-05	1.3	3.0E-05	8.2E-05	2.7
50th	5.5E-06	1.2E-05	2.3	1.8E-05	2.2E-05	1.2	4.6E-06	2.3E-05	5.0
25th	1.5E-06	3.8E-06	2.5	9.6E-06	1.1E-05	1.2	1.8E-06	8.4E-06	4.7
10th	5.8E-07	1.8E-06	3.2	6.2E-06	7.2E-06	1.2	9.7E-07	3.4E-06	3.5
Min	2.0E-08	2.0E-07	10.0	3.9E-07	7.3E-07	1.9	1.5E-07	4.7E-07	3.2
Mean	9.2E-05	1.0E-04	1.1	7.9E-05	8.9E-05	1.1	8.2E-05	1.2E-04	1.4
Contributors to cumul. OP pulses	Terbufos, phorate with sulfoxide/ sulfone transformation products			Terbufos, phorate, & disulfoton with sulfoxide/ sulfone; acephate			Terbufos + sulfoxide/ sulfone; phostebupirim		
Oxon-formers	AzM, chlorpyrifos, dimethoate			Chlorpyrifos, dimethoate			Chlorpyrifos, dimethoate, malathion, MePara, phostebupirim		

	Cumulative OP Distribution, ppm		Ratio no treat: 10X oxon	Cumulative OP Distribution, ppm		Ratio no treat: 10X oxon	Cumulative OP Distribution, ppm		Ratio no treat: 10X oxon
	No treatment effects	Convert to oxon w/ 10X increase in RPF		No treatment effects	Convert to oxon w/ 10X increase in RPF		No treatment effects	Convert to oxon w/ 10X increase in RPF	
Region	G (Mid-south)								
Max	8.7E-03	9.0E-03	1.0						
99th	4.3E-03	4.4E-03	1.0						
95th	1.9E-03	2.0E-03	1.0						
90th	1.0E-03	1.1E-03	1.1						
80th	4.4E-04	5.2E-04	1.2						
75th	3.1E-04	3.8E-04	1.2						
50th	4.1E-05	7.4E-05	1.8						
25th	8.4E-06	1.5E-05	1.8						
10th	4.2E-06	6.8E-06	1.6						
Min	1.4E-06	1.8E-06	1.3						
Mean	3.6E-04	4.1E-04	1.1						
Contributors to cumul. OP pulses	Dicrotofos; acephate; terbufos + sulfoxide/ sulfone								
Oxon-formers	Chlorpyrifos, dimethoate, malathion, MePara, phostebupirim								

The assumption of oxon conversion with a 10X increase in toxicity had no impact on the upper percentile of the concentration distributions for OPs in water in the two regions with the highest estimated cumulative OP load in drinking water – Region A or Region G . In Region B, the assumptions regarding oxon transformation increased the maximum estimated cumulative OP concentration by a factor of 2, but had little effect on the 99th or lower percentiles of the water concentration distribution. This resulted in two spikes off the peak OP pulses in two years of simulations, but a lower impact during other times.

7. Conclusions

A multi-route, calendar-based risk assessment for a single chemical requires the assessor to consider a variety of new issues in designing and interpreting a risk assessment. The issues are more complex when the analyses address the simultaneous exposures to more than one pesticide. OPP advanced its risk assessment methods, across the board, as it developed this specific OP cumulative risk assessment.

Many questions arise when interpreting results generated in a complex, highly refined assessment. The detailed outputs allow in-depth analysis of interactions of data sets to estimate the possible risk concerns and identify the sources of exposures. In this assessment, assumptions are replaced with data from surveys and monitoring studies and, as a result, the assessment provides a more refined picture of what is likely to be encountered in the real world. In most cases the assessment uses distributions of data. This practice permits expression of the full range of values for each parameter.

This revised assessment presents results as a range of estimated Margins of Exposure (MOEs) using one-day and seven-day rolling averages at different percentiles of exposure distribution. After careful analysis, the Agency believes that the real world exposure is somewhere between the one-day and seven-day rolling average, and generally these MOEs do not represent a concern. OPP is analyzing the sources of exposure that are significant at the lower end of the MOE range at the high percentiles of exposure distribution.

One of the major factors influencing the results at the highest portion of the range (99.9th percentile) of exposure is the fact that for a few individual OPs, risk assessments and mitigation actions have not been finalized. This is particularly true for DDVP and dimethoate. This conclusion is supported by the results of the analysis that removed pest strips containing DDVP from the assessment. The resulting total (food, water and residential) MOE is essentially identical to that for a food-only MOE analysis.

OPP has identified that a few uses of OP pesticides on food crops generally play a larger role in the results of the food risk assessment. Overall evaluation of the risk from exposure to OPs in foods suggests that, with the exception of completion of outstanding single chemical assessments, the cumulative MOEs from exposure to OPs in foods do not raise a concern.

The results of the residential risk assessment indicate that remaining uses of OPs in a residential setting are anticipated to provide only minimal contributions to the cumulative risks from OPs with the exception of pest strips containing DDVP. The single chemical risk mitigation activities for DDVP have not been completed. The impact of these activities may significantly reduce the contribution of DDVP to the cumulative risk assessment.

OP cumulative risk from drinking water is generally at least one order of magnitude lower than the contribution from OPs in food at percentiles of exposure above 95th for all subpopulations evaluated. As the percentile of exposure increases, the difference between the food and water contributions increase. Below the 95th percentile of exposure, the water risk comes within one order of magnitude of the food contribution. This pattern is consistent for all regions in the current risk assessment. OP exposure from drinking water does not play a significant role in the cumulative risk from OP use in the US

I. Revised OP Cumulative Risk Assessment

I. Future Work

The Revised OP Cumulative Risk Assessment provides a detailed picture of possible exposure to 32 OPs. Details retained in the assessment are sufficient to evaluate the impact of the methods and assumptions on the results of the assessment. This process is particularly important for a cumulative OP assessment because of its complexity and much additional data compared to single-chemical assessments. It uses distributions of data in place of point estimates to the extent possible. Appropriate information submitted during the comment period has been incorporated as appropriate as have comments from the March 2002 SAP review. This revised assessment utilizes the same innovative methodologies as that in the preliminary document. Since the issuance of the preliminary assessment OPP has analyzed the results presented therein and revised the outputs as necessary. Also further risk mitigation on individual chemicals which has occurred since December 2001 is incorporated in this revised assessment. This document also contains a section discussing the FQPA safety factor as it was applied in this cumulative assessment. That Section of the assessment will be reviewed by the SAP in June of 2002. This revised assessment will undergo an additional comment period during June and July. EPA will evaluate the SAP's comments as well as other comments or data that it receives and will modify this assessment as appropriate. In addition, as existing analyses are revised or new information is obtained, EPA will review this assessment and make further changes as appropriate.

With respect to the next steps discussed in the preliminary assessment, the revised document reflects essentially all of the proposed short term actions. In that document some of the activities were flagged as long term activities. These activities are not necessary for completion of the OP cumulative risk assessment, but are actively being pursued by OPP at present in the interest of improving OPP's risk assessment process. These long term steps are listed below categorized by discipline. Please note that no long term steps were discussed in the food and risk assessment methodology sections of the preliminary cumulative risk assessment and therefore there are no listings in these sections below.

As with the preliminary assessment, new information submitted during the comment period that will serve to improve the accuracy of the assessment will be incorporated into the assessment as appropriate. Also, further risk mitigation on individual chemicals which may have occurred since December of 2001 is incorporated in this revised assessment.

1. Hazard Assessment

① Long term: Research to develop and implement physiologically based pharmacokinetic [PBPK] models, which describe the time course disposition of chemicals and their metabolites, are well suited to provide more refined estimates of relative toxic potencies and points of departure for future cumulative risk assessment. OPP is currently working with the EPA's Office of Research and Development on the development and testing of such models for common mechanism pesticides.

② Long term: Pursue with ORD investigations on the interactions among simple mixtures of common mechanism pesticides to better understand the concept and application of dose additivity.

2. Food Exposure Assessment

To be determined.

3. Drinking Water Exposure Assessment

① Long term: What aspects of the modifications to the water residue modeling process can be applied to the conduct of single chemical aggregate assessments? What differences in assumptions may be needed for implementation of that process for single chemical assessments?

4. Residential Exposure Assessment

① Long term: Develop a science-based process for incorporation of spray drift and other sources of exposure into residential exposure assessment.

② Long term: What aspects of the modifications to the residential exposure estimation process can be applied to the conduct of single chemical aggregate assessments? What differences in assumptions may be needed for implementation of that process for single chemical assessments?

③ Long term: Develop better data defining the hand to mouth behavior of children in a variety of settings and for active and quiet play.

5. Risk Assessment Methodology

To be determined.

I. Draft OP Cumulative Risk Assessment

(*Please note: This section is still undergoing editing*)

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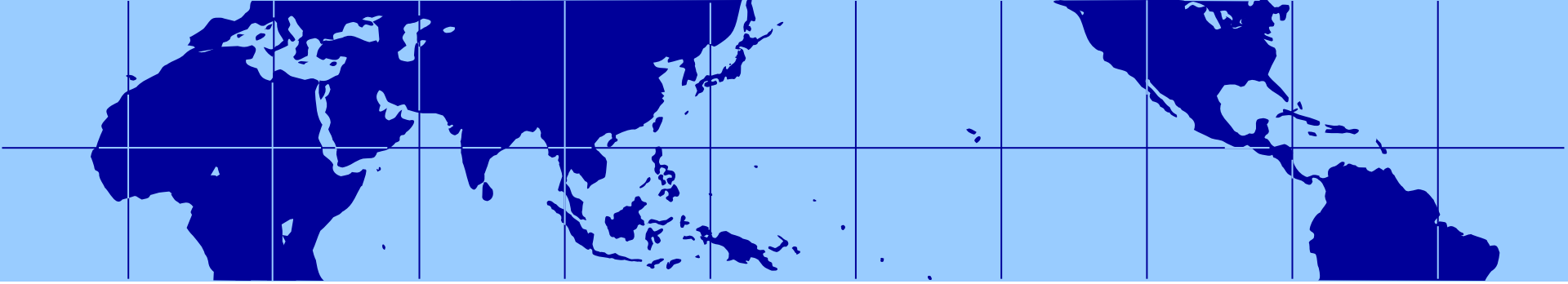
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Preliminary Cumulative Risk Assessment: Organophosphorus Pesticides

Presentation to the FIFRA Scientific Advisory Panel

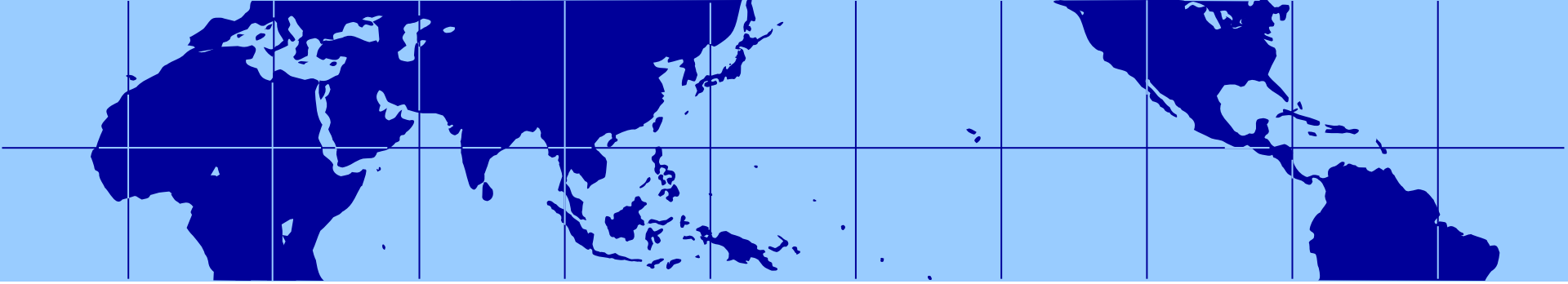
U.S. Environmental Protection Agency
Office of Pesticide Programs

February 5 to 8, 2002



Introduction and Welcome

Marcia Mulkey, Director
Office of Pesticide Programs



Historical Perspective and Agenda

Margaret J. Stasikowski, Director
Health Effects Division
Office of Pesticide Programs

Where We've Been: Milestones

Common Mechanism Guidance
January 1999

Final Aggregate Guidance
November 2001

Draft OP Risk Assessment
December 2001

Final Cumulative Guidance
January 2002

Final OP Risk Assessment
June 2002

How We Got There: SAP Advice Dose-Response and Hazard

- **March 1997.** Common Mechanism Guidance
- **March 1998.** OP Common Mechanism of Toxicity
- **September 2000.** Endpoints and RPF's: A Pilot Study
- **September 2001.** Preliminary Hazard and Dose-Response

How We Got There: SAP Advice Exposure Assessment

- **September 1997.** Residential Scenarios
- **December 1997.** Drinking Water
- **March 1998.** Probabilistic for Dietary, Residential, and Common Mechanism
- **July 1998.** Estimating Pesticide Concentrations in Drinking Water
- **May 1999.** Statistical Methods for Acute Dietary and Drinking Water
- **September 1999.** Residential
- **March 2000.** Models for Dietary and Drinking Water
- **June 2000.** Drinking Water Survey
- **September 2000.** Residential and Dietary Models and Drinking Water
- **March 2001.** Dietary Model

How We Got There: SAP Advice Assessment Methodology and Other

- **March 1997.** Aggregate Methodology
- **March 1998.** Probabilistic Risk Assessment Methodology
- **February 1999.** Aggregate Guidance
- **September 1999.** Cumulative and Aggregate Methodology
- **December 1999.** Cumulative Methodology
- **September 2000.** Risk Assessment Models
- **December 2000.** Case Study of 24 OP's and Cumulative Assessment Methodology

Key SAP Recommendations

Hazard Dose-Response

- Dose-response modeling: use of exponential model and several other recommendations

Dietary

- Use of PDP and other monitoring data
- Use of publicly-available databases and recipes
- Finer division of age groups:
  - New CSFII have more data for children

Key SAP Recommendations

Drinking Water

- Devote resources to surface water impacts, define higher assessment tiers and develop techniques for estimating concentration distributions for probabilistic risk assessments
- Regional modeling
- Shift focus to monitoring programs to support model development and evaluation

Key SAP Recommendations

Residential and Non-occupational

- Hand-to-mouth variables
- Use of uniform distribution

Next Steps

- Revise December 2001 Preliminary Organophosphate Risk Assessment based on:
  - This week's advice from the Panel;
  - Comments received during the 90-day public comment period
- Intended completion date: June 2002

This Week…

SESSION 1: Hazard Dose-Response

SESSION 2: Dietary

SESSION 3: Drinking Water

SESSION 4: Residential and Non-occupational

SESSION 5: Risk Characterization

Participants

Kevin Costello, MA
Geology
Princeton University

Jeff Evans, BS
Agronomy
Delaware Valley College

Vicki Dellarco, Ph.D.
Genetics
Iowa State University

Anna B. Lowit, Ph.D.
Environmental Toxicology
University of Tennessee

Elizabeth Doyle, Ph.D.
Toxicology
American University

Participants

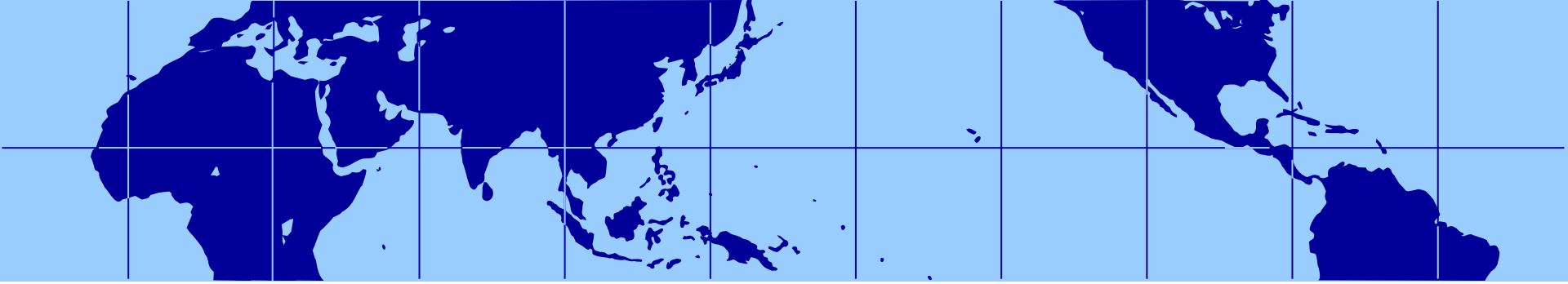
David Miller, MS and MPH
Environmental Science Engineering
Virginia Tech
Environmental Chemistry
University of Michigan

Randolph Perfetti, Ph.D.
Chemistry
Virginia Tech

R. Woodrow Setzer, Ph.D.
Population Biology
State University of New York at Stony Brook

William O. Smith, Ph.D.
Plant Physiology
University of Kentucky

Nelson Thurman, MS
Soil Science
West Virginia University



Session on Hazard and Relative Potency Factor

Organization of Presentation

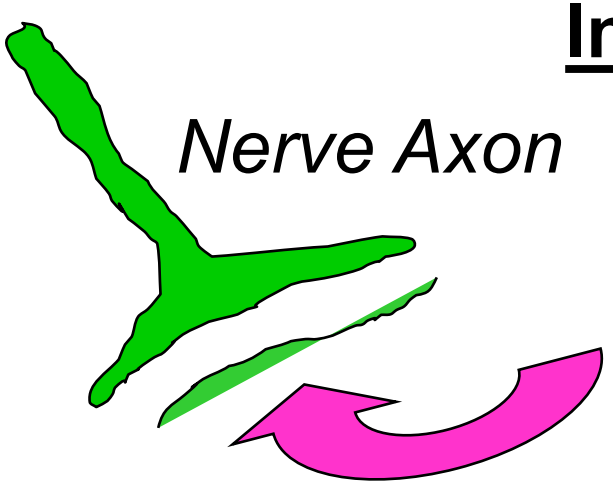
- Introduction & Background
  - Anna Lowit, Ph.D., OPP
- Methods: Oral Toxic Potency Determination and Points of Departure
  - R. Woodrow Setzer, Ph.D., ORD

Introduction & Background

Anna B. Lowit, Ph.D.
Toxicologist
Health Effects Division
Office of Pesticide Programs

Identifying a Common Mechanism: Organophosphate Pesticides

- U.S. EPA 1999 Policy Paper



Inhibition of Acetyl Cholinesterase

- Brain
- Peripheral Nervous System (e.g., diaphragm, muscles)
- Surrogate (RBC, Plasma)

Timeline of Methodology Development

- Pilot Hazard & Dose-Response OP Case Study
  - Presented to SAP in September 2000
- Preliminary Hazard & Dose-Response: July 2001 document
  - Presented to SAP in September 2001
- Revised Preliminary Hazard & Dose-Response: December 2001 document

OPs Considered in Hazard & Dose-Response Assessment

- 29 Organophosphate Pesticides
  - Exposure through food, water, and/or residential
- Determination of relative potency of chlorethoxyphos, profenofos, and phostebupirim is on-going

Relative Potency Factor Method

- Relative toxic potency of each chemical was calculated in comparison to “index chemical”
- Exposure equivalents of index chemical are combined in the cumulative risk assessment

Toxicity Data Used

- Oral, Dermal, and Inhalation Routes:
  - Sub-chronic and chronic toxicity studies collected
  - Same studies were used in July and December 2001 documents
  - Electronic dataset of oral ChE data is available to the public at: http://www.epa.gov/pesticides/cumulative/EPA_approach_methods.htm

Key Refinements to Hazard and Dose-Response Assessment

- Relative potency factors used in Preliminary Cumulative Risk Assessment
- Method for combining ChE data
- Modeling of low dose region
- Measure used in potency determination

RPFs Used in Preliminary CRA

- **Male RBC RPFs** were proposed in July 2001 document
  - RBC selected primarily on availability of large database and ability to consider time course information
  - Males selected

RPFs Used in Preliminary CRA

- **Female Brain RPFs** were selected in December 2001 document
  - Why Brain?
    - Compared to RBC, tighter confidence limits on potency estimates were observed
    - Target tissue
  - Why Female?
    - Sexes equally sensitive for most
    - Female rats more sensitive for ~5 OPs

Key Refinements to Hazard and Dose-Response Assessment

- Relative potency factors used in Preliminary Cumulative Risk Assessment
- Method for combining ChE data
- Modeling of low dose region
- Measure used in potency determination

Methods: Oral Toxic Potency Determination and Points of Departure

R.Woodrow Setzer, Ph.D.
Mathematical Statistician
National Health and Environmental Effects Laboratory
Office of Research and Development

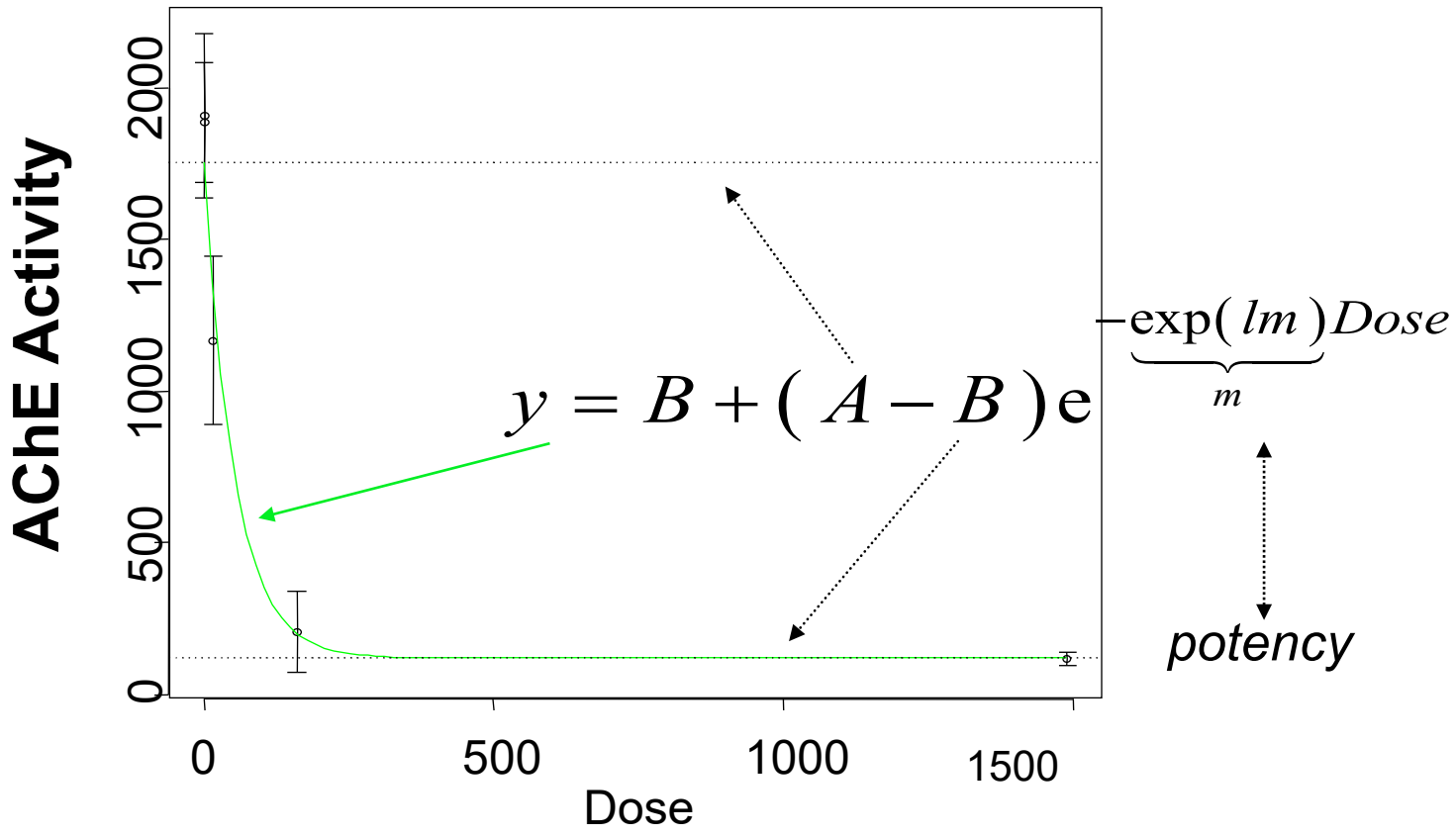
Overview

- Review the methods used in July draft of hazard and dose-response assessment chapter.
- What issues raised in September SAP report will be addressed here?
- How have those issues been addressed?
- What have we done since release of the December document?

SAP Report, September 2001

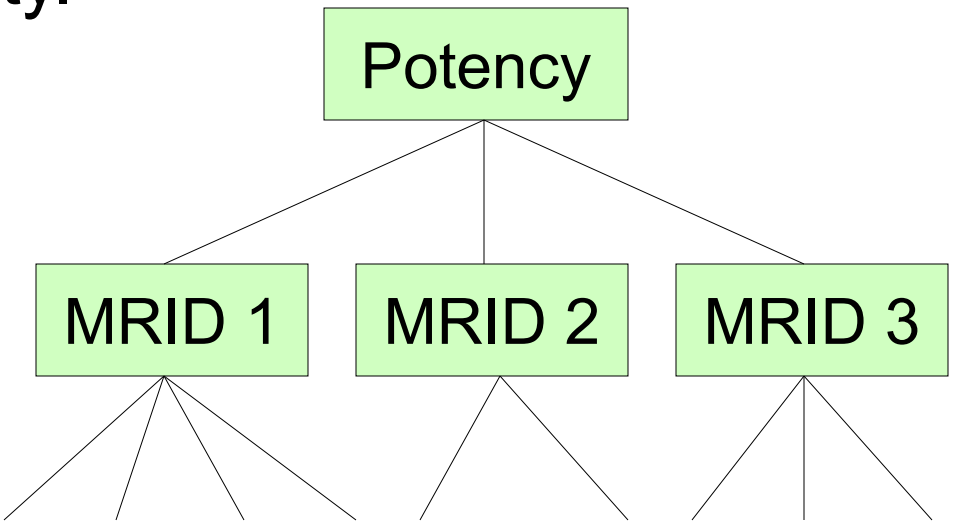
- Overall, SAP was supportive of the approach used by the Agency
  - Exponential model
  - Multiple studies and time points
  - R software for statistical analysis.
- Recommended further exploration of dose-response modeling issues which could impact the low dose region.
- Comprehensive list described in appendix of preliminary CRA (III.B.3) and can be found at http://www.epa.gov/pesticides/cumulative/.

July: Estimate of Potency and DR



July: Combining Estimates

- Fit a model to each dataset, estimating BMD (and estimated standard error) for each dataset.
- Use the global two-stage method (Davidian and Giltinan, 1995; 138-142) twice, once for each level of variability.



July: Estimating Parameters

- Use generalized least squares and assume constant coefficient of variation
- Sequential approach to fitting:
  - Fit full model to all data
  - If no convergence or inadequate fit,
    - Repeat (until good fit or # remaining doses < 3):
      - ***set B ≡0***
      - refit to dataset
      - drop highest dose

Issues from the September SAP Report:

- The approach to estimating *B* could result in biased estimates of *m* (the potency measure).
- The weight function underestimated the variance at low doses and overestimated it at high doses.
- The dose response curves for some chemicals appeared to have a “low dose shoulder,” which the basic exponential model did not capture.

Updates to Methods

- Change the way models are expressed in terms of the parameters (same model, different parameters).
- Use 1/BMD as measure of potency instead of *m*.
- Use nonlinear mixed effects method to fit model to combined data.

Updates to Methods (continued)

- Use *profile likelihood* to estimate a value of *B* consistent with the data when the standard approach does not converge.
- Develop a model for low-dose shape that was inspired by saturable metabolic clearance.
- Weights are proportional to means (instead of squares of means).

Model Parameterization

- **July model (for comparison)**

$$y = B + (A - B)\mathrm{e}^{\underbrace{-\exp(lm)}_{m}Dose}$$

- **December model**

$$y = A\left[P_B + (1 - P_B)\mathrm{e}^{-m \times Dose}\right]$$

(factoring out *A* and replacing *B/A* with P_B)

Model Parameterization (cont.)

- Current model (same shape, but in terms of *BMD* instead of *m)*:

$$y = A\left[P_B + (1 - P_B)\mathrm{e}^{\underbrace{\frac{\log\left(\frac{1-P_B-BMR}{1-P_B}\right)}{BMD}}_{m} \times Dose} \right]$$

Here BMR is the benchmark response (say, a 10% reduction in mean AChE activity), and BMD is the corresponding benchmark dose.

Model Parameterization (cont.)

- Advantages of current model:
  - More stable estimation, since BMD and P_B are relatively less correlated than were m and P_B.
  - Simplifies computation of BMD and its standard error.

Model Parametrization (cont.)

- Parameters actually estimated:
  - $lA=\ln(A)$
  - $lBMD=\ln(BMD)$
  - $B=\ln(P_B/(1-P_B))$
- Mainly, to assure legal parameter values (for example, A and $BMD>0$, $0<P_B<1$)

Model Fitting

- Use nonlinear mixed effects models (*nlme* in *R*):
  - Estimate a separate mean value for *lA* for each sex X unit combination, and a separate value of *B* and *lBMD* for each sex.
  - Estimate a random effect for each parameter for each level of nesting: maximum of among studies and among datasets within studies.

Model Fitting (cont.)

- Weights based on error variances proportional to means.

Model Fitting (cont.)

- Sometimes nlme failed to converge to estimates for this full model. Then try (in order:)
  - Full model (Sex-specific values for *B*, random effects)
  - Single value for *B*, with random effects
  - Sex-specific values for *B*, no random effects
  - Single value for *B*, no random effects
  - Fix sex-specific values for *B* that are consistent with the data, and estimate other parameters given the sex-specific values

Model Fitting (cont.)

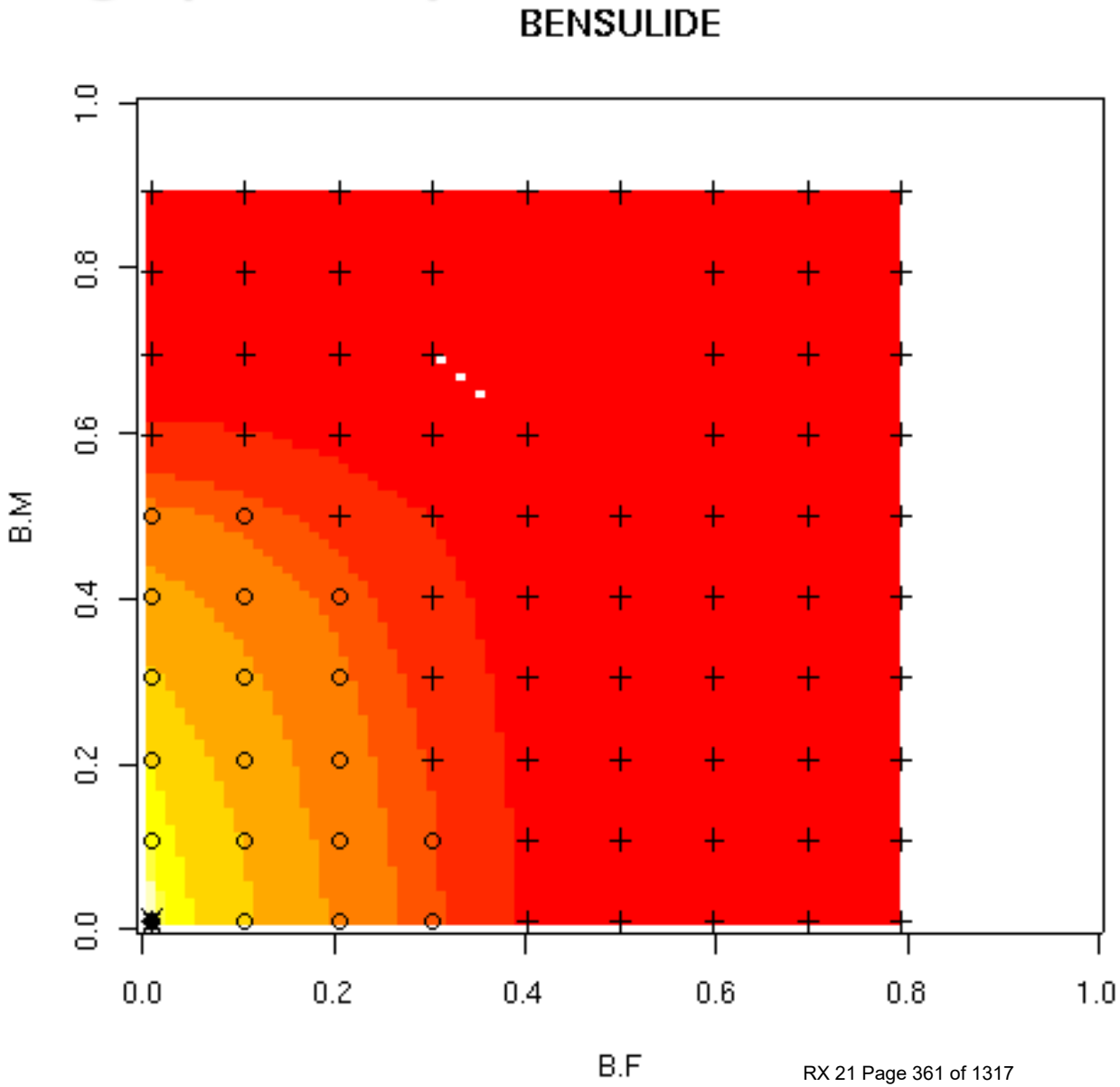
- Select P_B for males and females by choosing the value that maximizes the *profile likelihood*:
  - Likelihood (more usually, its natural logarithm, the log likelihood) is a measure of the degree to which the data support a particular parameter value.
  - Profile likelihood for a parameter (or parameters) results when the parameters in question are fixed, and the remaining parameters estimated given those values (so, fix P_B, and estimate A and BMD). The log likelihood of the resulting fit is plotted versus the parameter values. The data most support the parameter value associated with the maximum.

Model Fitting (cont.)

- Profile Likelihood (cont.)
  - P_B (males and females) were fixed in turn to each point on an 11 X 11 grid from 0.001 to 0.999.
  - Log likelihood plotted for each grid point (to aid visualization, values were linearly interpolated between grid points).
  - The grid point with the largest log likelihood was selected as the value of P_B.

Model Fitting (cont.)

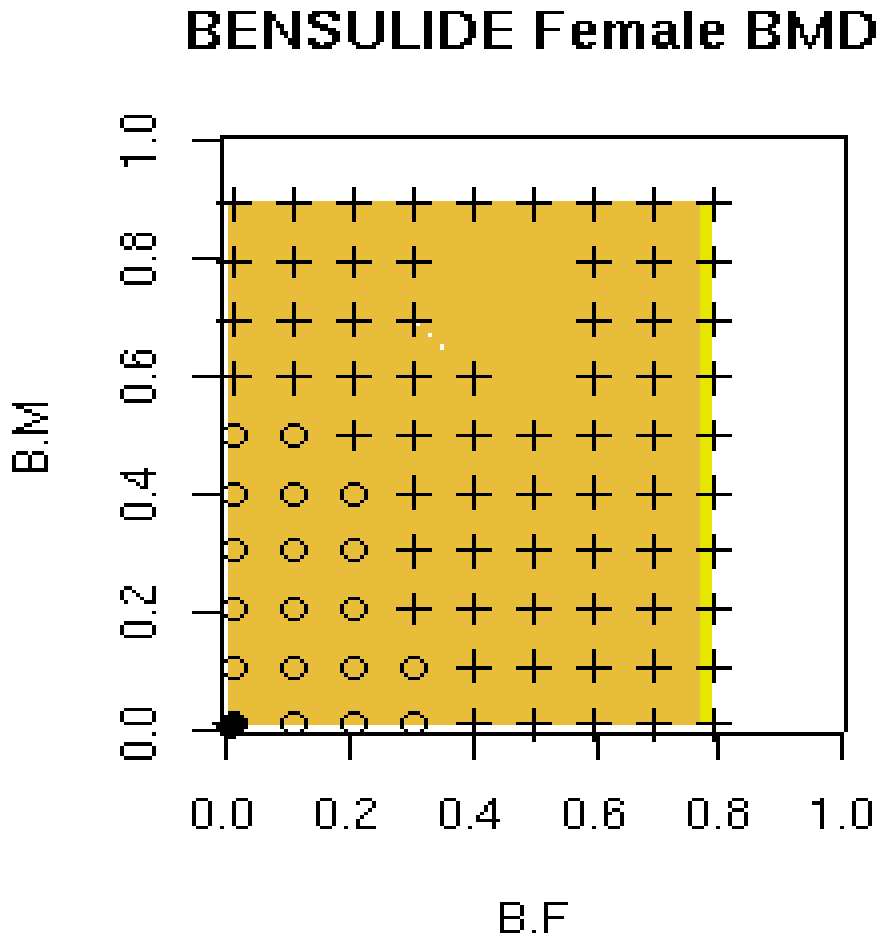
- Bright yellow (highest value) to Red (lowest value)
- Circles: points not significantly different (P>0.05) from best point (likelihood ratio test)
- Plus signs (P<0.05)

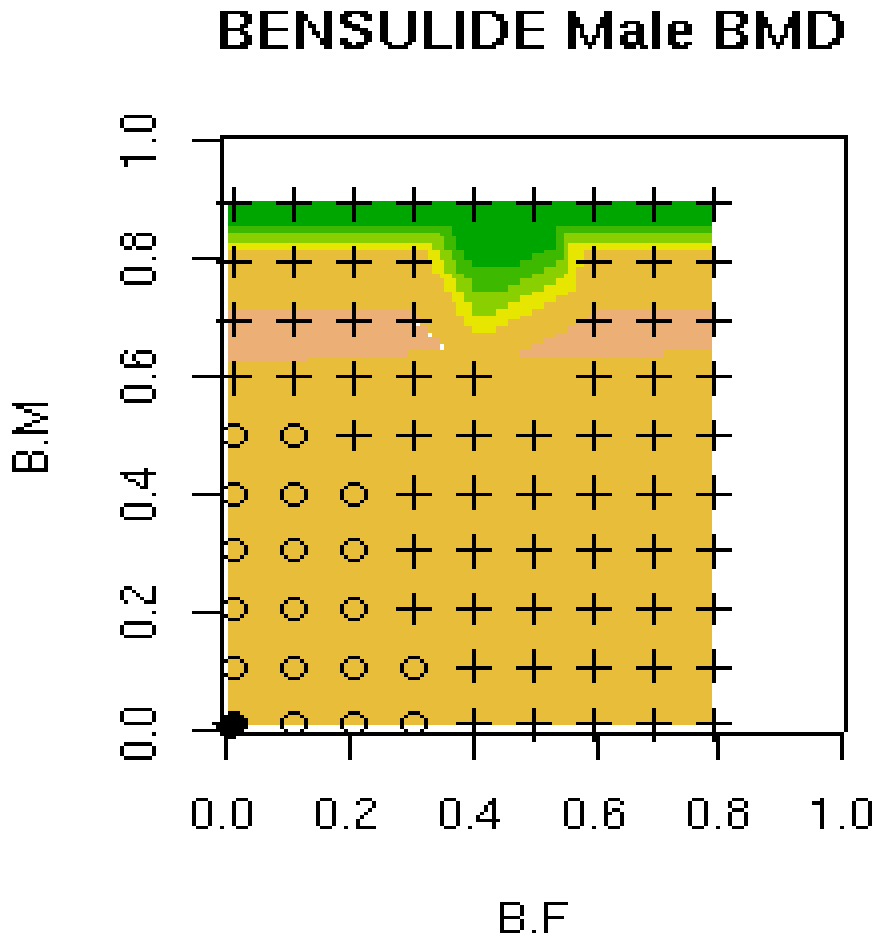


Model Fitting (cont.)

- Sensitivity: How much does the choice of *B* effect the estimate of the BMD? Only relevant when we cannot estimate P_B with the other parameters.
  - For the same grid of values for P_B, plot BMD as a fraction of the value at the selected point.
  - Plot contours (in the figures, the smallest contour represents ±25%).

Model Fitting (cont.): Sensitivity



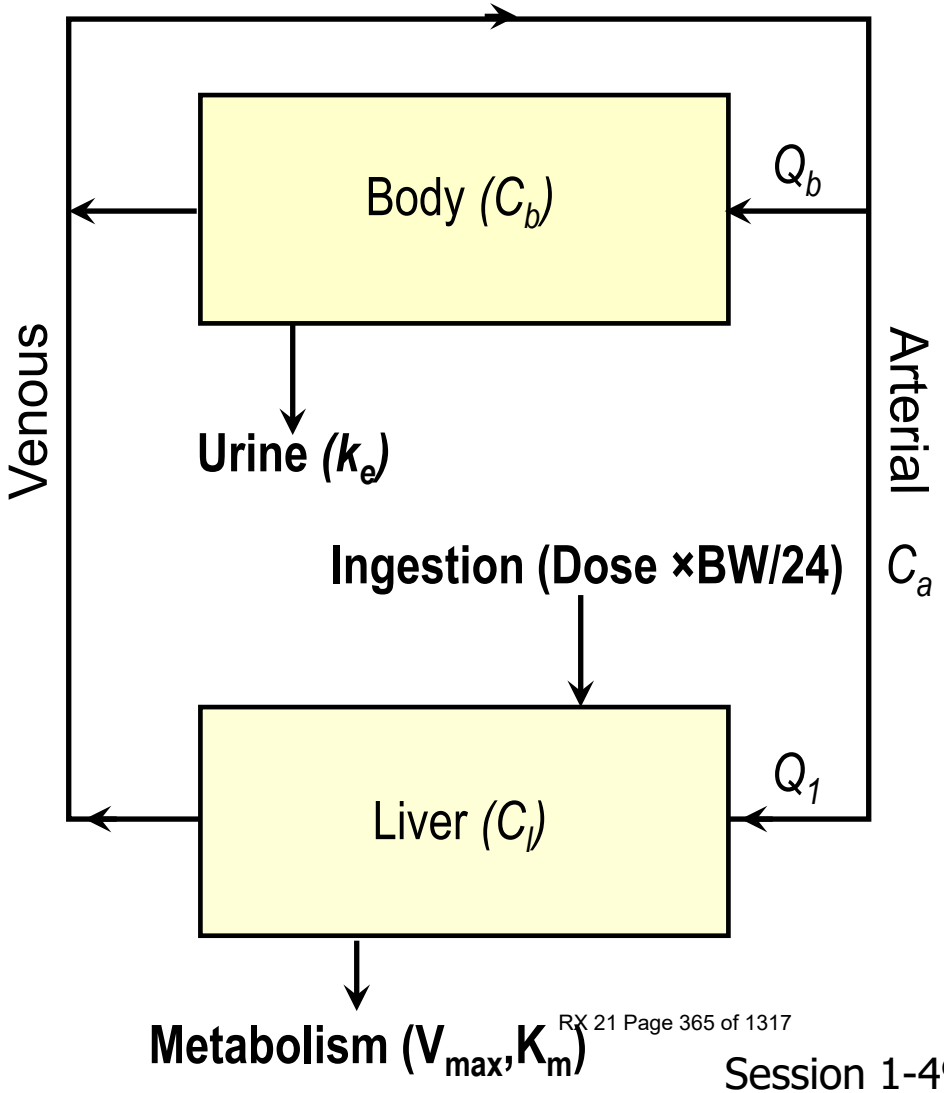


The D-R Shape at Low Doses

- Some of the data look as if there were a shoulder at the low-dose end of the dose-response.
- A **proposed** explanation is saturable metabolic clearance.
- Add a submodel, inspired by this mechanism, to the basic model already described, to create a low-dose shoulder.
- *Keep it simple!*

A Simple PBPK Model

- Two compartments: liver and everything else.
- Oral dosing, assume 100% into the portal circulation.
- Only consider saturable metabolic clearance and first order renal clearance.
- Run to steady state.



D-R Shape at Low Doses (cont.)

- Solve the system of differential equations implied by the model for steady state.
- The concentration of non-metabolized parent OP in the body (*idose*) as a function of administered oral *Dose* rate is:

$$idose = 0.5 * \left\{ \left(Dose - S - D \right) + \sqrt{\left(Dose - S - D \right)^2 + 4 \times Dose \times S} \right\}$$

$$S = \frac{24 Q_l Q_b K_m k_e}{BW \left(Q_l k_e + Q_b k_e + Q_l Q_b \right)}; \; D = \frac{24 V_{\max}}{BW}$$

D-R Shape at Low Doses (cont.)

- This model was called the internal dose model.

- The utility of this extension to the basic model does not depend on its biological interpretation. The model was treated as purely empirical, with *S* and *D* fitted to the data, along with the other parameters, *A*, P_B, and *BMD*.

D-R Shape at Low Doses (cont.)

- Dashed lines are an example of *idose* plotted versus *Dose.*
- Solid are dose-responses from combining with the basic model.
- *S* controls shape, *D* controls displacement.

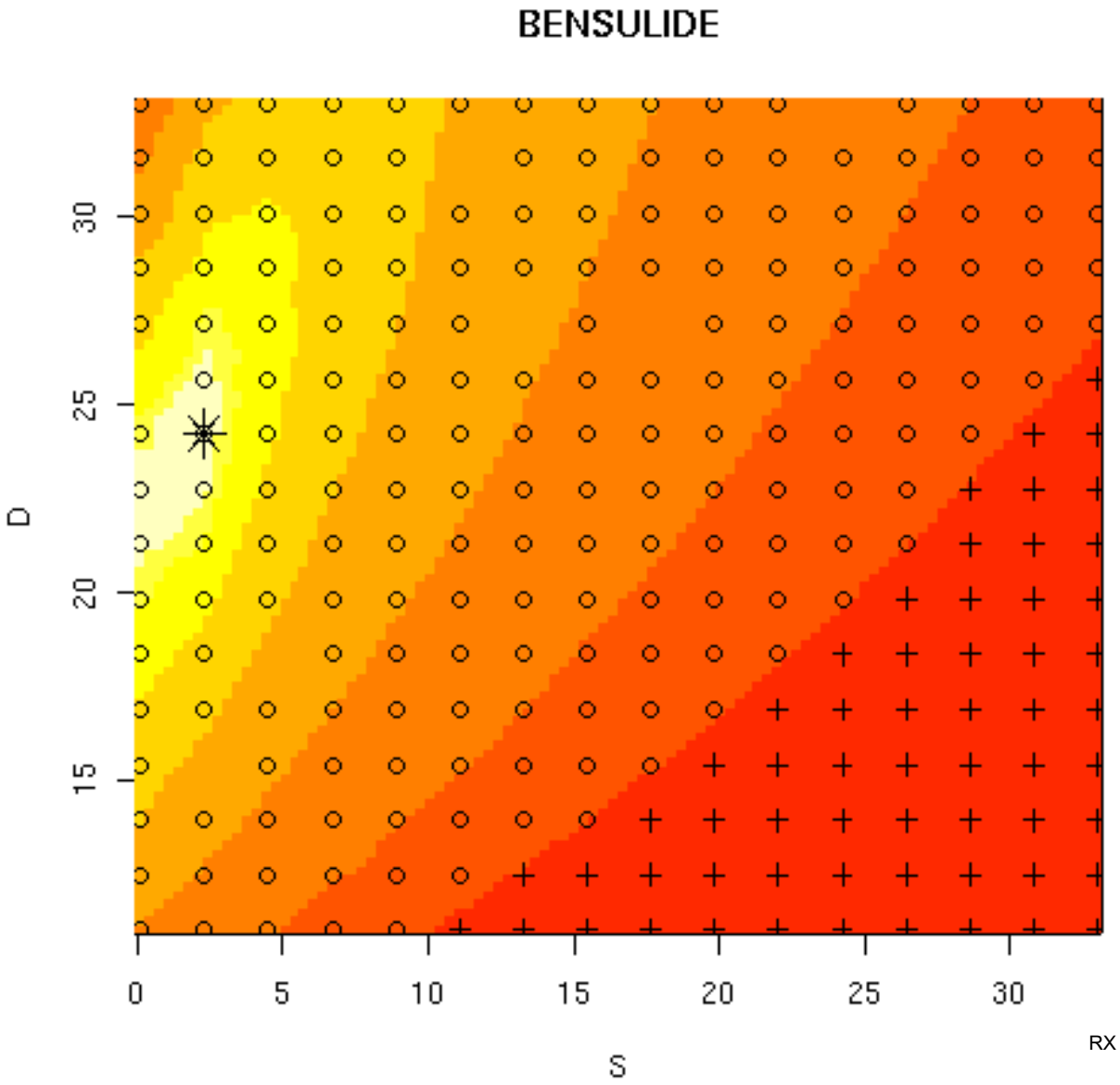
D-R Shape at Low Doses (cont.)

- Currently difficult to estimate parameters in this model using nlme.
- However, *S* and *D* can be estimated by maximizing the profile likelihood.
- This mainly effects the estimate of confidence intervals for the BMD.

D-R Shape at Low Doses (cont.)

- Due to two programming errors, the profile likelihood plots for *S* and *D* in the December draft were in error.
- The main consequence of the programming errors was to limit the number of chemicals for which BMDs could be calculated using the expanded model.
- 17 of 29 Chemicals have significantly improved fits using the expanded model:
  - azinphos-methyl, bensulide, chlorpyrifos, diazinon, disulfoton, fenthion, fosthiazate, malathion, methidathion, methyl parathion, mevinphos, phorate, phosmet, pirimiphos-methyl, terbufos, tribufos, trichlorfon

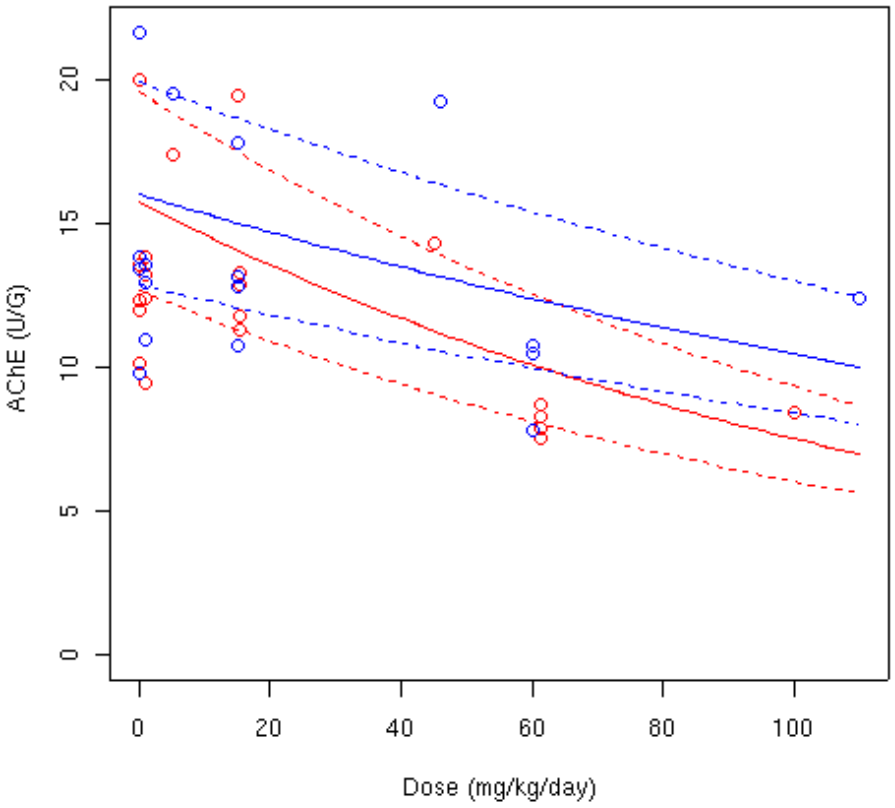
D-R Shape at Low Doses (cont.)



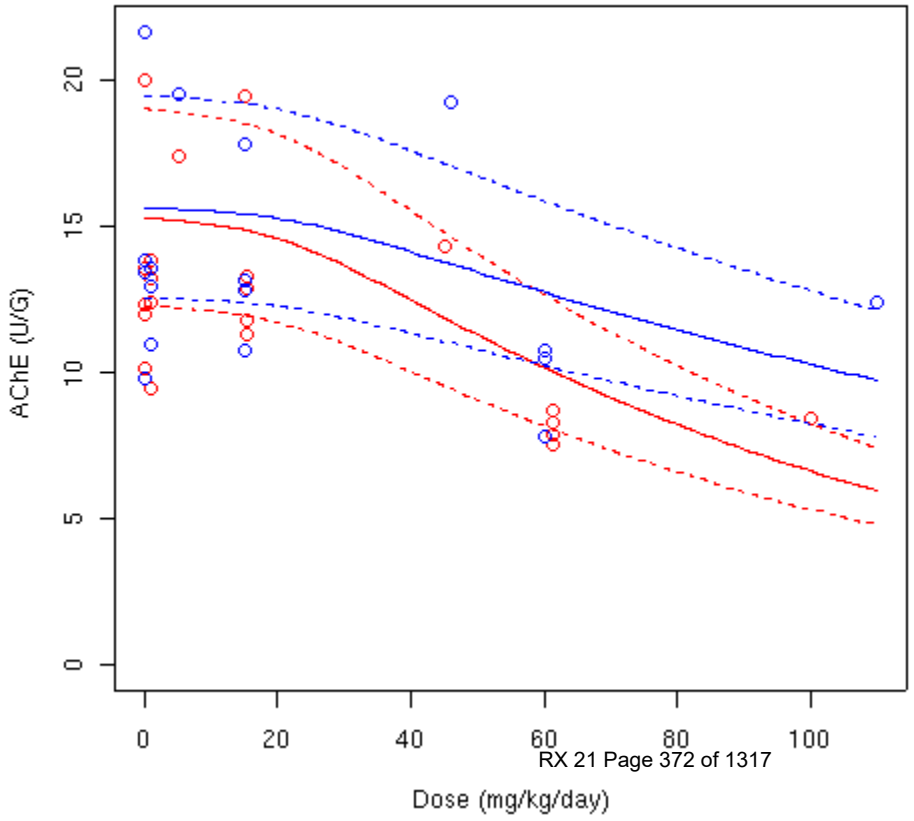
D-R Shape at Low Doses (cont.)

Bensulide

Basic Model

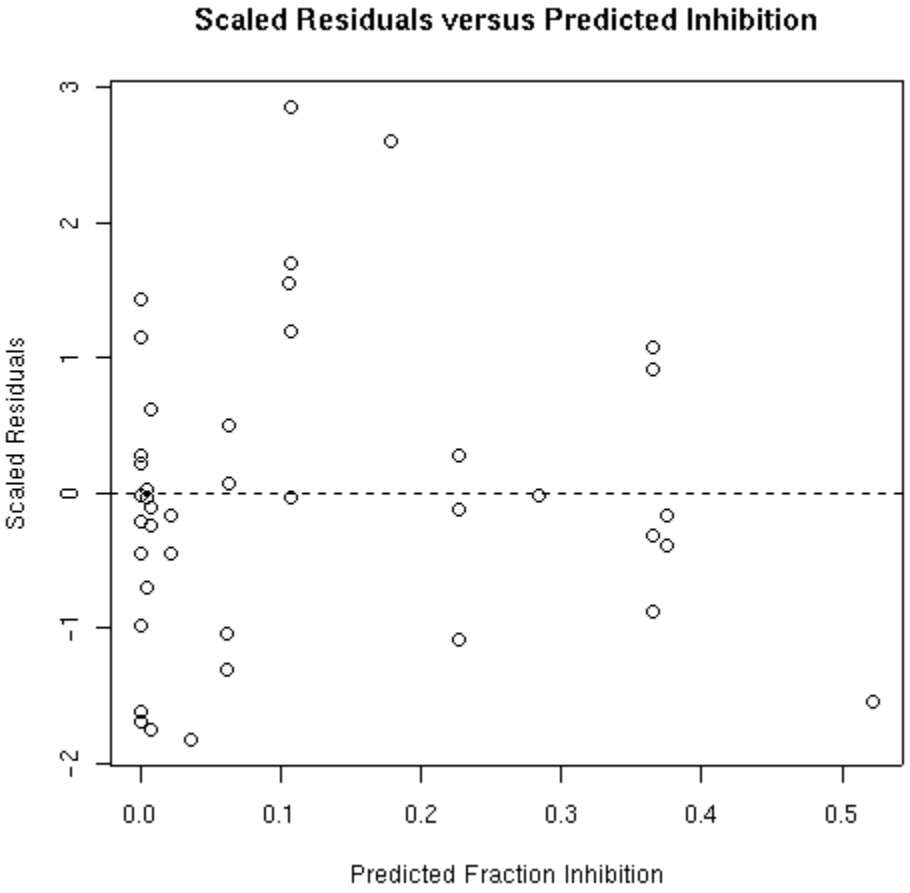


Expanded Model



D-R Shape at Low Doses (cont.)

Bensulide Residual Plots



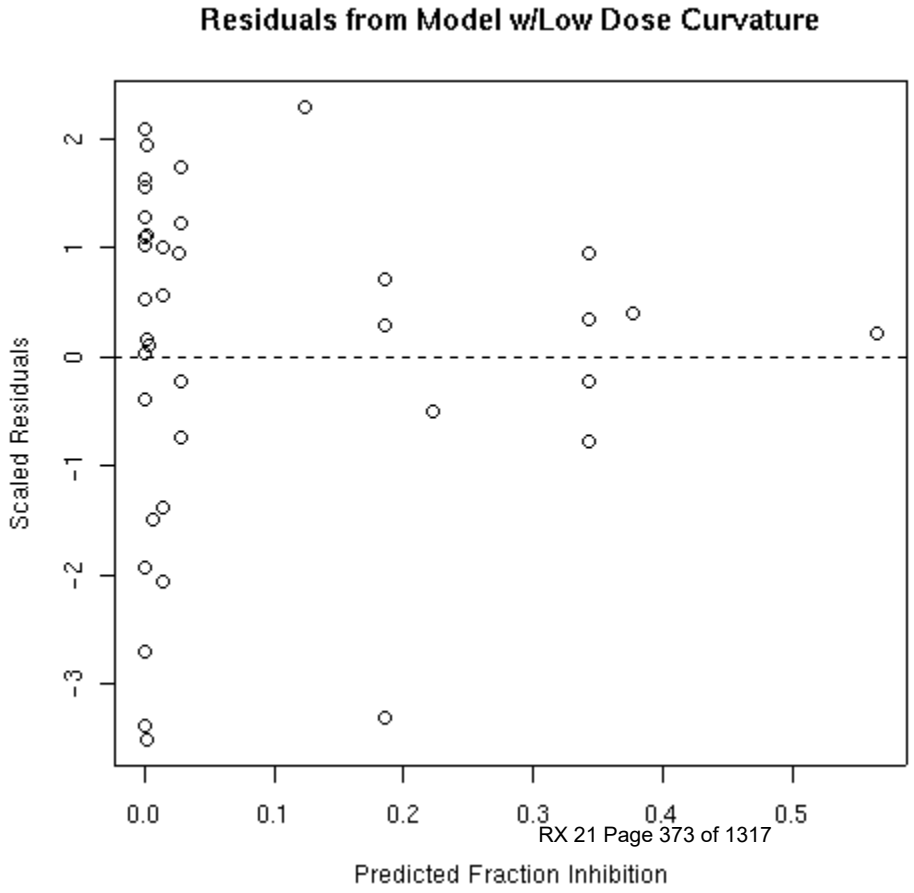


Table of Chemicals and RPFs

Chemical	Oral	Dermal	Inhalation
RPFs based on brain cholinesterase activity measured from female rats.			
Acephate	0.13	0.0025	0.208
Azinphos-methyl	0.092		
Bensulide	0.003	0.0015	
Chlorpyrifos	0.1		
Chlorpyrifos-methyl	0.012		
Diazinon	0.024		
Dichlorvos	0.037		0.677
Dicrotophos	1.95		
Dimethoate	0.33		
Disulfoton	1.23	0.47	6.596
Ethoprop	0.049		
Fenamiphos	0.039	1.5	0.315
Fenthion	0.35	0.015	
Fosthiazate	0.16		
Malathion	0.0003	0.015	0.003
Methamidophos	1	1	1
Methidathion	0.37		
Methyl-parathion	0.058		
Mevinphos	1.36		
Naled	0.083	0.075	0.82
ODM	0.9		
Phorate	0.39		
Phosalone	0.024		
Phosmet	0.02		
Pirimiphos-methyl	0.029		
Terbufos	0.84		
Tetrachlorvinphos	0.0008	0.00075	
Tribufos	0.045		
Trichlorfon	0.014	0.0075	0.087

Points of Departure for Index Chemical (Methamidophos) by Route of Exposure for Brain Cholinesterase Activity Measured in Female Rats

Route of Administration	Brain	
	BMD_{10}	BMDL*
Oral	0.08	0.07
Dermal	2.12	1.77
Inhalation	0.39	0.21

*BMDL is the lower 95 percent confidence interval

Summary

- SAP recommendations were considered, resulting in improvements in BMD calculations:
  - Using profile likelihood to estimate the horizontal asymptote results in value consistent with data
  - BMD is less sensitive to estimate of horizontal asymptote than was m
  - Reweighting

Summary (cont.)

- Basic model was reparameterized to improve the stability of estimator.
- Estimating parameters for combined datasets allows more complicated models that describe the low-dose shoulder of the dose-response.
- Including the low-dose shoulder improves the fit to the data and the BMD estimate for a substantial number of chemicals.

Questions for the SAP on Hazard and Relative Potency Factor

Question 1

A) In September 2001, the FIFRA SAP made some specific recommendations to EPA concerning refinements of its dose response analysis of cholinesterase data on OPs such as:

- the derivation of the adjustment factor "B" and modification of the decision tree for use of "B;"
- a formal analysis of residuals;
- minor revision to the Agency's OPCumRisk program (i.e., revision of the calculation as of the goodness of fit statistic and deletion on p- and t-values);
- consideration of the appropriate measure of relative potency;
- expression of inhalation exposure in the same units as the oral doses and adjustment for actual treatment durations;
- consideration of the impact of individual animal data instead of summary information;
- and derivation of oral doses from the actual dietary intake rates.

Question 1 (continued)

Please comment on how the Agency addressed the recommendations listed above (I.B and III.B.3).

B) Several of these issues were addressed by the application of the nonlinear mixed effect model for combining cholinesterase data. In addition, EPA utilized the profile likelihood method for estimating horizontal asymptotes when they could not be estimated jointly with the other parameters.

Please comment on the use of these statistical procedures in the dose-response assessment of the organophosphate pesticides

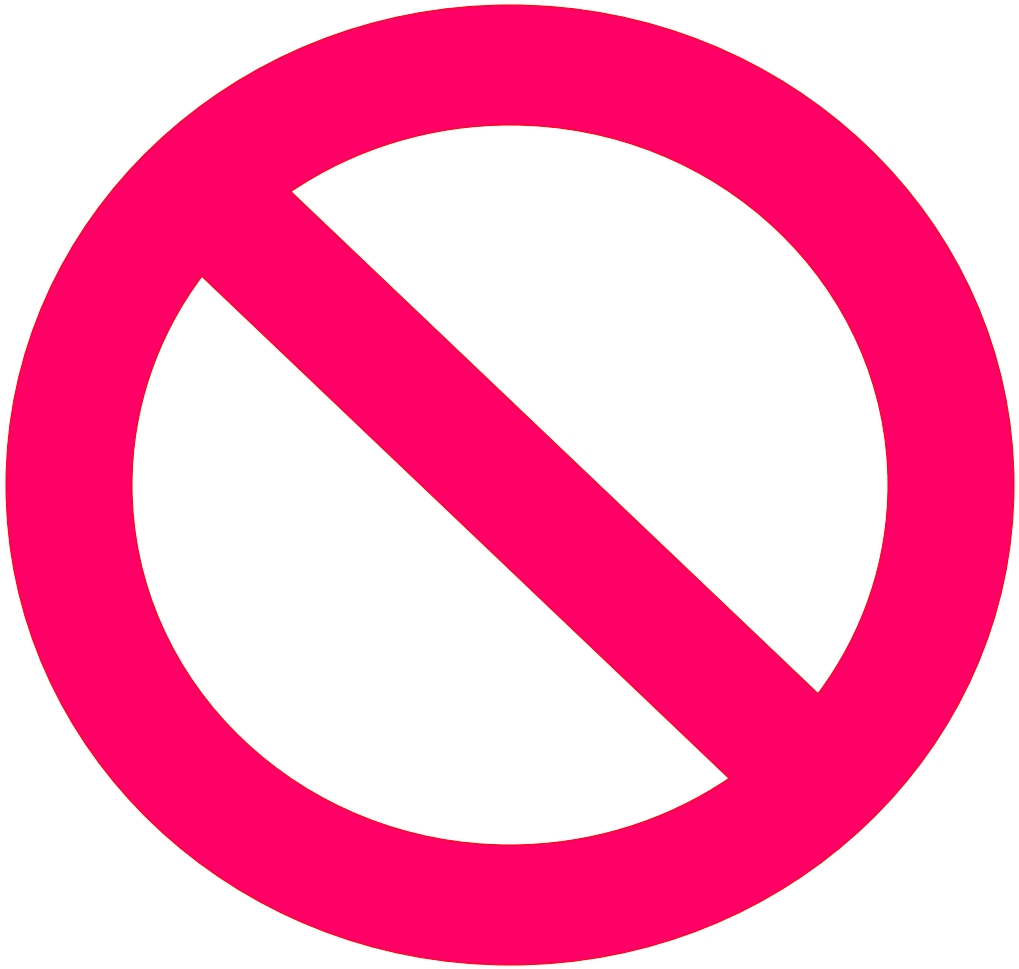
Question 2

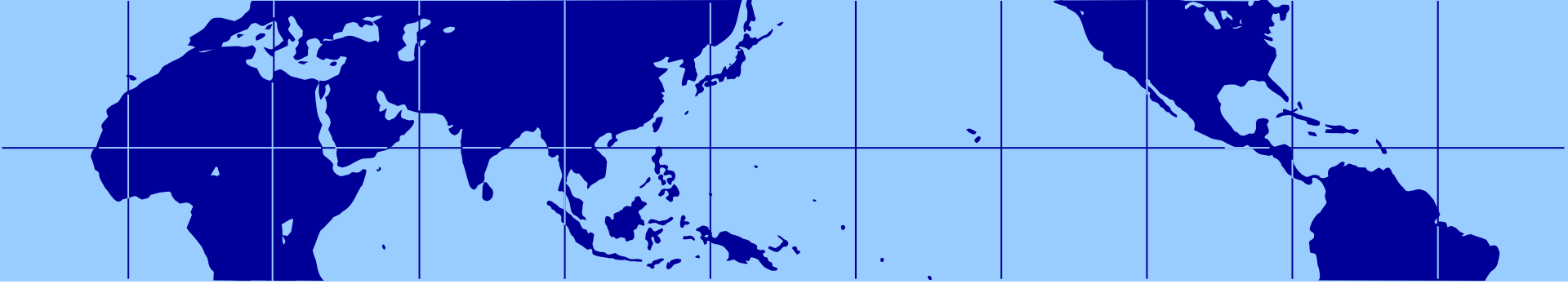
An exponential model was utilized by EPA in the July, 2001 Preliminary Hazard and Dose-Response Assessment of the Organophosphate Pesticides. Based on the equation used in the July 2001 document, cholinesterase activity decreases linearly in the low dose region of the dose response curve. Stakeholders present at the Technical Briefing (August 2001) and also a few members of the SAP (September 2001) suggested that a flat low dose region may be a more appropriate modeling approach. In response to this issue, EPA has further investigated the shape of the low dose region of the dose-response curve.

Question 2 (continued)

Two versions of the exponential model were used in the December 2001 hazard and dose-response assessment. One version, called the basic model, describes a linear low dose region and is similar to the approach used in the July 2001 document. All 29 OPs were fit to the basic model. The second version, called the expanded model, incorporates two additional variables, shape and displacement, which describe a flat low dose region of the dose-response curve. The female brain ChE data supported a flat low dose region for eight OPs (azinphos methyl, bensulide, disulfoton, malathion, methyl parathion, phorate, phosmet, and terbufos).

Please comment on the mathematical derivation of the expanded model in addition to the profile likelihood method for estimating the shape and displacement parameters when they could not be estimated jointly with the other parameters (I.B and III.B.1).





Session on Assessment of Food Exposure

Food Exposure

William O. Smith, Ph.D.
Chemist
Health Effects Division
Office of Pesticide Programs

Outline of Presentation

- Exposure Input parameters
  - Residues (USDA/PDP & FDA/CFSAN)
  - Consumption (USDA CSFII 1994-96/1998)
- Residue Manipulations
  - Index Equivalent Residues (RPF method)
- Probabilistic Exposure/Risk Assessment

Sources of Residue Data

- USDA Pesticide Data Program (PDP)
  - http://www.ams.usda.gov/science/pdp
- FDA Center for Food Safety & Applied Nutrition
  - http://www.cfsan.fda.gov/~lrd/pestadd.html
  - Pesticide Residue Monitoring Program
  - Total Diet Study (TDS)

OPs Included in Current Food Assessment

acephate, azinphos methyl, chlorpyrifos, chlorpyrifos-methyl, disulfoton, diazinon, dichlorvos, dimethoate, ethoprop, fenamiphos, malathion, methidathion, methamidophos, mevinphos, oxydemeton-methyl, methyl parathion, phorate, phosolone, phosmet, pirimiphos methyl, terbufos, & tribufos

PDP Foods Included in Assessment

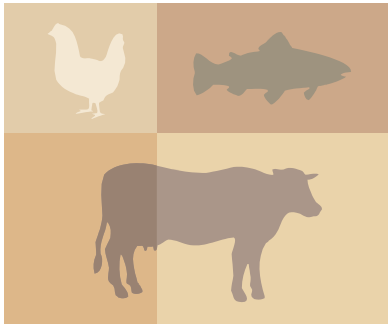
Apples
Apple Juice
Bananas
Broccoli
Celery
Cantaloupe
Carrots
Sweet Corn
Cucumbers
Corn Syrup
Cherries
Rice
Green Beans
Grapes
Grape Juice
Lettuce
Milk
Oats
Oranges
Orange Juice
Peaches
Pears
Nectarines
Pineapple
Potatoes
Bell Peppers
Strawberries
Sweet Potatoes
Soybean
Spinach
Sweet Peas
Tomatoes
Wheat
Winter Squash
Poultry
Peanut Butter

Foods Based on Translated PDP Data

Eggplant
Pepper(other than green)
Citrus (other than orange)
Apricots
Plums/Prunes
Rye
Beets-garden
Horseradish
Parsnips
Radishes
Rutabagas
Turnips
Various leafy greens
Brussels sprouts
Cabbage
Cauliflower
Melons (other than cantaloupe)
Pumpkins
Squash-summer

Foods Based on FDA Monitoring Data

- Eggs
  - Assume negligible based on FDA monitoring data
- Seafood
  - Assume negligible based on FDA monitoring data
- Meat from Beef, Pork, Sheep & Goats
  - Used maximum residues found in FDA/TDS



Foods Assumed Negligible Contributors

- Sugarcane, Sugar Beet & Maple
  - Molasses, syrup & sugar
- Assume negligible residues because…
  - Highly processed/refined
  - No residues in sugar or pancake syrup analyzed by FDA/TDS
  - No residues in corn syrup analyzed by PDP

The Proportion of the Diet of Children (3-5) Covered in the Cumulative Assessment

Source of Residue Estimate	% of Diet
PDP (RACs & processed)	85.7
Translation of PDP	1.3
FDA	6.3
Assumed negligible	3.1
Not included	3.6

The Proportion of the Diet of Children (3-5) Covered in the Cumulative Assessment

- Top 30 foods are included in this assessment
- Top 95% of Diet=56 foods
- 52 of 56 top foods included

Foods Not Included in Preliminary Assessment

- Not expected to impact significantly on assessment
  - Many are highly processed or blended foods
  - Infrequently detected residues and/or low levels

Cumulative Dietary Exposure

MOE=Point of Departure/Exposure

Exposure=Residue X Consumption



Cumulative Residues

Relative Potency Factor Method of Estimating Cumulative Residues

Converted chemical specific residues on food samples to a common residue

Index Equivalent Residue (Residue)

Calculation of Cumulative Residues

$$\text{Residue}_{IE} = \text{Residue} \times \text{PF} \times \text{RPF}$$

Residue: PDP residue data by sample

PF: Processing factor (if applicable)

RPF: Relative potency factor

$$\text{Cumulative Residue}_{IE} = \Sigma\ \text{Residue}_{IE}\ \text{(per PDP sample)}$$

Residue Inputs for Cumulative Assessment

Distributions of cumulative residues

OR

Average cumulative residues for highly blended foods

Cumulative Dietary Exposure

Exposure=Residue X Consumption



CSFII 94-96/98

CSFII 1994-96/1998

- Intakes of individuals residing in U.S.
- 20,607 individual participants interviewed over two discontinuous days (~3-10 days apart)
- 1998 Supplemental Children's Survey
  - 5,559 additional children
  - Birth through 9 years old

CSFII 1994-96/1998

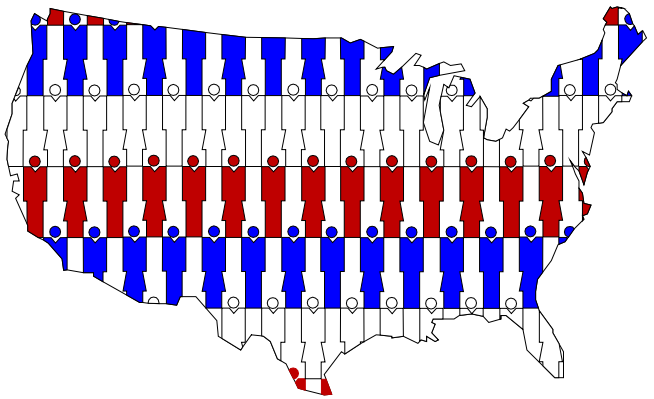
- The 1994-96/1998 CSFII significantly increases the number of children in the survey compared to the 1989-91 survey data currently being used by OPP

Comparison of Number of 1-day and Complete Intakes, by Children's Age Group 1994-96/1998 vs. 1989-91 CSFII

Age Group	1994-96/1998 CSFII		1989-91 CSFII	
	No. Individuals	No. Person-days	No. Individuals	No. Person-days
<1	1151	2940	197	579
1-2	2179	4114	574	1314
3-5	4579	8464	806	1812
6-11	2000	3706	1476	3441

Populations Groups Assessed

- Separate assessments were based on survey information on the following age groups:
  - Children 1-2 years old
  - Children 3-5 years old
  - Adults 20-49 years old
  - Adults 50+ years old



Exposure Assessment Models

- DEEM™ and Calendex™ were used to estimate cumulative food exposure and risk
- The use of Calendex™ and related issues will be discussed next by David Miller

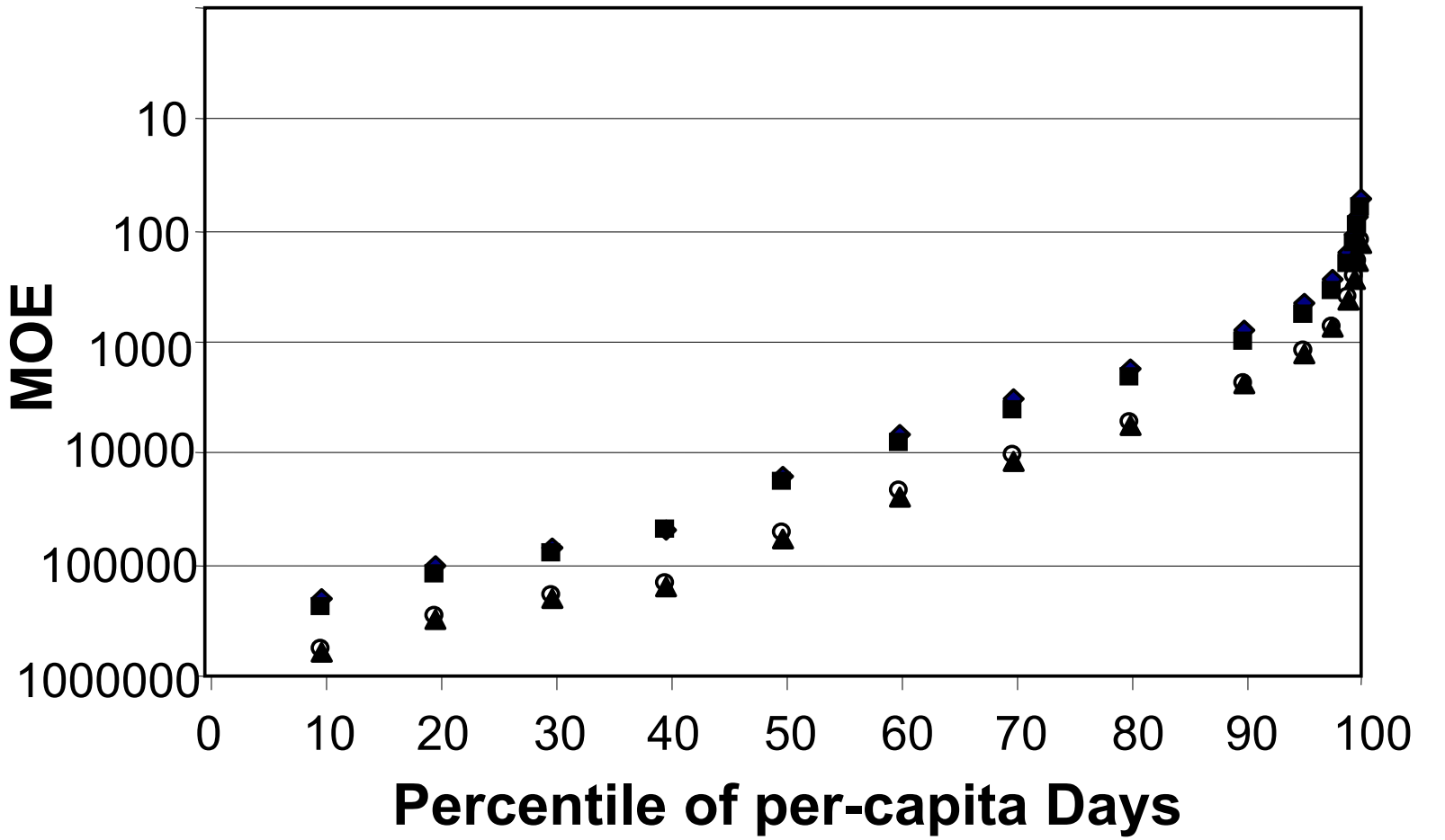
DEEM Model

- Dietary Exposure Evaluation Model: DEEM-FCID™
- Probabilistic (Monte-Carlo) procedure
- Input:
  - Distributions for consumption
  - Distributions or point estimates for residue concentrations
- Output:
  - Distribution of one-day dietary exposures
  - Distribution of associated risks, i.e., MOEs

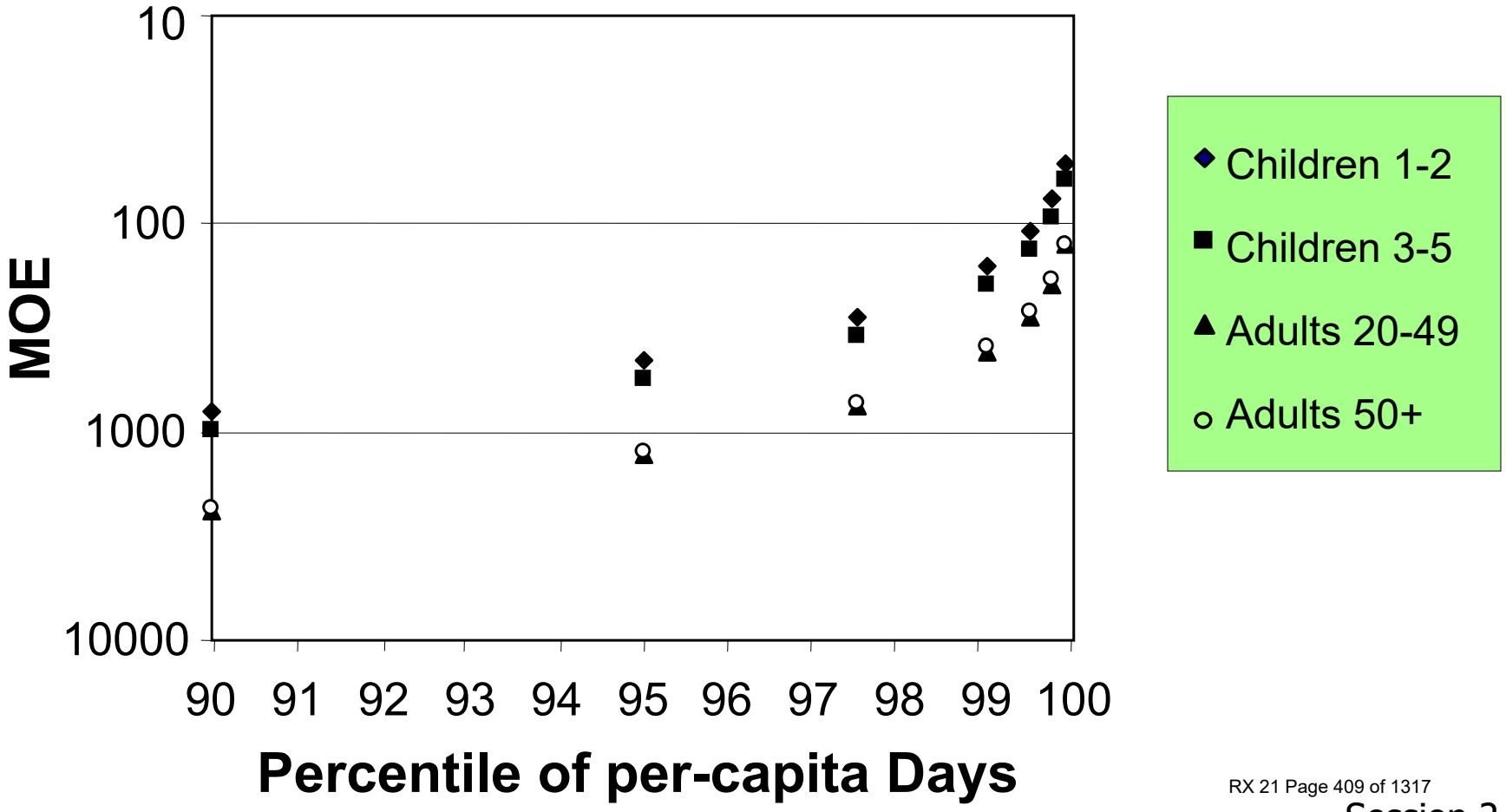
Dietary Exposure Evaluation Model DEEM-FCID™

- Uses EPA's Food Commodity Intake Database
- Commodity definitions are based on EPA's Food Commodity Vocabulary
- Recipes for relating foods consumed to raw commodities are publicly available

Preliminary Cumulative Food Exposure



Preliminary Cumulative Food Exposure- Upper Portion of Distribution



Preliminary Cumulative Exposure Assessment

Margin of Exposure (MOE) at Upper-End of Distribution

	Percentile					
	90th	95th	97.5th	99th	99.5th	99.9th
Children 1-2	800	454	280	160	108	51
Children 3-5	994	562	348	196	133	62
Adults 20-49	2415	1280	755	415	281	127
Adults 50+	2321	1228	720	393	264	125

MOE = POD/exposure; POD = 0.08 mg/kg body wt/day

Preliminary → *Final*

Work to be completed…

- Further refinements to inputs
- Interpretation of results

Potential Effects of Input Assumptions & Refinements on the Assessment

- Translation of PDP residue data to other foods
- Use of processing factors to estimate residues in processed food forms (cooked, dried, juices, etc.)

Effect of Translation of PDP Data

MOEs for Children 1-2 at Selected Points in the Exposure Distribution

	Mean	95th	99th	99.5th	99.9th
Full Assessment	2001	457	160	110	52
Only PDP Foods	2082	470	165	114	53

MOE=POD/exposure; POD=0.08 mg/kg body wt/day

Effect of Baby Foods

MOEs for Children 1-2 at Selected Points in the Exposure Distribution

	Mean	95th	99th	99.5th	99.9th
Full Assessment	2001	457	160	110	52
No OP/Baby Food	2087	471	164	112	52

MOE=POD/exposure; POD=0.08 mg/kg body wt/day

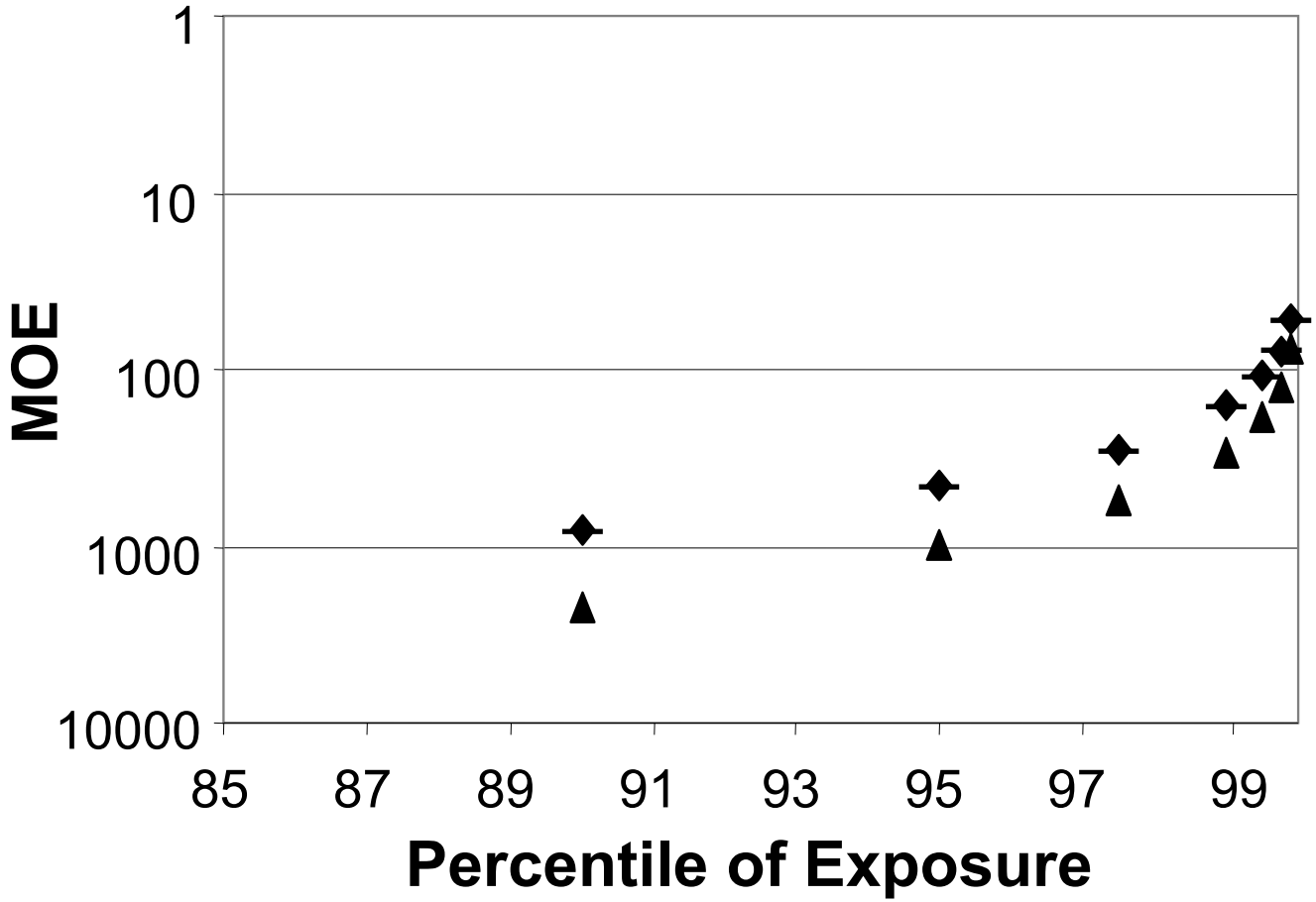
Impact of Processing & Translations

MOEs for Children 1-2 at Selected Points in the Exposure Distribution

	Mean	95th	99th	99.5th	99.9th
Full Assessment	2001	457	160	110	52
No Extrapolations	4895	988	293	188	77

MOE=POD/exposure; POD=0.08 mg/kg body wt/day

Cumulative Exposure Distribution-Effect of Translations and Extrapolation of Data



- ♦ Full Assessment
- – PDP-only
- ▲ No Extrapolation

Effect of Older Data on Assessment

- PDP foods analyzed 1994-2000
- One to 5 years PDP data per food
- Evaluating later data to see if they better represent current use practices

Effect of Older Data on the Assessment

MOEs for Children 1-2 at Selected Points in the Exposure Distribution

	Mean	95th	99th	99.5th	99.9th
Full Assessment	2001	457	160	110	52
≤2 Years Data	2205	503	181	125	58

MOE=POD/exposure; POD=0.08 mg/kg body wt/day

Effect of Older Data on Assessment

- Analysis not complete
- Complex factors
- Multiple distributions representing different segments of time

Analysis of Contributors to the Exposure Distribution

- DEEM Critical Exposure Commodity Analysis identifies major contributors to exposure
- Currently analyzing the top food contributors & the factors related to their contributions
  - Chemical residues (potency, frequency, levels)
  - Sampling details (origin & date of sample)

Analysis of Contributors to the Exposure Distribution

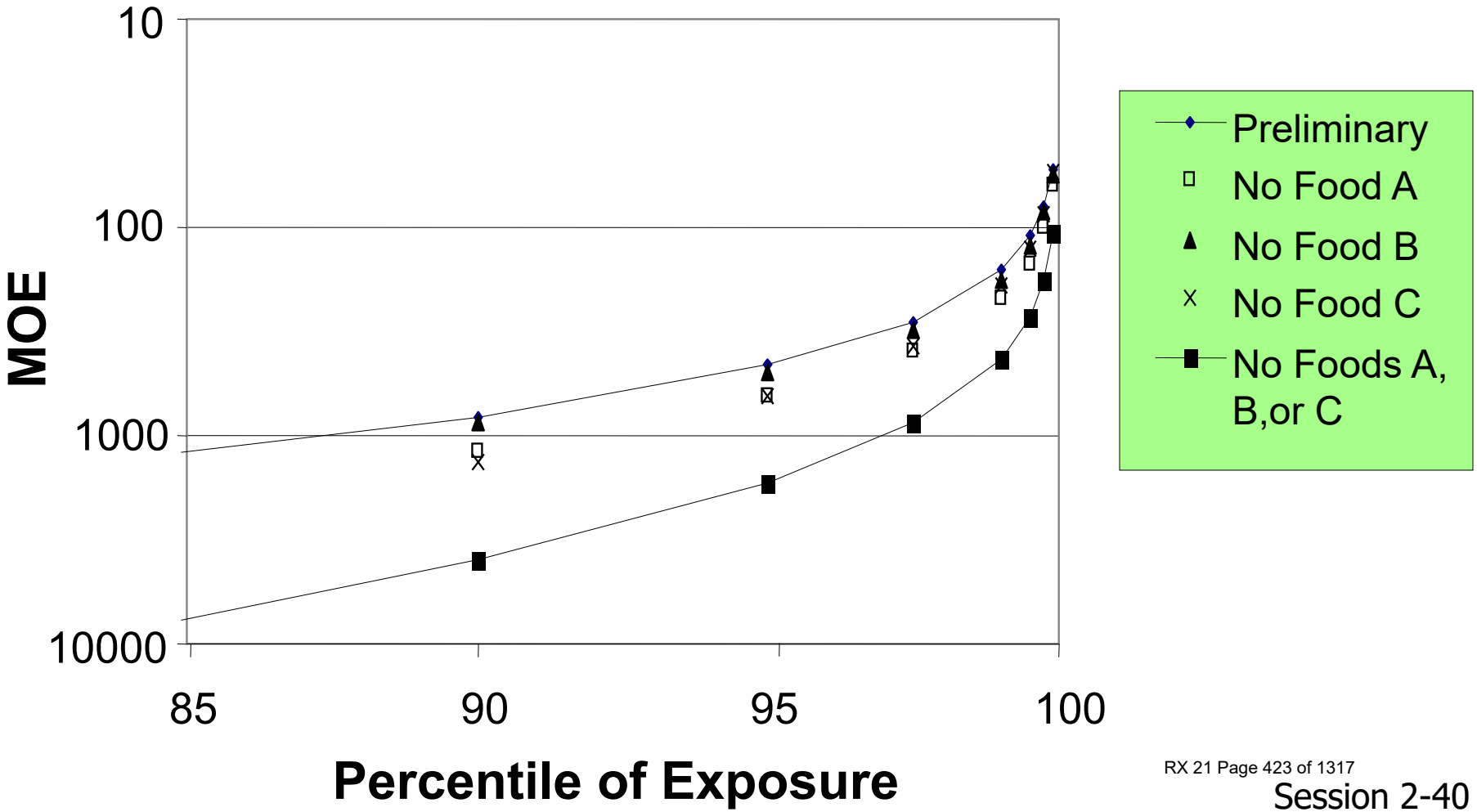
- Foods A, B, and C
  - Highest contributors to exposure between 99.8th & 100th percentile
  - Examined impact of removal of OP residues from all forms of each of these foods from the cumulative assessment

Impact of Foods A, B, & C on Assessment

MOEs for Children 1-2 at Selected Points in the Exposure Distribution

	50th	95th	99th	99.5th	99.9th
Full Assessment	16606	457	160	110	52
Minus Food A	47676	651	222	149	63
Minus Food B	19920	495	178	121	56
Minus Food C	60737	652	192	126	55
Minus A & B	57494	727	255	174	75
Minus A,B,& C	149770	1666	428	268	105

Impact of Foods A,B, & C on Assessment



Impact of Foods A, B, & C on Assessment

Ratios of $MOE_n/MOE_{full\ assessment}$

	50th	95th	99th	99.5th	99.9th
Full Assessment	1	1	1	1	1
Minus Food A	2.9	1.4	1.4	1.4	1.2
Minus Food B	1.2	1.1	1.1	1.1	1.1
Minus Food C	3.7	1.4	1.2	1.2	1.1
Minus A & B	3.5	1.6	1.6	1.6	1.4
Minus A,B,& C	9	3.7	2.7	2.4	2

Interpretation of The Food Risk Results

- PDP residue data cover the major food consumption items
- Further refinements of PDP data not likely to drastically alter the results at the higher end of the exposure distribution
- Complex factors are contributing to the exposure distribution

Calendar-Based Exposure Assessment

- Calendex™ was used to estimate cumulative exposure from food, water, and residential uses as a series of daily exposure distributions for a year

- This time-series food exposure assessment and related issues will be discussed next by David Miller

Time-Frame Considerations

David Miller
Chemist (USPHS)
Health Effects Division

Outline of Presentation

- Introduction/Background information
- DEEM(FCID)™ vs. DEEM(FCID)/Calendex™
- Time-Frame Considerations
- Modes in which Calendex™ can be used for a cumulative risk assessment
  - Consecutive daily estimates
  - Rolling (or sliding) time-frame
- Strengths and limitations of these modes
- Questions for the SAP

Points to Remember…

- Presentation will not review step-by-step mechanics of DEEM(FCID)/Calendex™ algorithms:
  - DEEM/Calendex™ reviewed in previous SAPs
- Presentation concentrates on exposure through food
  - Principles apply to all routes
- No decision has been made on an appropriate MOE or threshold percentile for regulation

Introduction

- DEEM(FCID)/Calendex™ provides a probabilistic assessment of exposures through food, water, and residential pathways
  - DEEM(FCID)/Calendex™ incorporates concept of a Calendar to evaluate aggregate or cumulative exposures
    - Time-based approach
  - Calendar-based approach looks at each individual day of the year
  - Calendar-based approach allows appropriate “temporal matching” of exposures through food, drinking water, and residential pathways
    - Temporal aspect of exposure important for OP’s due to expected seasonal use-patterns

Introduction

- Calendex™ uses probabilistic techniques to appropriately combine exposures from the food, water, and residential pathways in a manner which incorporates:
  - probabilities of exposure,
  - use and application practices,
  - human activity patterns,
  - etc.
  - and considers their associated seasonality and timing
- Result is a collection (or distribution) of aggregate exposures (food, residential, and drinking water combined) for each day of the year for the relevant region

These **exposures** can be plotted as a **"time-line"** or profile of daily exposures for any **given percentile** in the distribution

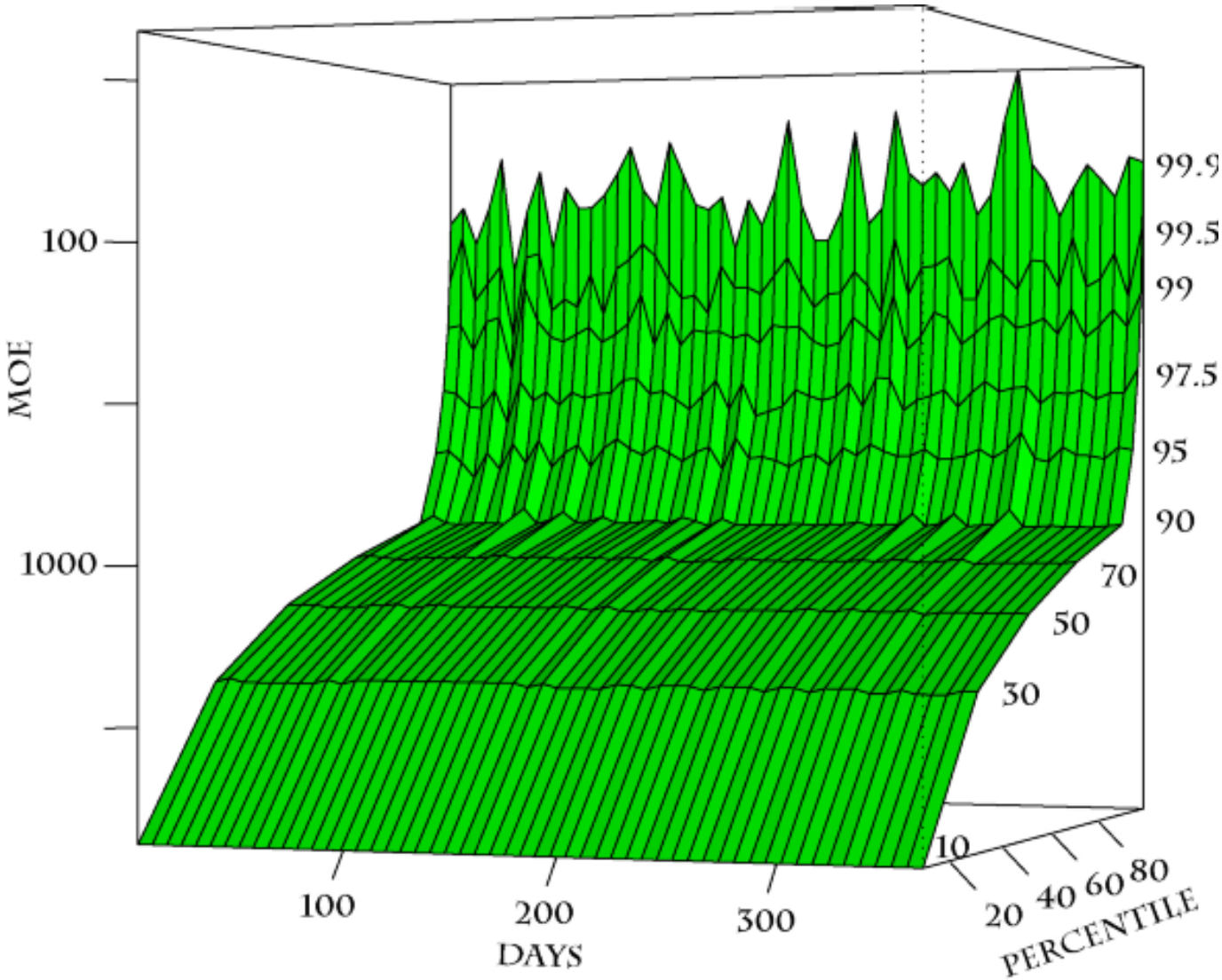


Figure I.F-1. Three-dimensional plot of the total MOE by day of the year and percentile of exposure

How Does DEEM(FCID)/Calendex™ differ from DEEM(FCID)™?

- DEEM(FCID)™ analysis assesses exposure from food alone without respect to timing/seasonality issues
  - Randomly matches reported food consumption, by individual, with residue data
    - No time component
  - Result is a single distribution of exposures and a single-valued estimate of risk at any given percentile of exposure

How Does DEEM(FCID)/Calendex™ differ from DEEM(FCID)™?

- In an aggregate or cumulative assessment in which pathways are combined, timing considerations are important
- DEEM(FCID)/Calendex™ performs analysis in a manner in which timing considerations are incorporated
  - Does this by performing separate analyses for each day of the year
  - Result is 365 separate distributions of exposures for each of the day of the year
  - Exposures at any given percentile can be plotted as a time-based exposure profile

DEEM(FCID)™ vs. DEEM(FCID)/ Calendex™

DEEM (FCID)™

- Considers Food Alone
- Timing is not considered
  - No day-to-day variation
- Single exposure estimate at any given percentile

DEEM (FCID)/Calendex™

- Considers all pathways
- Timing is considered
  - Some Day-to-day variation in diet
- 365 sequential daily exposure estimates at any given percentile

Time-Frame Considerations

- Important to consider how estimated exposure is compared with toxicity endpoint
  - Toxicity endpoint in PCRA is based on BMD_{10} which reflects multi-day dosing studies

Time-Frame Considerations

- September 2001 SAP Meeting considered this issue of how to compare time component of toxicity endpoints and exposure:
  - CRA should ideally compare toxicity endpoints and exposure durations of same time-frame
  - To the extent possible, comparison should take into account the pattern of human exposure

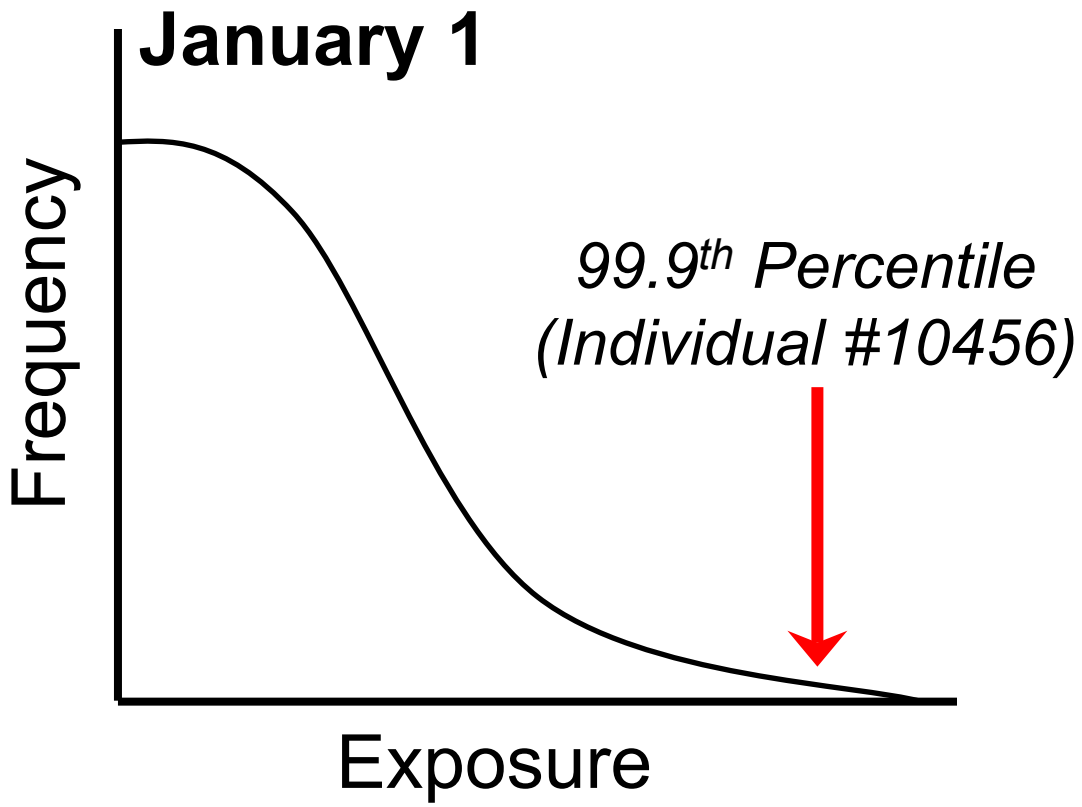
Time-Frame Considerations

- DEEM/Calendex™ program can perform analysis using a variety of time-frames
- This presentation considers two specific modes of analysis:
  - Single Consecutive daily estimates
  - Rolling (or sliding) time-frame
- Examples here are illustrative only

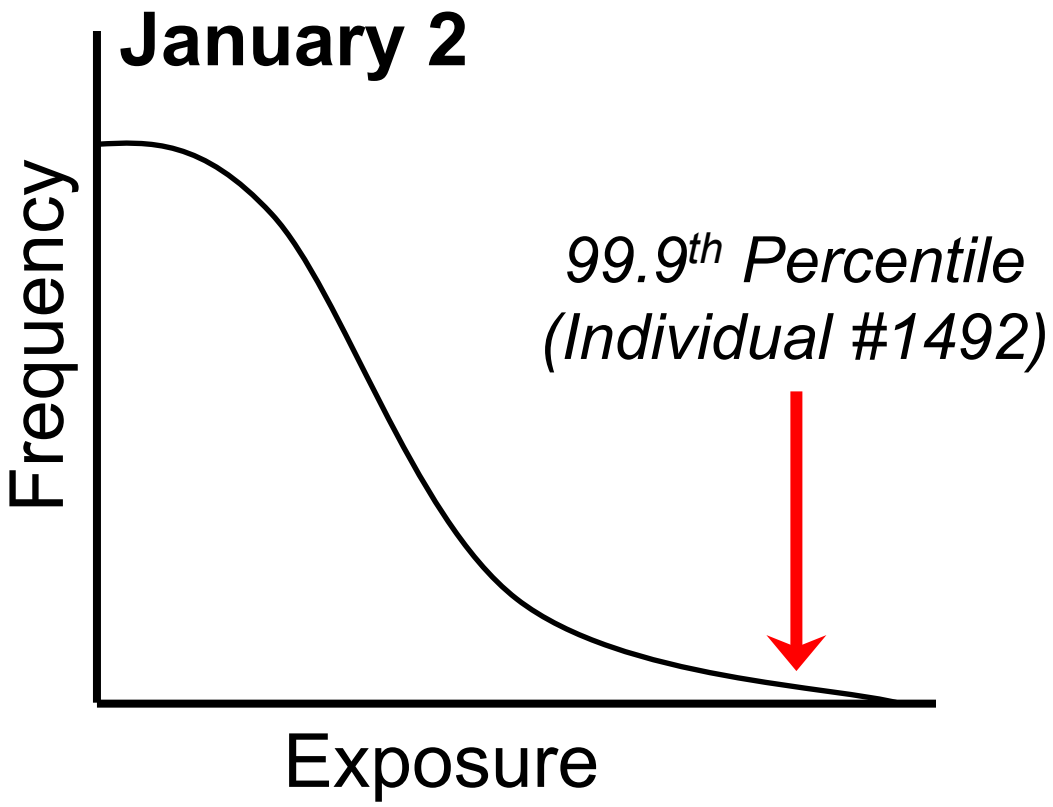
Single (Consecutive) Day Analysis

- Single Consecutive Day Option
  - Separate independent exposure and risk (MOE) estimates made for each day of the year
  - Estimates are arrayed chronologically into an exposure time line for any selected percentile and graphed
    - These represent independent, daily estimates of risk on each day of the year
      - Not necessarily the same individual on consecutive days

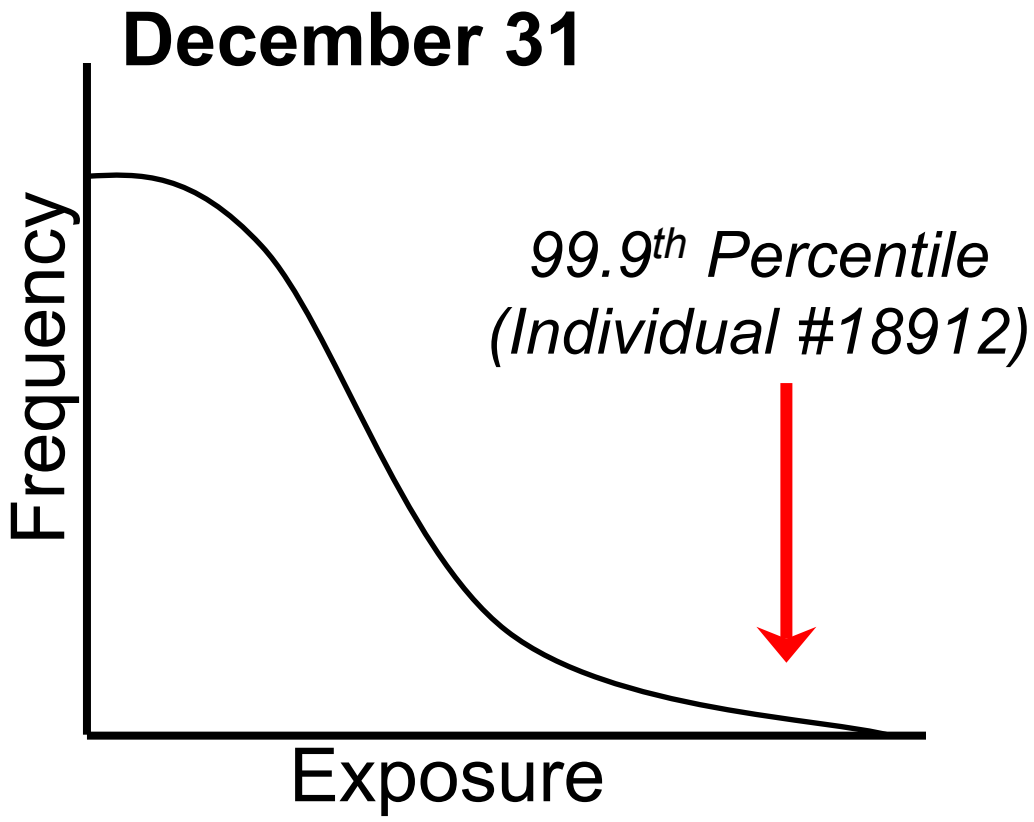
Single (Consecutive) Day Analysis



Single (Consecutive) Day Analysis



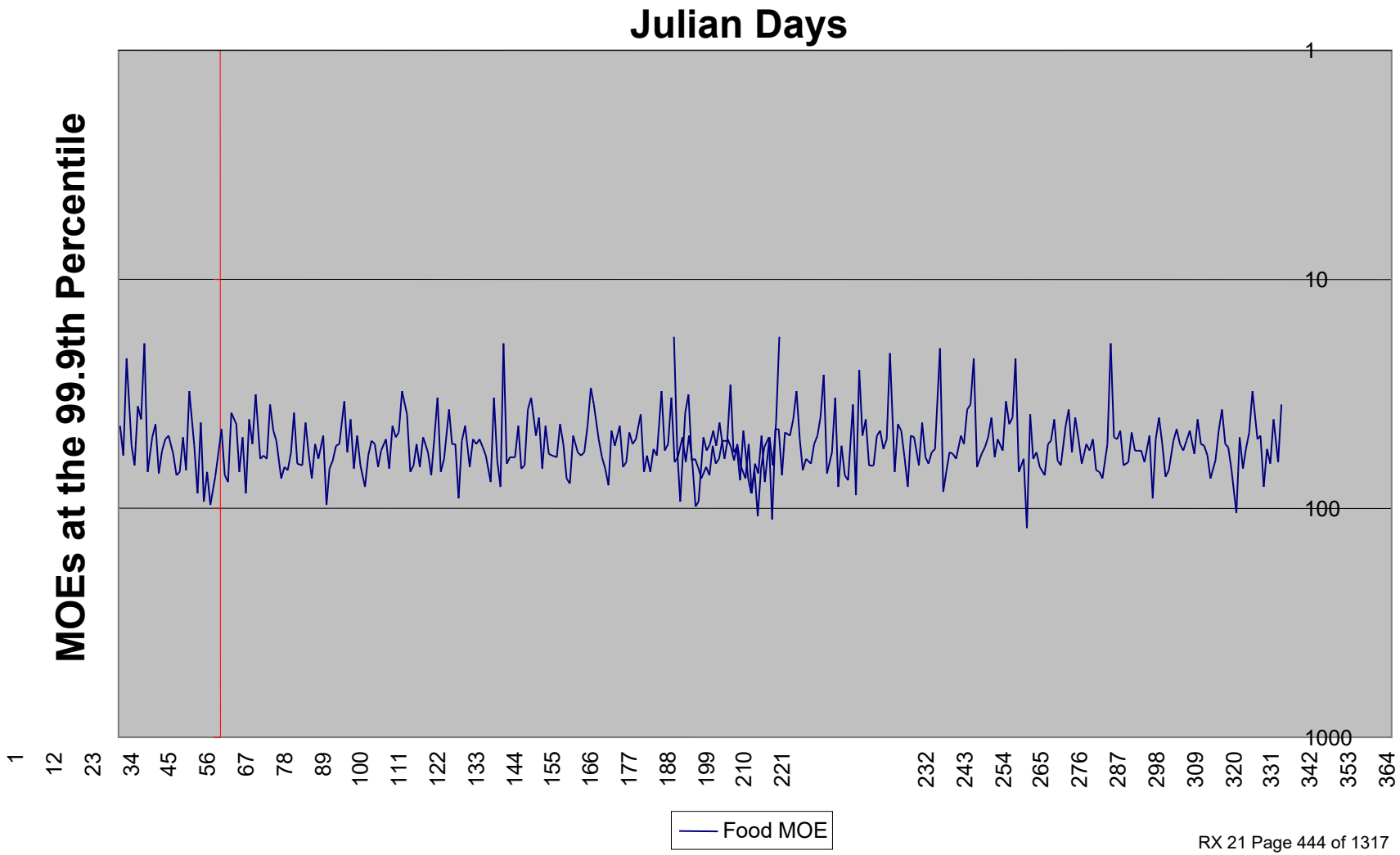
Single (Consecutive) Day Analysis



Single (Consecutive) Day Analysis

- Plot, for each day, a fixed population exposure percentile (e.g., 99.9th)
- Resulting time-based exposure profile represents 99.9th percentile exposure for each day of the year
  - each day of year considered independently

Example Exposure Profile for Food



Example Exposure Profile for Food

- On Day 31, the MOE_F at the 99.9th percentile is 58
  - Translation:
    - Exposure to the 99.9th percentile individual on Day 31 is 58 times lower than the POD

- On Day 32, the MOE_F at the 99.9th percentile is 66
  - Translation:
    - Exposure to the 99.9th percentile individual on Day 32 is 66 times lower than the POD
      - This is likely to be a different individual than the 99.9th percentile individual on Day 31

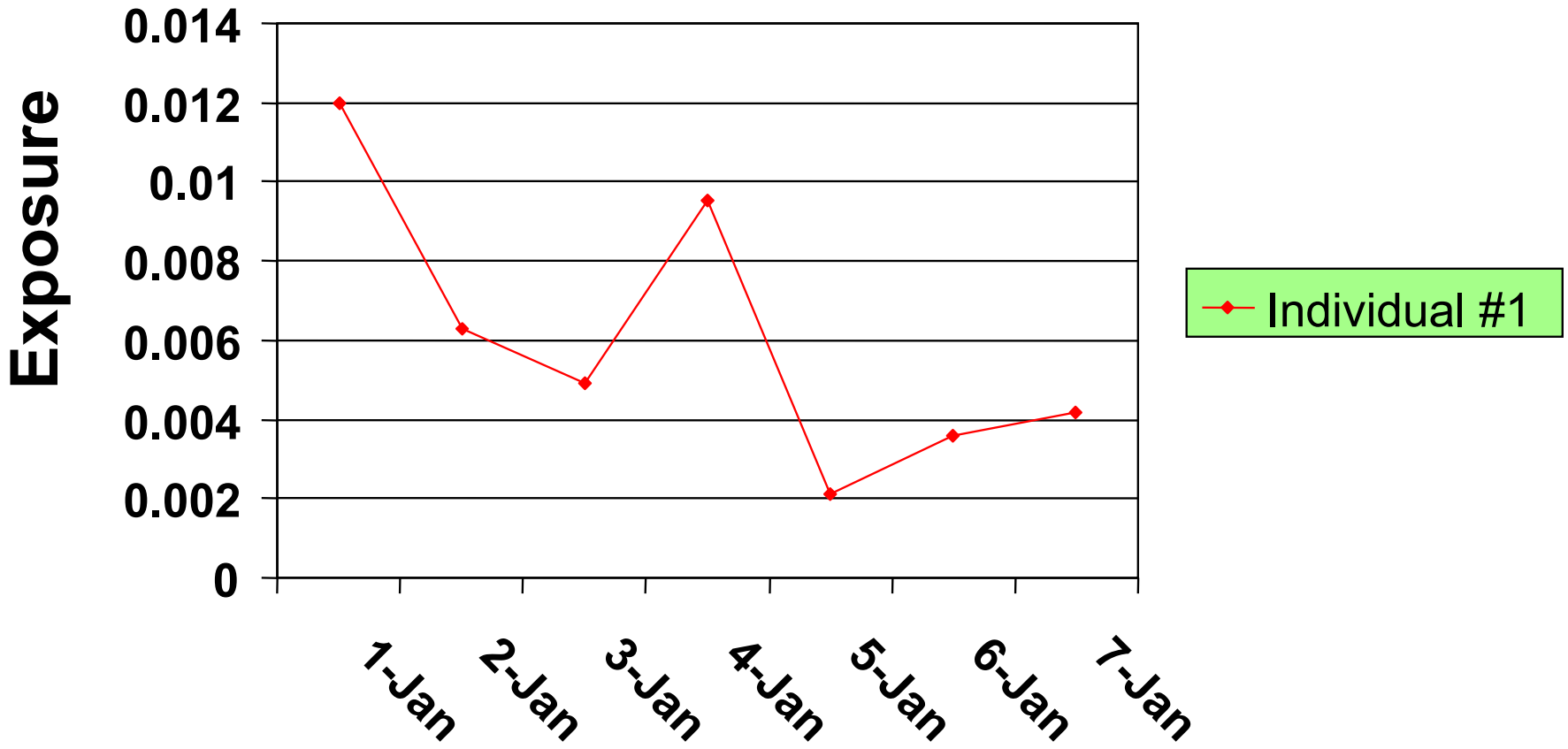
Pros and Cons for Single-Day Based Estimate

- **Pros:**
  - Easier to identify risk contributors
  - Health protective
    - unlikely to underestimate average exposure over multiple days
- **Cons:**
  - Point of Departure is based on multi-day exposure
    - Relevance of comparing a series of single-day exposures to multi-day endpoint
  - Consecutive daily estimates are likely to overestimate multi-day exposures to an individual (at higher percentiles)
    - e.g., not possible to interpret extended series of elevated exposures on consecutive days as representing extended period of exposure to the same individual.

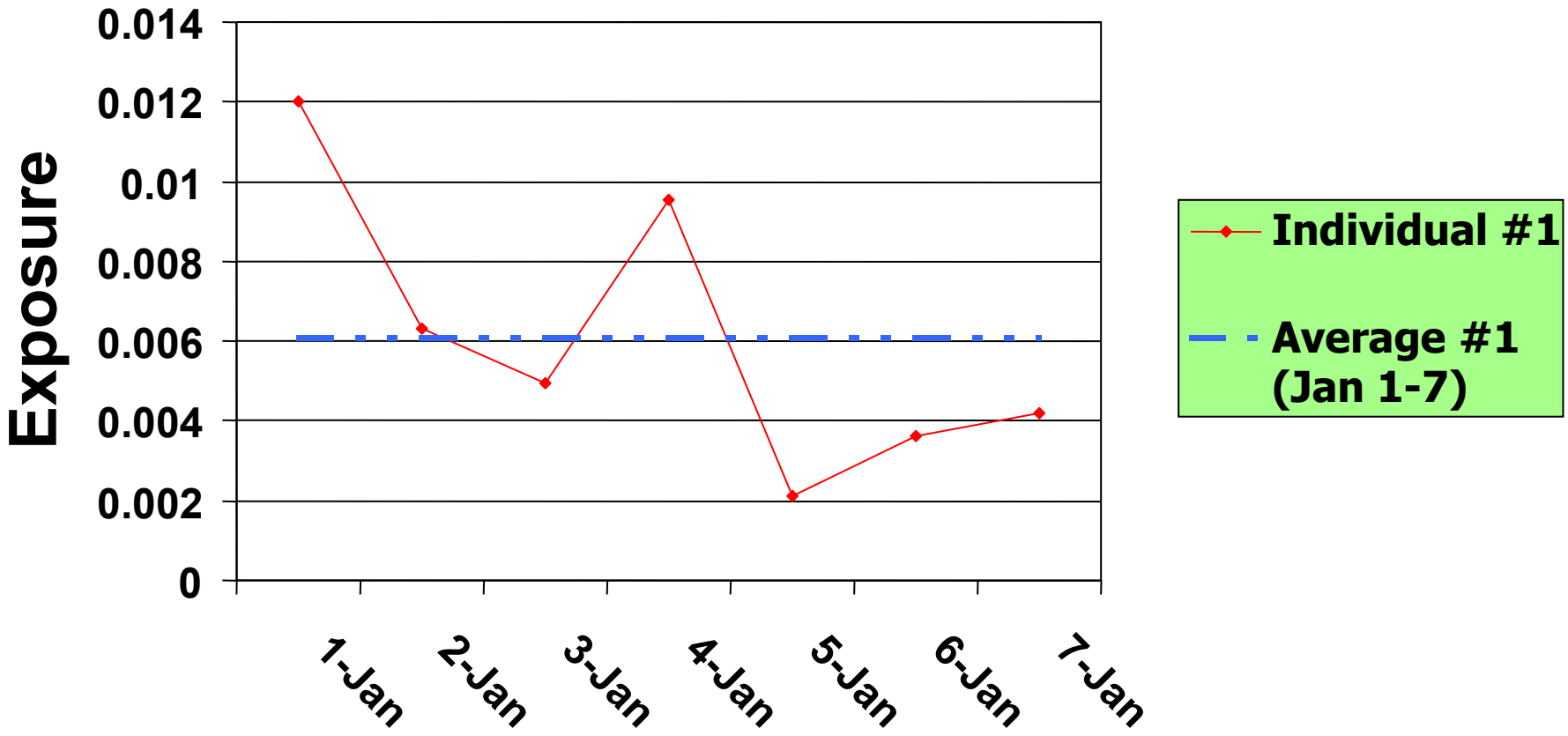
Rolling Time-Frame Approach

- Multiple Sequential Day Option (a.k.a. rolling time-frame)
  - In a rolling time-frame approach, average exposures over multiple days are calculated for each individual
    - e.g., January 1 through 7, then January 2 through 8, January 3 through 9, etc.
  - This series of **multi-day average exposures** serves as basis of comparison with POD
    - This distribution of multi-day average exposures serves as basis of comparison with (multi-day) BMD_{10}

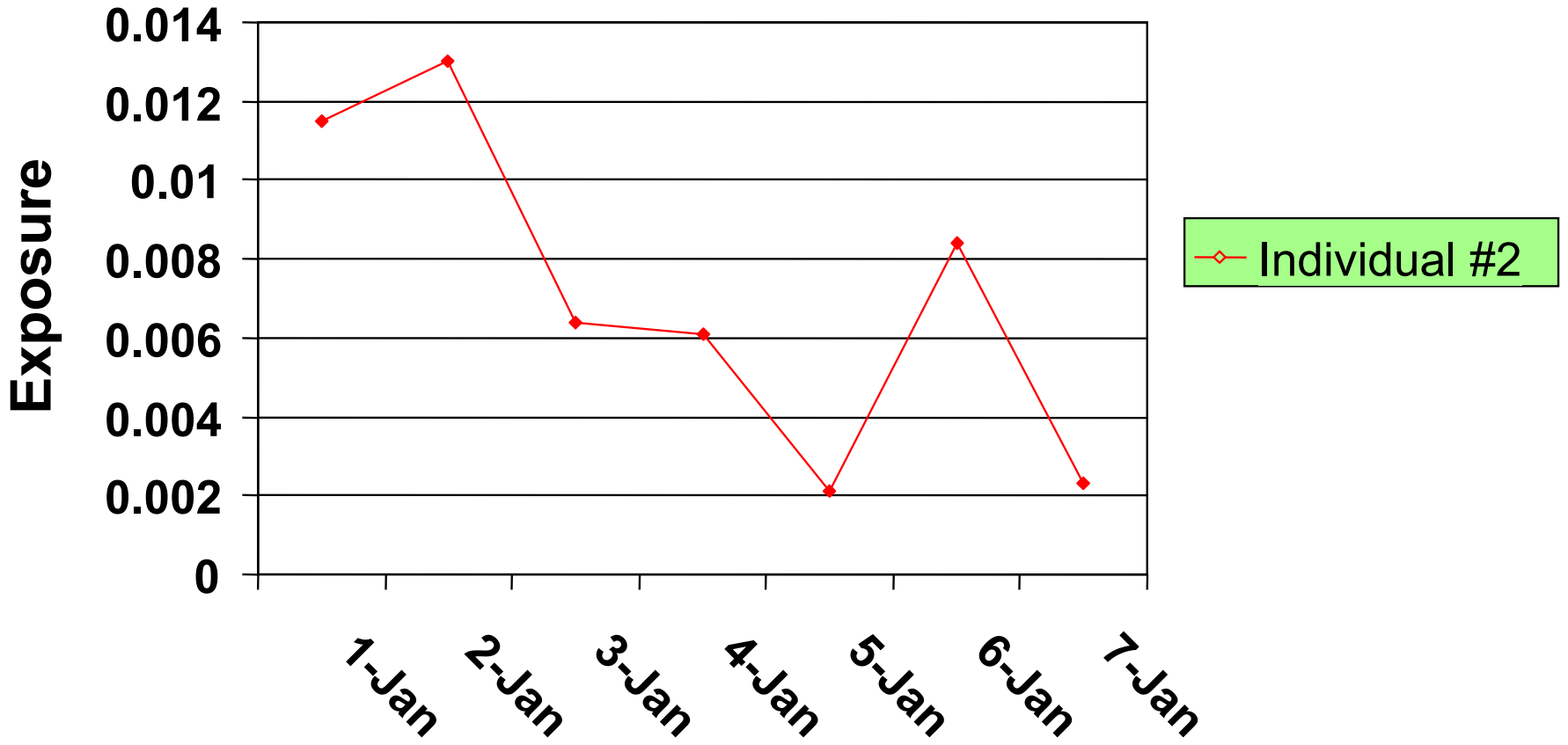
Rolling Time-frame Approach



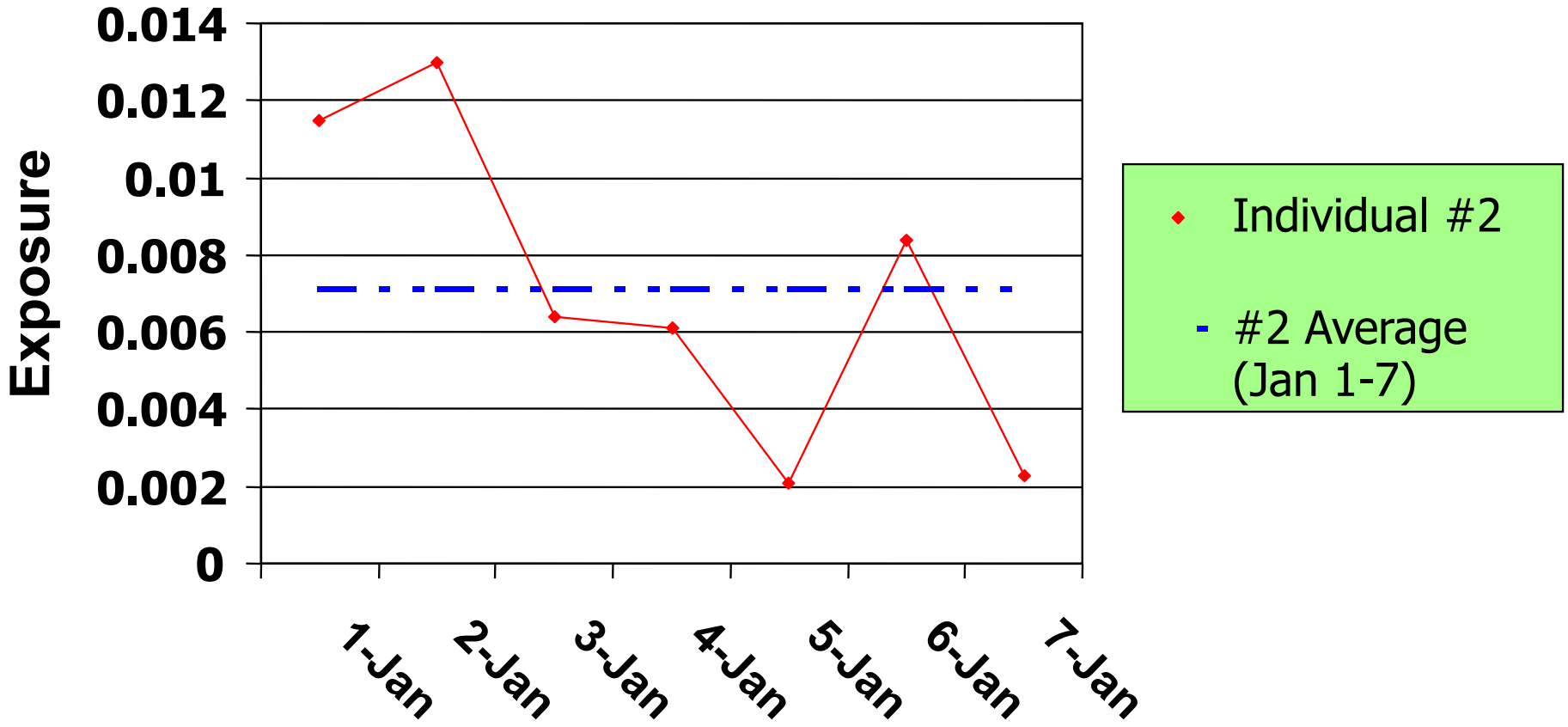
Rolling Time-frame Approach



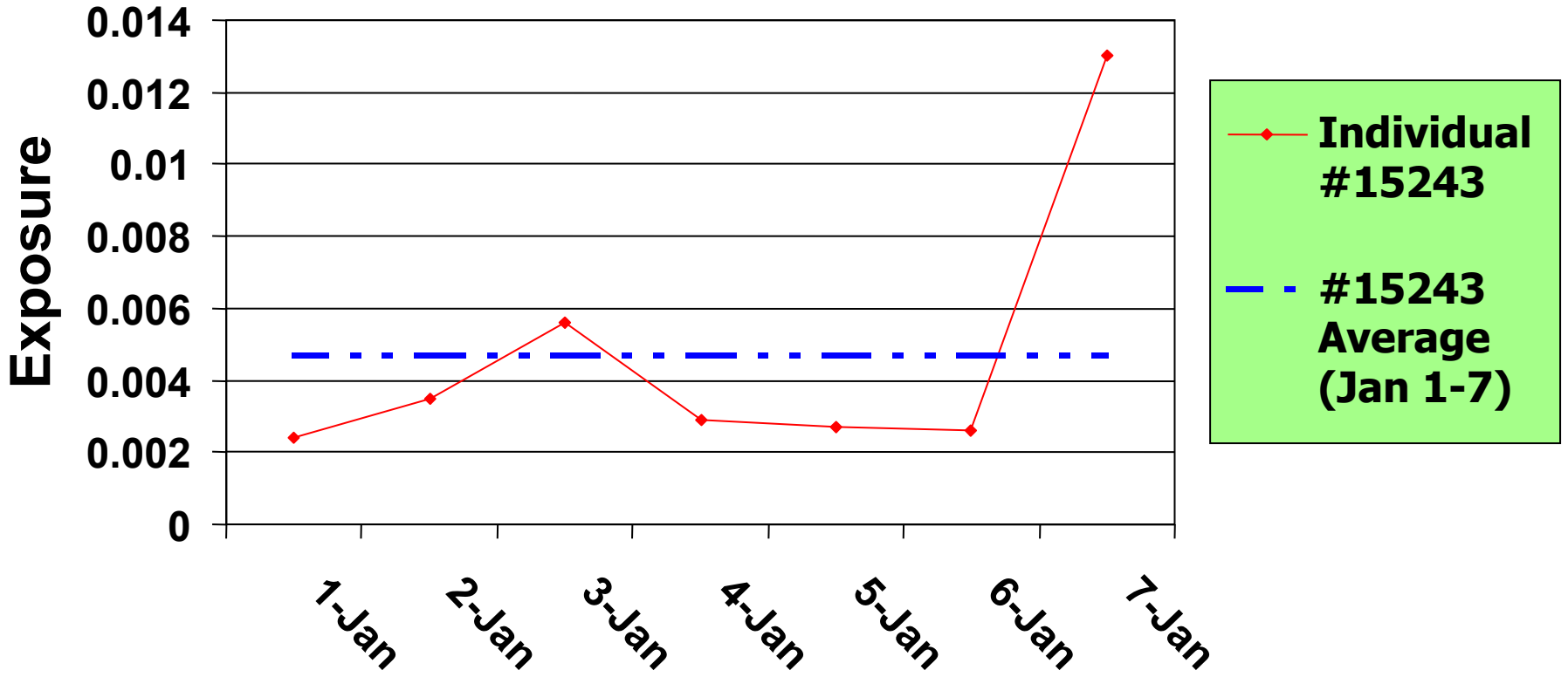
Rolling Time-Frame Approach



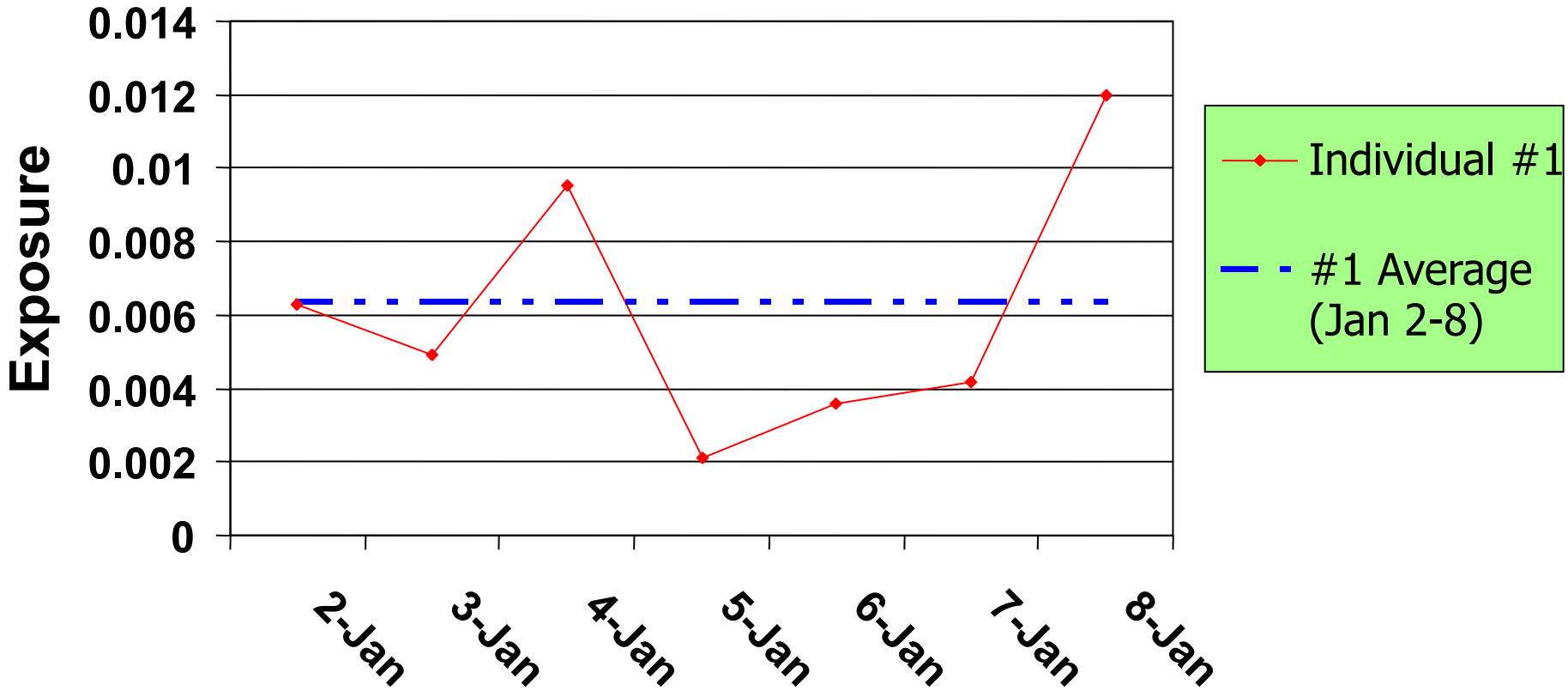
Rolling Time-Frame Approach



Rolling Time-Frame Approach



Rolling Time-Frame Approach



Pros and Cons for Rolling-Average Based Estimates

- **Pros:**
  - Incorporate variability in exposure for an individual <u>across multiple days</u>
  - Likely to provide a more realistic estimate of exposures across multiple days
  - Flexible with respect to matching time-frame associated with POD

Pros and Cons for Rolling-Average Based Estimates

- **Cons:**
  - USDA's CSFII does not provide consumption data across the multiple consecutive days which would be of interest
    - Limited to two days of reported intake
    - Two days are not consecutive (3-10 days apart)
    - Multi-day average exposure for any individual uses only two days of reported consumption data for that individual
      - and repeats these (randomly) through the time-frame of interest
  - No "longitudinal" residue data is available

Issues: Food Consumption

- Any consecutive day period of interest for an individual will contain a series of repeated diets which tend to underestimate variability
  - This will tend to overstate potential exposure at upper tails of distribution to the extent that reported diets (food choices) are associated with higher exposure

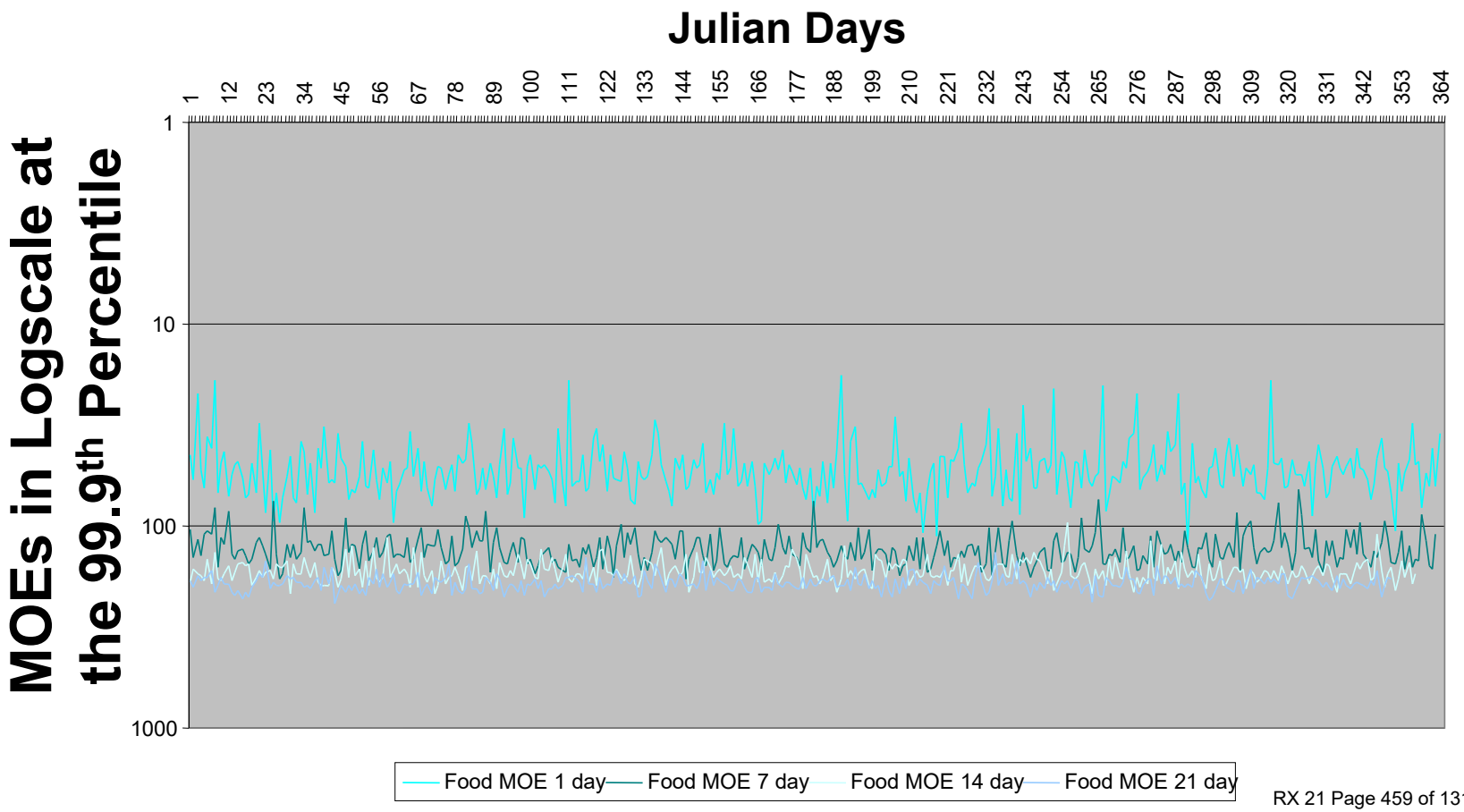
Issues: Residues

- Since residue values are drawn (anew) at random for each day during the time-frame of interest, true correlations that may exist between residues on subsequent days may not be accurately reflected
  - This will tend to understate potential exposure at the upper tails of the distribution to the extent that an individual's exposure is associated with pesticide residue concentrations
    - Juices
    - Bags of Produce

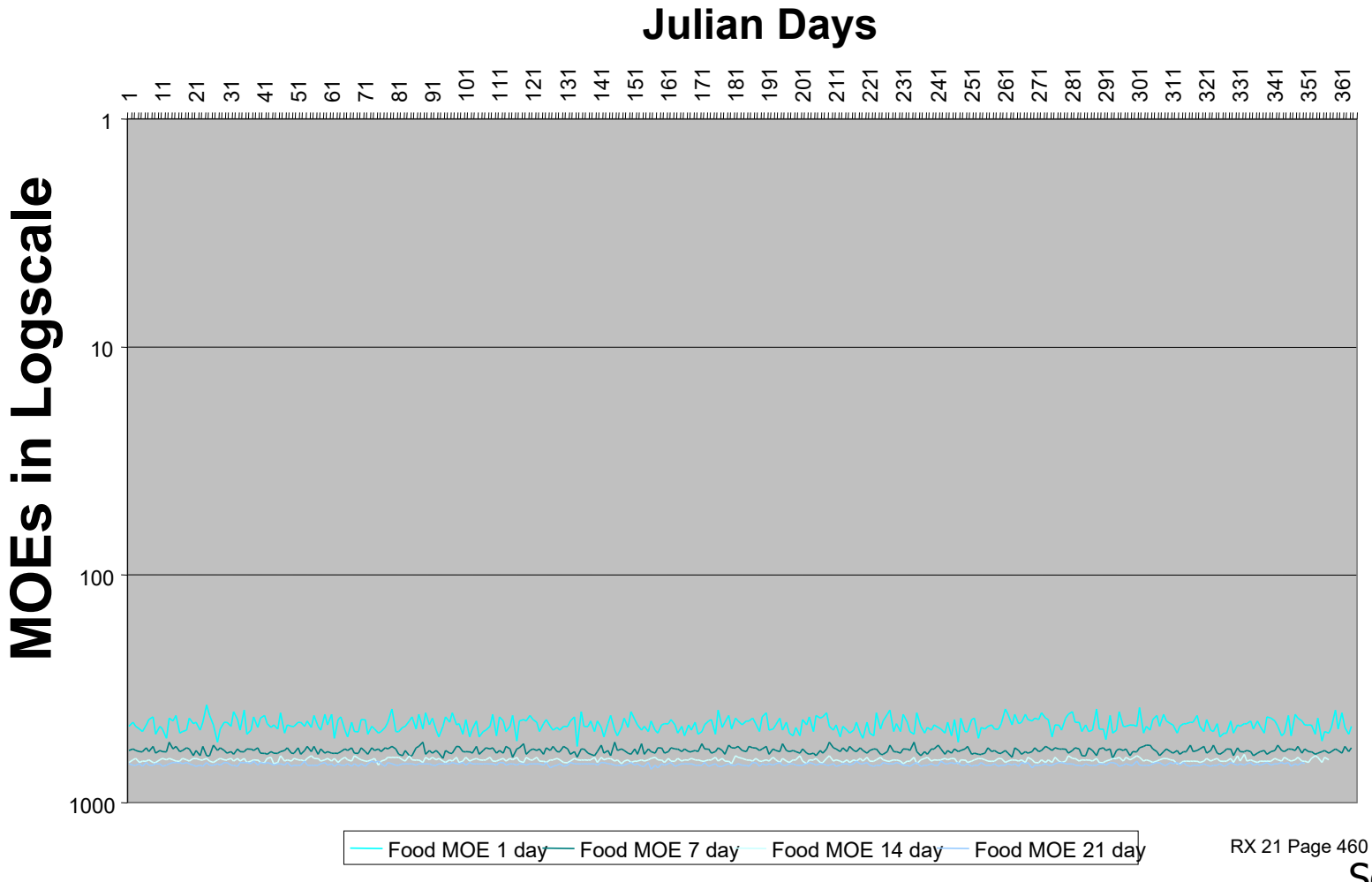
Comparison of MOE Using Different Time-Frames

- DEEM(FCID)/Calendex™ software has various pre-defined options for duration of time-frame
  - 7-, 14-, 21-, and 28-day rolling time-frames
    - Multi-day averaging process
  - Increases in time-frame over which averaging performed results in:
    - Attenuation of variability
    - Increase in the MOE (decrease in exposure)
  - Degree to which these changes occur dependent upon selected percentile

Comparison of Exposure Windows in the Cumulative PCRA Higher Percentile Example



Comparison of Exposure Windows in the Cumulative PCRA Lower Percentile Example



Questions for the SAP on Assessment of Food Exposure

Question 1

In the In the Preliminary OP Cumulative Risk Assessment, OPP used all available PDP monitoring data generated since 1994 as the basis for the residue distributions of pesticides in treated foods. As a result, some foods have multiple years of data (as many as 5), while others have only a single year of data. All years of data were included to provide the most robust residue data set possible. These data were extended to cover foods and processed forms of foods for which data are not directly available. Additionally, some foods were included in the analysis based on less robust data from FDA.

OPP is conducting a sensitivity analysis in which the residue contributions from specific foods (either one at a time or in combination with other foods) are removed from the analysis. This analysis is being conducted as part of an effort to determine the contributions of specific food commodities and chemicals to the upper tail of the exposure distribution. Some preliminary results are shown in Table 1 of the addendum to this document.

Question 1

Partly as a result of this exercise, OPP has observed that the more variables (e.g., commodities, chemicals, years of data) that are included in the exposure distribution, the more difficult it becomes to affect the tail of the distribution by removing commodity/pesticide combinations from the calculations. While removal of most exposure contributors results in a demonstrable change in the lower portion of the distribution, the exposures at the upper end of the tail (for example the 99.9th percentile) are relatively unaffected by removal of a single commodity, even if it is identified by DEEM as a frequent contributor to the high end of the exposure distribution.

Please discuss the significance of this observation and its potential impact on interpretation of the output distributions and results from highly complex distributional analyses such as the Preliminary OP Cumulative Risk Assessment.

Question 2A

The Calendex model can be used in a number of modes to develop a profile of exposure estimates. In the current assessment, OPP conducted a series of single-day assessments arrayed chronologically to develop a response surface of exposures. A constant percentile of exposure was selected to represent the potential exposure to a given percentile of the population. For example, the 99th percentile for each day would be arrayed for 365 days to reflect the population estimate across the calendar year. Calendex can also be used in a multi-day sequential series analysis, also referred to as a "rolling time-frame mode." A rolling time-frame provides an estimate of the average of daily exposures for an individual calculated over multiple (7, 14, 21, or 28) days, for each multiple day period over the course of a year, (e.g., days 1-7, then days 2-8, then days 3-9, etc.). In this mode, an individual's food exposure is tracked across the calendar year by randomly selecting day one or day two of that individual's reported consumption from the CSFII and combining each commodity which comprises that consumption with randomly selected residue values for each day of the calendar year. These rolling averages for each individual are assembled to develop a distribution of rolling average exposures.

Question 2A (continued)

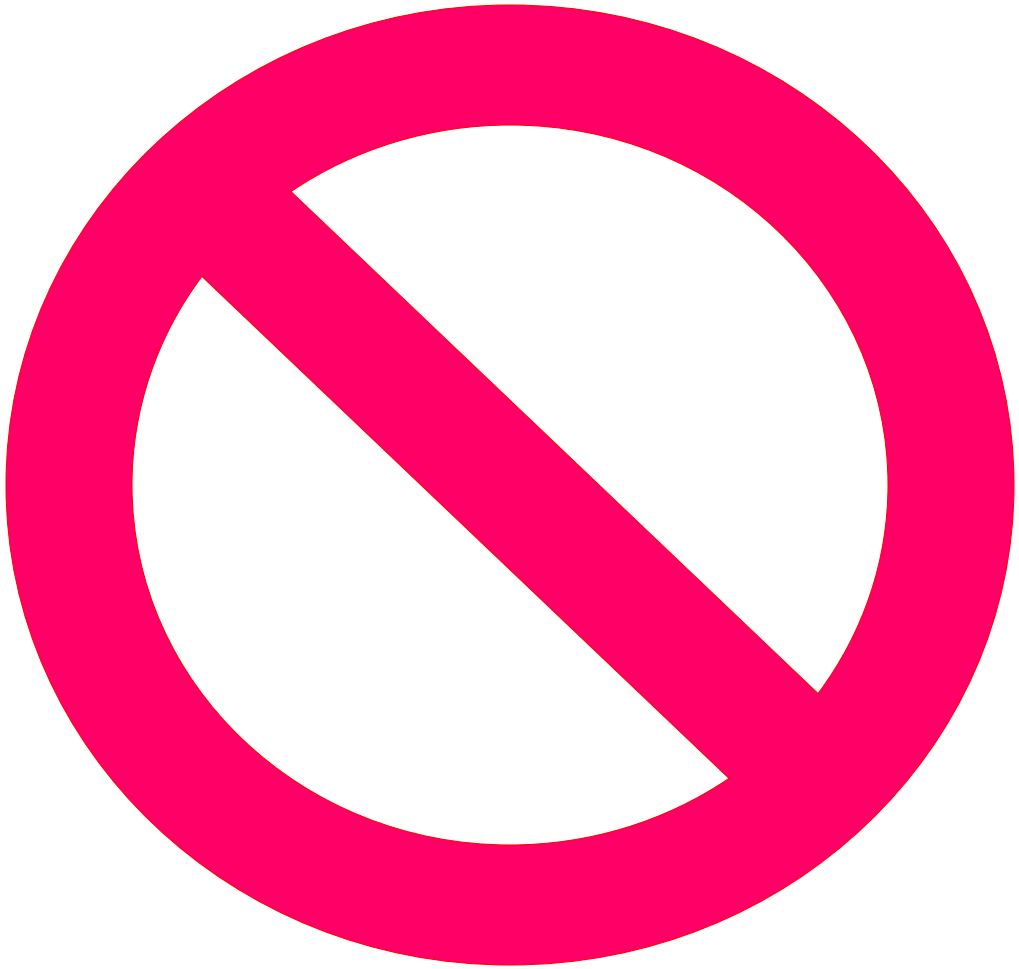
During previous SAP meetings, the Panel has expressed concern about the use of CSFII records to represent longitudinal consumption patterns for individuals. Concern arose as a result of the design of the CSFII study, in which two **nonconsecutive** days of data (separated by 3 to 10 days) were collected for each individual.

Please comment on the use of CSFII data to support each of these two modes of Calendex as they pertain to the cumulative risk assessment of pesticides in foods.

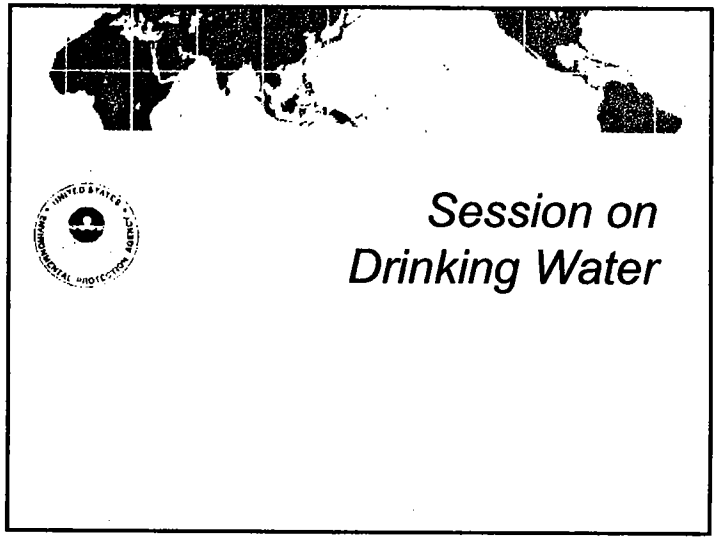
Question 2B

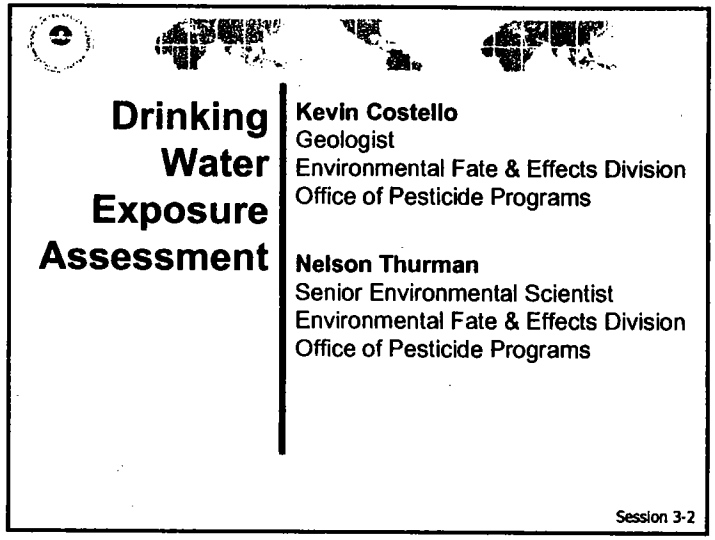
The random selection of PDP residue values assumes that the residues in foods consumed across a series of days are independent of each other. In other words, foods consumed are from unrelated sources and there is no carryover from one day to another. This assumption may be inappropriate given that many consumers obtain food in bulk (i.e., multi-day) quantities that may have similar treatment history and would typically consume this food over a short multi-day period (e.g., leftovers). In such a case the residues contained in the foods would violate the assumption of independence.

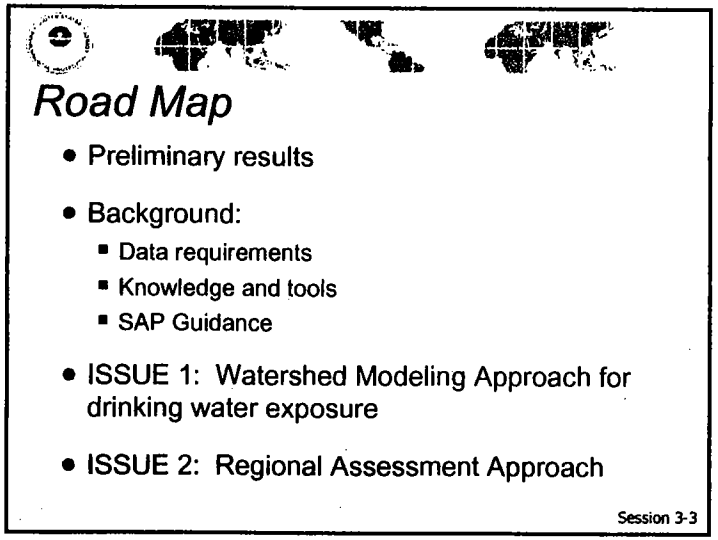
Please comment on the use of PDP data to support each of these two modes of Calendex as they pertain to the cumulative risk assessment of pesticides in foods. What issues are likely to accrue from the assumption of independence in residue data?

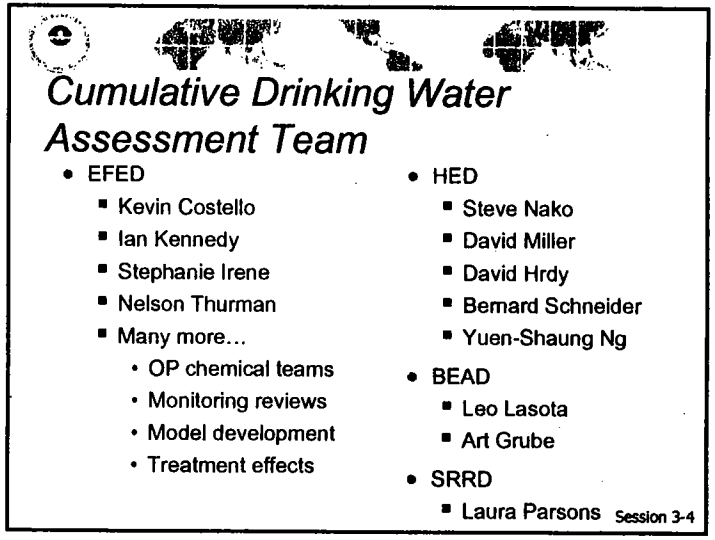


US EPA ARCHIVE DOCUMENT


Session on
Drinking Water

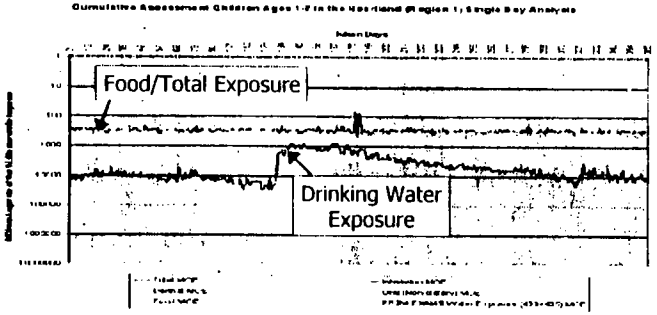

Drinking Water Exposure Assessment
Kevin Costello
Geologist
Environmental Fate & Effects Division
Office of Pesticide Programs
Nelson Thurman
Senior Environmental Scientist
Environmental Fate & Effects Division
Office of Pesticide Programs
Session 3-2


Road Map
• Preliminary results
• Background:
▪ Data requirements
▪ Knowledge and tools
▪ SAP Guidance
• ISSUE 1: Watershed Modeling Approach for drinking water exposure
• ISSUE 2: Regional Assessment Approach
Session 3-3


Cumulative Drinking Water Assessment Team
• EFED
▪ Kevin Costello
▪ Ian Kennedy
▪ Stephanie Irene
▪ Nelson Thurman
▪ Many more...
• OP chemical teams
• Monitoring reviews
• Model development
• Treatment effects
• HED
▪ Steve Nako
▪ David Miller
▪ David Hrdy
▪ Bernard Schneider
▪ Yuen-Shaung Ng
• BEAD
▪ Leo Lasota
▪ Art Grube
• SRRD
▪ Laura Parsons
Session 3-4

Preliminary Results

- Drinking water is not a major contributor to total cumulative risk



Calendar-Based Approach

- Daily concentrations are the "building blocks" for estimation of exposure for any time period
  - Daily exposures can be combined to build a longer time of exposure whether it's a week, month or longer
- DEEM™/Calendex™ uses a calendar-based approach looks at each individual day of the year
- Appropriate "temporal matching" of exposures through food, drinking water, residential pathways
  - Critical for OP's due to expected seasonal pulses and seasonal use-patterns for water, residential exposure

Session 3-6

The Water Assessment Must…

- Provide distribution of daily concentrations for probabilistic exposure assessment
- Account for variations in time (daily, seasonally, yearly)
- Account for variations in place for drinking water
- Reflect co-occurrence of multiple chemicals as they occur together in place and time

Session 3-7

Starting Point

- 24+ individual OP assessments
  - Pesticide properties
  - Individual water assessments
  - Regulatory actions taken
- Monitoring
- Water assessment approach for individual chemicals (screening and refined)
- SAP guidance on water assessments

Session 3-8

Available Monitoring

- OPs are found in drinking water sources
  - Not usually frequently or at high levels
  - Surface water sources generally more vulnerable
  - Chlorpyrifos, diazinon, malathion most frequent
- Co-occurrence is likely
  - Multiple OPs detected together
  - Related to usage in watershed

Session 3-9

Available Monitoring

- Covers a number of sites, but not all high use areas
- Sampling not frequent enough for daily fluctuations
- Limited number of years
- Not all OPs are included in monitoring
- Few or no OP degradates of toxic concern are included
- Does not reflect most recent regulatory actions

Session 3-10

Guidance From SAP

- **December 1997 SAP:** "Estimating Drinking Water Exposure as a Component of the Dietary Risk Assessment"
  - Implement existing models, including PRZM-EXAMS, for use in individual chemical screening assessments
  - Devote resources to surface water impacts, define higher assessment tiers and develop techniques for estimating concentration distributions for probabilistic risk assessments
  - Use both modeling and monitoring data in assessment

Session 3-11

Guidance from SAP

- July 1998 SAP: "Proposed Methods for Basin-Scale Estimation of Pesticide Concentrations in Flowing Water and Reservoirs for Tolerance Reassessment"
  - Move forward on Index Reservoir and account for amount of cropping in the watershed
  - Geometry and hydrology based on actual vulnerable reservoir from Midwest US (Shipman City, Illinois reservoir)
  - Evaluate existing watershed models for use in refined assessments (currently in progress)

Session 3-12

Guidance from SAP

- **May 1999 SAP:** "Proposed Methods For Determining Watershed-Derived Percent Crop Areas and Considerations for Applying Crop Area Adjustment to Surface Water Screening Models"
  - Method for calculating percent crop areas (PCA) for major crops (Corn, Soybeans, Wheat, Cotton)
  - Due to concerns about scale differences (large hydrologic units compared to size of drinking watersheds, extrapolating state- or county-level data to watersheds), did not recommend using PCA for minor crops or percent treated without further monitoring
  - Recommended regional modeling

Session 3-13

Guidance from SAP

- **March 2000 SAP:** "Development and Use of Distributions of Pesticide Concentrations in Drinking Water for FQPA Exposure Assessments"
  - Two proposed regression modeling approaches from USGS (WARP, SPARROW) showed promise
- **June 2000 SAP:** "National Drinking Water Survey Design for Assessing Chronic Exposure"
  - Shift focus to monitoring programs to support model development and evaluation

Session 3-14

Guidance from SAP

- **December 2000 SAP:** "A Case Study of the Cumulative Risk of 24 Organophosphate Pesticides"
  - Used WARP regression model in the case study
  - SAP concluded that additional monitoring data was needed to complete model (model is only as good as the data going into it)
  - WARP addressed spatial, not temporal, variability
  - WARP was not ready for use in cumulative OP assessment, is still in development

Session 3-15

Guidance from SAP

- **September 2000 SAP:** "Literature review on effect of water treatment on pesticides"
  - Cannot assume that water treatment is a viable pesticide removal process in drinking water based on the limited data on water treatment effects
  - Drinking water assessments should be conducted on raw water rather than treated water unless data was available
  - Need to consider impacts of transformation products

Session 3-16

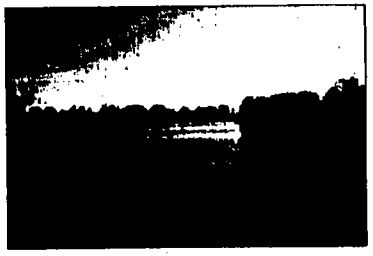
Water Treatment Effects

- Limited evidence parent OP residues are likely to be reduced by water treatment
- Limited evidence for transformation to products that are of toxic concern
- Not enough information to make quantitative adjustments

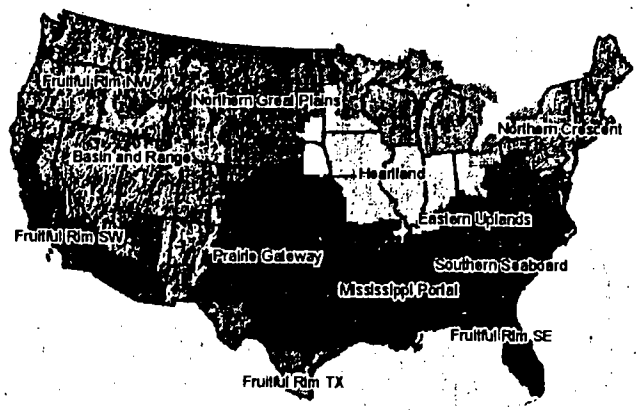
Session 3-17

Watershed Modeling Approach

- Adapted PRZM/EXAMS to estimate pesticide levels in a small drinking water reservoir
- Daily distributions over multiple years (weather variability) for 12 regional assessments
- Multiple chemicals used on crops in multiple fields in the watershed
- Typical use patterns (rates, area treated)
- Region-specific inputs



Regional Framework



Source: USDA ERS

Factors in Building the 12 Regional Cumulative Assessments

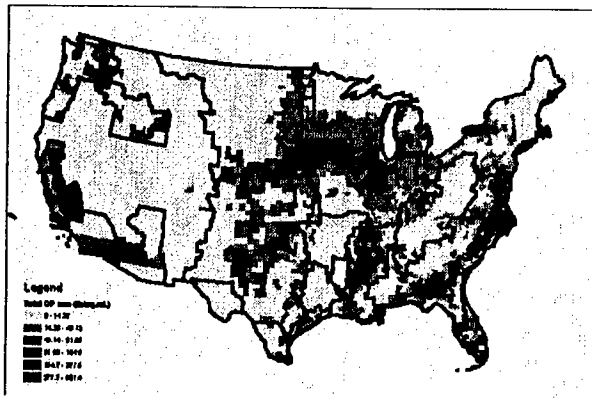
- OP usage
  - What crops?
  - What OPs and how much?
- Sources of drinking water
- Vulnerability of drinking water sources
  - Runoff for surface water
  - Leaching, depth for ground water



Session 3-20

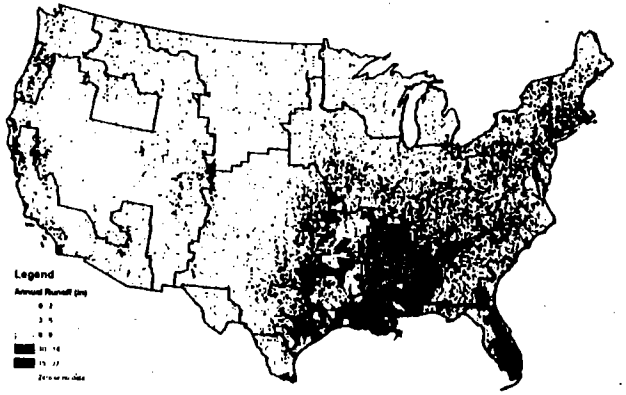
Building the Cumulative Assessment

- Identify high OP usage areas within each region



Building the Cumulative Assessment

- How vulnerable are surface water sources of drinking water in OP use areas?



Watersheds Represent Regions

- Geographic areas with high apparent potential for cumulative exposure chosen to represent each region
  - Coincide with surface water sources with high runoff potential
  - Account for impact of multiple OP pesticides
  - Not necessarily highest exposure for any single pesticide
- Expect combined OP exposure to be among the highest in each region

Session 3-23

Tailored Assessment to Selected Area(s)

- Location-specific environmental data (soil/site, weather, crops)
- Major crop-OP combinations within that area
  - Crops that actually occur together
  - OPs that are actually used on those crops
  - Account for approximately 95% of OP use in area

Session 3-24

Key Components in the Cumulative Water Assessment

- Regional framework
- Watershed-based modeling
  - Multiple fields with multiple chemical uses
  - Adjustments for area treated
- Probabilistic for weather over multiple years
- "Typical" usage patterns
  - application rates and timing

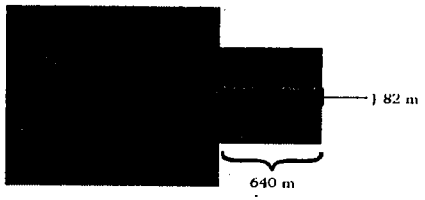
Session 3-25

Paired Model System

- PRZM: Pesticide Root Zone Model
  - Field scale simulation of chemical movement
  - Hydrology: Runoff, erosion, infiltration, evapotranspiration
  - Chemical transport: runoff, erosion, adsorption, transformation, volatilization, infiltration, plant uptake, foliar washoff & decay
- EXAMS: Exposure Analysis Modeling System
  - Chemical Fate in the Water Body: ionic and sorptive equilibria, advective and dispersive transport, chemical transformation, volatilization

Session 3-26

Scenarios: Fixed Inputs



- Geometry & hydrology of reservoir and watershed
  - 178 ha watershed, 5.3 ha reservoir, 2.7 m deep

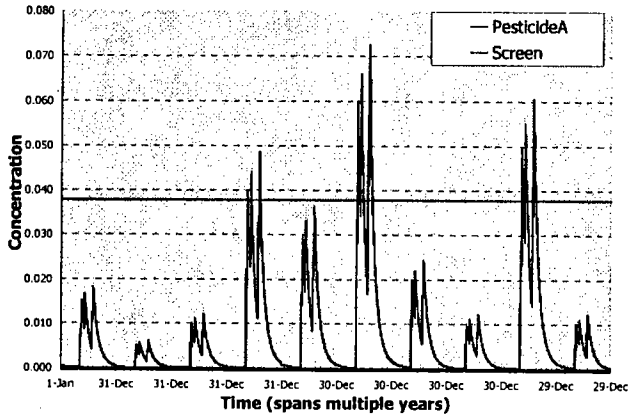
Session 3-27

Scenarios: Variable Inputs

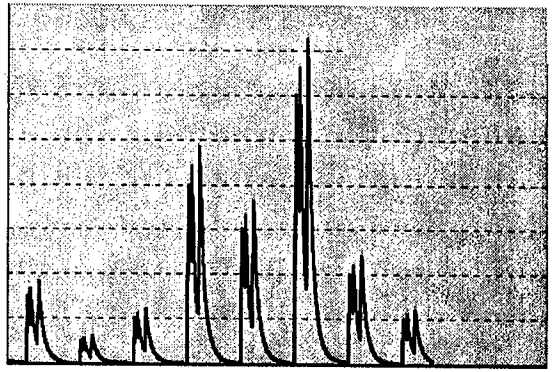
- Weather from nearest available station
- Site: soil, runoff, slope
- Management practices
  - Planting harvest represent local practice and conditions
  - Use the reasonably prevalent management practices
  - Pesticide use and timing

Session 3-28

Daily Distributions/ Multiple Years, Single Chemical



Co-Occurrence: Timing of Use



Watershed Assessment: Multiple Fields

- PRZM is a field-scale model
  - In individual screens, PRZM simulated a watershed
- For cumulative, PRZM simulated multiple fields in the watershed
  - No spatial distinction w/in the watershed
  - All runoff flows into the reservoir

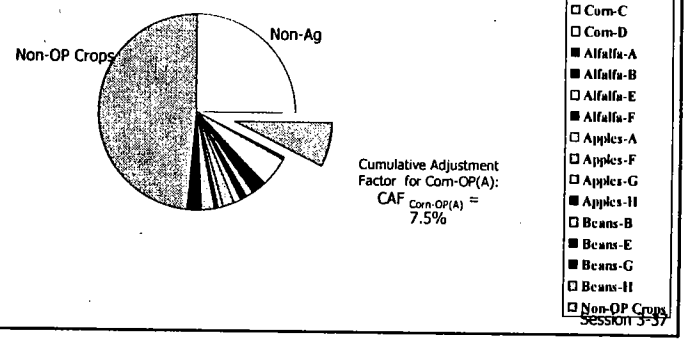
Session 3-31

Watershed Assessment

- To estimate cumulative OP impacts, the assessment considered...
  - Not all land in the watershed is planted to OP crops
  - Not all OP crops are treated with OP's
  - Those OP crops which are treated with OP's are treated at specific rates, at specific times, and with specific frequencies

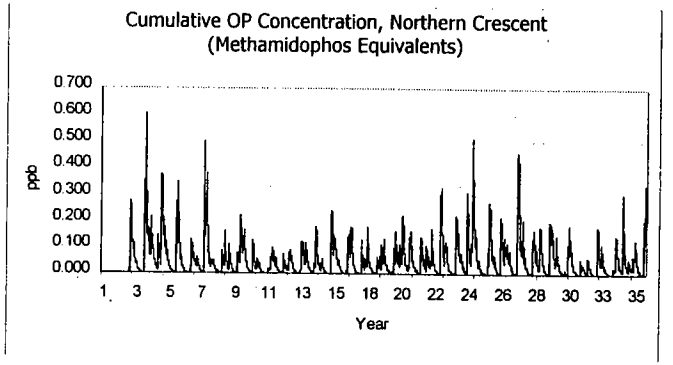
Session 3-32

Illustration of CAF Adjustments



Session 3-37

Cumulative Distribution Over Time



Session 3-38

CAF Issues: PCA

- SAP concern regarding different scales for data sources
  - County, state level use information
  - Large HUCs in relation to drinking watersheds
  - Problems with crops covering small area
- Calculated Cumulative OP PCA
  - Started with total agricultural PCA (same as in SAP), adjusted for total OP uses

Session 3-39

CAF Issues: Acre Treatments

- Adjusting for amount of crop treated with any single OP
- Acres treated factor based on survey data compiled at the state level
  - Data available at state-level: Assumes uniformity across all watersheds in the state
  - Assumes uniformity in time (no yearly variability)

Session 3-40

CAF Issues: Illustration in Red River Valley

- Counties on either side of the Red River
  - ND: Walsh, Grand Forks, Pembina
  - MN: Polk, Norman, Clay
- Terbufos use on sugar beets
  - ND: 1.97 lb/a; 69% acres treated
  - MN: 1.75 lb/a; 51% acres treated
- Azinphos Methyl use on potatoes
  - ND: 0.48 lb/a; 19% acres treated
  - MN: 0.39 lb/a; 10% acres treated

Session 3-41

Reflecting "Typical" Use

- Based on survey data, not forecasting
- OP use in most recent year
  - Application rate (average, not maximum)
  - Number of applications (average)
  - Method of application (aerial/ground)
- Primary Source: National Agriculture Statistic Service (NASS) Usage Reports

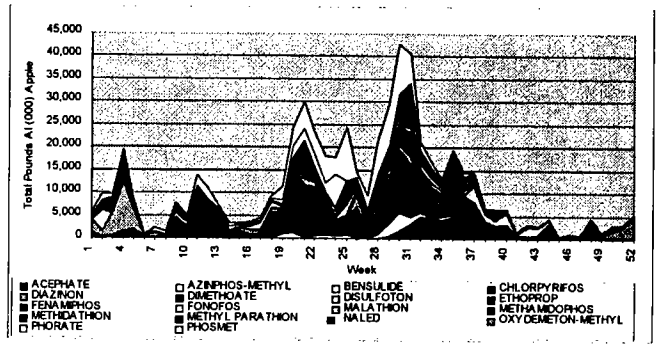
Session 3-42

Temporal Variability in Pesticide Use

- Pesticides may be applied throughout the year
- Various factors contribute to this temporal variability, including:
  - Applications to different crops/planting dates
  - Timing in pest infestations
  - Different pests treated

Session 3-43

Co-occurrence Based on Use (CA)



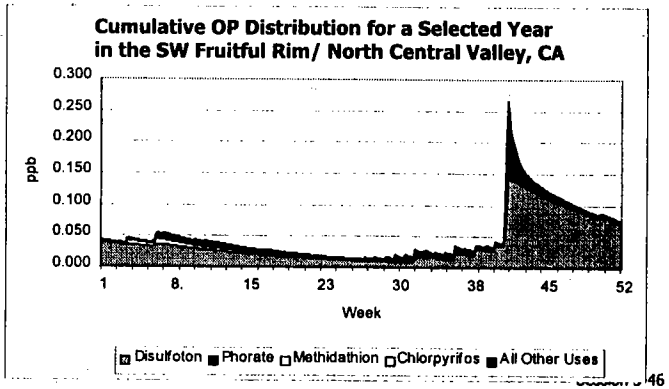
Session 3-44

Accounting for Temporal Variability

- CA: CDPR Pesticide Use Reports
  - 5 dates each representing 20% of applied
- Other regions: USDA chemical usage, planting/harvest reports, crop profiles to identify use window
  - Single application with no distribution information: applied at the beginning of use window
  - Single application with distribution information: applied at midpoint of active window
  - Multiple applications: distributed evenly across window

Session 3-45

Preliminary Cumulative Distributions



46

Comparison to Monitoring Data

- Most estimated concentrations and monitoring were comparable
- A few known detections of one or more OP occurred at higher levels than estimated
  - Some attributed to uses being canceled
  - Some detects not necessarily in area of highest cumulative impacts
- A few pesticides with known detections significantly less than estimated

Session 3-47

Questions for the SAP on Drinking Water

Session 3-48

FIFRA SAP Meeting on the Preliminary Cumulative Risk Assessment: February 5 to 8, 2002

Question 1

After evaluation of available monitoring data and consideration of the available tools for estimating pesticide exposure in drinking water, the agency adapted available tools to provide watershed-level estimates of residues in drinking water sources. These tools have been presented to the SAP in the past in relation to individual chemical assessments and have been improved as a result of panel feedback. Because of differences between individual and cumulative assessments, this assessment reflects novel uses for some of these tools. The approach used in the Preliminary OP Cumulative Risk Assessment:

Session 3-49

Question 1 (continued)

- Used PRZM/EXAMS with the Index Reservoir, along with local site characteristics to estimate concentrations in the drinking water reservoir
- Simulated multiple OP uses on multiple fields within that watershed
- Adjusted for area within the watershed that potentially contribu ted OP loads to the reservoir using a cumulative adjustment factor
- Provided a qualitative, rather than quantitative, assessment of treatment effects on residues

Are there significant flaws in this approach and its assumptions that would be likely to lead to consistent significant underestimation of daily levels of residues in surface water across the calendar year (for instance, an order of magnitude)? If such flaws exist, what can be done to correct them? What additional information and/or tools might be available that will meet the goals/needs of the cumulative OP assessment?

Question 2

It is not feasible to conduct drinking water assessments for every watershed in which OP pesticides are used. Therefore, regional w ater exposure assessments were used to represent exposures from typic al OP usage conditions at one of the more vulnerable surface watersheds in the region. Each regional assessment focuses on areas where combined OP exposure is likely to be among the highest within the region as a result of total OP usage and vulnerability of the drinking water sources. In this manner, OPP is confident that if the reg ional cumulative risk assessment finds that exposure in water is not a significant contributor to the overall OP exposure in that area, it will not be a significant contributor in other areas in the region.

Does the SAP see anything that would call this assumption into question? If the regional approach, with its assumptions is inadequate, what can be done to improve the approach?

Session 3-51



Session 3-52

Residential/ Non- occupational Exposure Assessment

Jeff Evans
Biologist
Health Effects Division
Office of Pesticide Programs



Purpose

- To present our use of a calendar based model (Calendex™), to address the temporal aspects of OP pesticide use
  - Approach is similar to the OP case study presented to SAP (12/7-8/00)
- To discuss the data used in our cumulative residential exposure assessment
- To discuss with the Panel:
  - Use of distributions of the available data
  - Additional ways to incorporate survey data and other pesticide use in future assessments

Residential OP Assessment: Uses

- Indoor use: DDVP (crack and crevice, pest strips)
- Pet use: DDVP and Tetrachlorvinphos (spray/dip, collars) – currently only qualitatively assessed
- Home Lawns: Bensulide, Malathion, Trichlorfon
- Golf Course: Acephate, Bensulide, Fenamiphos, Malathion, Trichlorfon
- Home Garden: Acephate and Disulfoton (ornamental) , Malathion (ornamental and edible food)
- Public Health: Fenthion, Malathion, Naled

Expression of Residential Risk

$$MOE = \frac{POD\ (mg/kg/day)}{Exposure\ (mg/kg/day)}$$

- Routes considered, as appropriate
  - **Oral, Dermal, Inhalation**

Age Groups

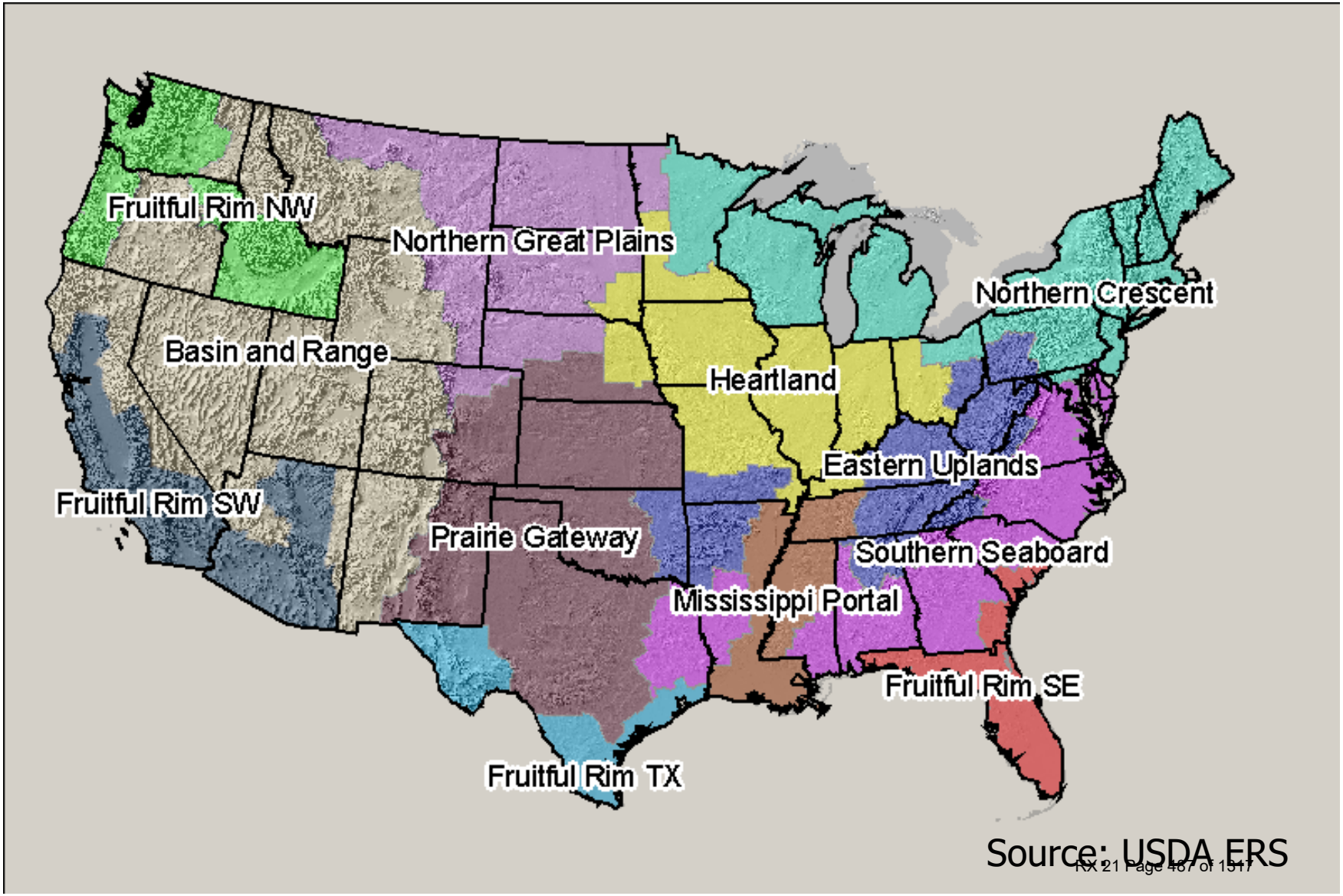
- Assessment performed for the following age groups:
  - Children 1-2 years old
  - Children 3-5 years old
  - Adults 20+



Scope

- Assessments conducted for 12 distinct geographical regions, reflecting climate & pest pressure differences
  - One region split into two residential assessments
- Includes remaining residential OPs that have significant exposure and appropriate exposure data
- Pet products not quantified
  - Only screening level SOPs available at this time

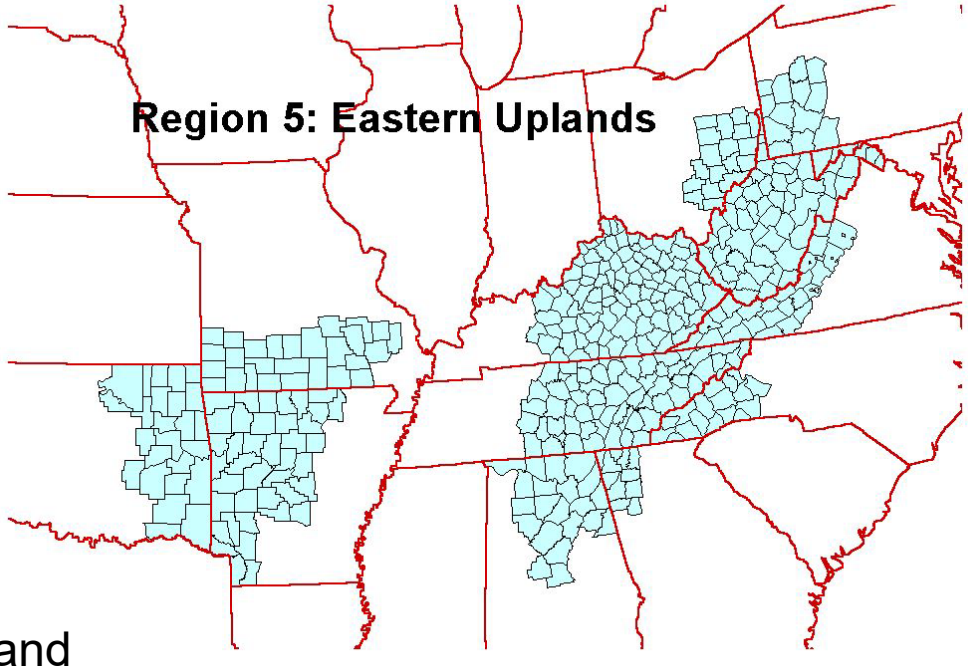
Regional Framework



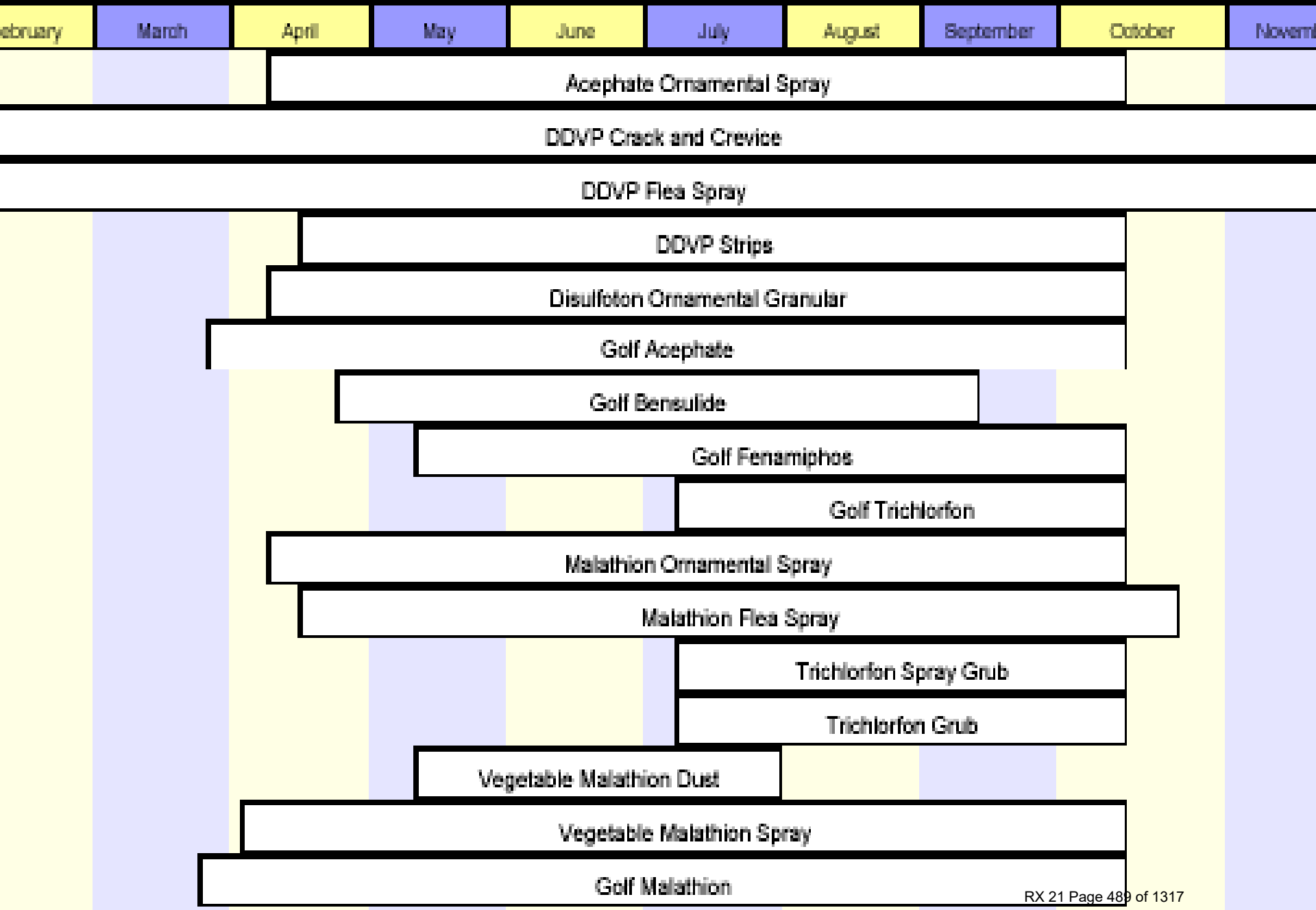
Source: USDA ERS

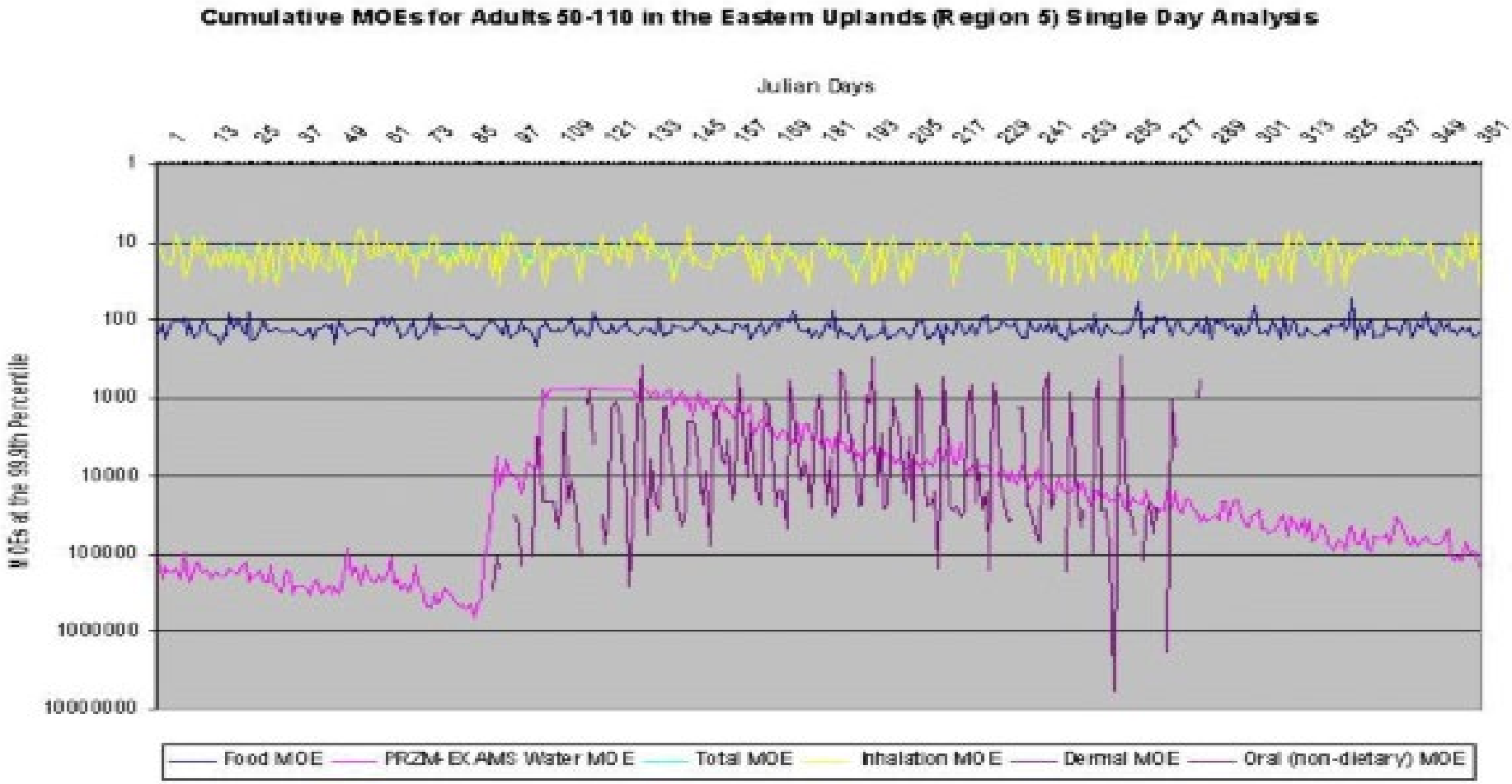
Region 5 – Eastern Uplands

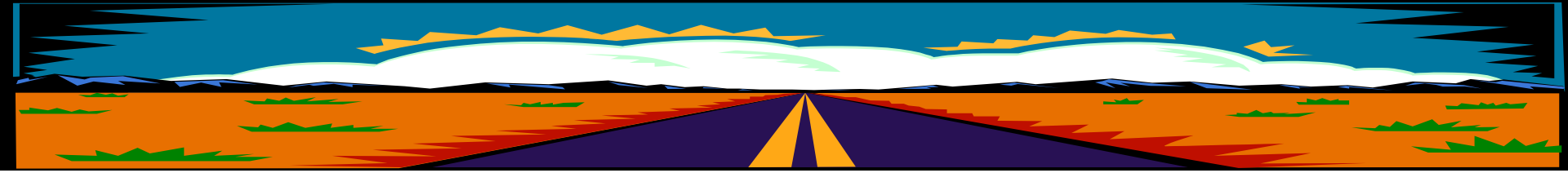
- Lawn: DDVP, Malathion, Trichlorfon
- Golf Course: Acephate, Bensulide, Fenamiphos, Malathion, Trichlorfon
- Ornamental Gardens: Acephate, Disulfoton, Malathion
- Home Garden: Malathion
- Indoor: DDVP (pest strips and crack and crevice treatments)



Residential Scenario Application and Usage Schedules for Eastern Uplands Region (Reg




Cumulative MOEs for Adults 50-110 in the Eastern Uplands (Region 5) Single Day Analysis
Julian Days
1
10
100
1000
10000
100000
1000000
10000000
100000000
MOEs at the 99.9th Percentile
Food MOE
PRZM-EXAMS Water MOE
Total MOE
Inhalation MOE
Dermal MOE
Oral (non-dietary) MOE



Road Map

- Key Data Used (distributions selected)
  - Lawn
  - Golf Courses
  - Public Health
  - Home Garden
- Characterization
- Future Consideration of Survey Data

Lawns – Use Information

- National Home & Garden Pesticide Use Survey (NHGPUS 1991)
  - percent of households using a given pesticide – regional distinctions
- Treated lawns based on regions using the *National Garden Survey* 1996-1997
  - Percent of population hiring lawn care services
- Lawn Size (Vinlove and Torla 1995 and ORETF Survey)

Lawn Size

- Uniform Distribution 500 – 15,000 ft^2
- Difficult to quantify
  - Only considers lot size minus footprint
  - Does not consider other structures/green space

Lawns: Use Information

- **Label**
  - site/pest relationships
  - application rates
- **State Cooperative Extension services**
  - Timing of applications to control common pests
- **Comparative Insecticide Effectiveness for Major Pest Insects of Turf in the United States**

Lawn: Applicator Exposure Data

- **Data source: ORETF**
- **Application Type:**
  - Granular push-type rotary spreaders
  - Hose-end sprayer – ready to use and one requiring the user to add the concentrate
- **Clothing types:**
  - Range of clothing
  - Short-sleeved shirt, short pants and long-sleeved shirt, long pants

Lawn: Applicator Exposure

- Unit Exposure (UE)
  - mg of exposure/amount of active ingredient (a.i.) used
  - UE x ai/sq ft x area treated
    - **Divided by body weight**

Lawn: Applicator Exposure Data

- Hose-end Sprayer
  - Uniform Distribution: 0.017 – 49 mg/lb ai
- Granular Applicator
  - Uniform Distribution: 0.02 – 7.6 mg/lb ai

Lawn: Applicator Exposure Data

- Well understood activity pattern
  - Easy to measure and develop distributions
- However, selected a uniform distribution that:
  - Reflects range of clothing that can be worn
  - Survey data suggest that clothing worn while applying pesticides changes as growing season progresses
    - seasonal changes are only based on formulation type not equipment used
    - Hose-end includes both “mix you own” and “ready to use”

Lawn: Post- Application Exposure Data

- Difficult activity pattern to determine what is representative
- Residue transfer to skin (transfer coefficient)
  - Choreographed Activities of Adults Measured Using Biological Monitoring, (*Vacarro 1996)*
    - Crawling, football, Frisbee
  - Non-Scripted Activities of Children Measured Using Fluorescent Tracers, (*Black 1993)*
    - Mostly solitary play with toys and books. Also activities such as cartwheels

Lawn: Post- Application Exposure Data

- Duration: up to 2 and 3.5 hrs for adults and children respectively (Cumulative, EFH)
- Adult TC: 1,930 – 13,200 cm^2/hr
  - Uniform distribution (n – 16 Vacarro)
- Child TC: 700 – 16,000 cm^2/hr
  - Uniform distribution Vacarro (n – 16) and Black (n – 14)

Lawn: Post- Application Exposure Data

- Turf Transferable Residues (TTR)
  - Chemical specific dissipation data (mg/cm^2)
    - Uniform distribution selected for each day's residues
      - Each day includes a range of values instead of mean
        - First day values include "as soon as dry" up to 8 hours after application
        - Watering in and not watering in
        - Other days include potential for rainfall

Lawn: Post- Application Exposure Data

- Non-Dietary Ingestion (Hand-to-Mouth)
- Most challenging activity pattern to assess
  - Hand-to-mouth frequency of events, (*Reed 1999)*
  - Adjust lawn residue data (TTR) to account for saliva wetted hands, (*Clothier 2000)*
  - Saliva extraction e.g., (*Camann 1995)*

Lawn: Post- Application Exposure Data

- Hand-to-mouth frequency of events (*Reed 1999)*
  - Children in day-care (n-20) at home (n-10)
  - Uniform distribution: 0.4 to 26 events/hr
  - Mean 9.5, median 8.5, 90th percentile 20
    - Issue: indoors vs. outdoors, active vs. quiet play
    - Freeman et al., 2001: outdoors (~2-3x less than indoors)
      - Small subset (4 out of 19)

Lawn: Post- Application Exposure Data

- Lawn residue data to account for saliva wetted hands (*Clothier 2000)*
  - Compared wet hand efficiency vs. dry hand efficiency (cyfluthrin, chlorthalonil and chlorpyrifos)
  - Dry hand transfer efficiency is similar to TTR measurements (0.9 to 3%) for 2 chemicals
    - Chlorpyrifos much lower overall (0.05 - 0.15%)
  - Wet palms: uniform distribution 1.4-3x higher than TTRs

Lawn: Post- Application Exposure Data

- Saliva extraction (uniform: 10 to 50%)
  - 50% removal by saliva wetted sponges – vigorous (Camann et al., 1995)
  - 20 – 40% hands rinsed with water/Ethanol and water/Isopropanol (Fenske and Lu, 1994)
  - ~10 – 22% soil removal from hands to account for possible residue/soil matrix (Kissel et al., 1998)

Golf Courses: Post- Application Exposure Data

- Percent of individuals participating in golf, 1992 Golf Course Operations by the Center for Golf Course Management
- Number of hours playing golf
- Percent of Golf Courses Applying Selected Pesticides (Doane GolfTrak, 1998-1999)
- An activity pattern that is easy to understand and measure

Golf Courses: Post- Application Exposure Data

- Residue transfer to skin (transfer coefficient)
  - Uniform distribution: 200 to 760 cm^2/hr
  - Small data set (less than 10) includes walking and using a cart.
- Chemical-specific turf residue data

Public Health: Post- Application

Range of residues that deposit onto lawns is based on a percent of public health use application rate (3.8 to ~30%) using values presented in Tietze et al., 1994 and the Spray drift model, AgDrift

- Once an estimate of deposition is made the post application is assessed in the same way that lawn chemicals are
- Estimates of % population based on percent of homes having lawns
- Timing and pesticide used based on personal communication and publications prepared by organizations such as the Florida Coordinating Council of Mosquito Control

Garden : Applicator Exposure Data

- An activity pattern that is easy to understand and measure
  - Shaker Can (n-20): uniform, 0.0034-0.356 mg/lb ai
  - Garden Duster (n-20) uniform, 7.99-1375.4 mg/lb ai
  - Small Tank Sprayer (n-20), uniform, 7.99-354.4 mg/lb ai
- Similar issues regarding clothing as in lawn applications

Garden: Applicator Exposure Data

- Area Treated
- Ornamental Gardens: uniform, 500 to 2,000 ft^2
  - No data. Defined in the assessment as the area consisting of the perimeter around a median home area 2,250 sq ft^2., with a 2.5 to 8 ft border
- Vegetable gardens: log-normal, 135 to 8,000 ft^2
  - May be easier for people to estimate than lawns

Garden: Post- Application Exposure

- Post-application dermal exposure
  - An easily defined activity in agriculture
  - Home gardens are more difficult due to wide variety of crops grown (fruits and vegetables) and a wide variety of activities
    - Uniform distribution of 100 to 5,000 cm^2/hr
  - Duration of garden activities: uniform, 5 to 60 min.
  - Chemical/regional specific residue data

Indoor: Inhalation Exposure Data

- Applicator – uniform range of inhalation exposure values for pressurized aerosol can (PHED)
  - 0.72 – 2.499 mg/lb ai
- Post application inhalation exposure (adults and children)
  - Pest Strips: 0.005 – 0.11 mg/m^3

    (Collins et al., 1973)
  - Crack and Crevice – 0.075 – 0.548 mg/m^3

    (Gold et al., 1983)
- Duration of time spent indoors, and breathing rates
  - Up to 24 hours, at rest to moderate

Methods Summary

- All available data considered
  - e.g.,Lawn residue data available for all compounds and made regional adjustments where feasible
- Addressed a variety of activity patterns
  - Some more straight forward : Application
  - Some more difficult : Hand-to-Mouth
- Tended to use uniform distributions when presented with scenarios that had confounding variables

Characterization

+ over estimate; - under estimate; ~ neutral

Input Parameter	Bias	Assumptions and Uncertainty
Lawn Applicator: hose-end	~	60 replicates, high confidence – issues re: clothing and percent of users for "mix your own" and 'ready-to-use"
Lawn Applicator: rotary	~	30 reps, high confidence, clothing issues
Lawn Size	~	Reasonable considering equipment used, may be a slight underestimate in areas that have larger lawns (Midwest)
Dermal Contact Transfer	- to +	Adults: activities appear to be representative, but distributions may be reflective of study design rather than actual activities Children: Includes above scripted activities and a range of non scripted activities. Study is based on a non-toxic substance (not a pesticide), high transfer efficiency (6%)

Characterization

+ over estimate; - under estimate; ~ neutral

Input Parameter	Bias	Assumptions and Uncertainty
Turf Residues: dermal	~	Reflects a range of high values (e.g., immediately after sprays dry to values influenced by rainfall)
Turf Residues: hand-to-mouth	~ to +	Based on surrogate data
Frequency	~ to +	Based on video-observations of children, indoor scenarios
Duration on Lawn	~	For children the value is time spent outdoors in addition to time on lawns – Does not account for survey responses of individuals that did not play on lawns or go outside
Public Health: Drift	~	Distribution of aerial and ground equipment values
Population Exposed	~ to +	Assumed large % of population based on those having lawns. Minimal exposure

Characterization

+ over estimate; - under estimate; ~ neutral

Input Parameter	Bias	Assumptions and Uncertainty
Home Garden Applicator: spray	~	20 reps, high confidence, clothing issues
Home Garden Applicator: dust	~	20 reps, high confidence, clothing issues
Home Garden Applicator: granular	~	chemical specific, high confidence, clothing issues
Garden Area Treated: ornamentals	~ to +	assumes all plants are treated
Vegetable	~	well studied variable for individual crops, but not for multiple crops and activities. Recognize it's a highly variable exposure scenario

Characterization

+ over estimate; - under estimate; ~ neutral

Input Parameter	Bias	Assumptions and Uncertainty
Frequency of Applications	~ to +	based on generic insecticides, not chemical specific
Post Application garden	~ to +	assumes all plants are treated
Residues	~	regional and chemical specific
Indoor Air	~	chemical specific data
Duration	~	rest to light activity - established values duration 0 - 24 hours
Population Exposed	~ to +	values based on use of all pest strips, not just those containing DDVP
Use patterns for all scenarios	~	based on percent of households using that particular pesticide.

Survey Data

- Overview of our use of survey data to address use and co-occurrence
- Future considerations:
  - Use of existing macro activity pattern data
    - SHEDS example
  - Upcoming pesticide use survey

Survey Data: Macro Activity Patterns

- Human Activity Patterns
  - Calendar based models present an opportunity to consider an individual's macro activity patterns that can lead to exposure to one or more chemicals
  - Macro Activity Patterns are broadly defined as where individuals spend their time
    - In the garden
    - Driving to work

Survey Data: Macro Activity Patterns

- Our Basic Approach (Independence/Dependence)
  - Identify households based on reported use of an OP for a given scenario (e.g., NHGPUS)
    - 6% of households in Region 5 use lawn chemical A
  - Identify the time individuals spend on lawns or other locations
    - In the Exposure Factors Handbook, there are recommended values taken from surveys such as the National Human Activity Pattern Survey (NHAPS)

Survey Data: Macro Activity Patterns

- **STEP 1**: Calculate Exposure from Food for Individual #1 on a given day (Food Exposure(from DEEM™))
- **STEP 2**: Select Residential Treatments for Individual #1 on a given day
  - Specific to region, time and demographics of individual
    - Were pesticides applied in/around home?
    - If so, which treatments?
      - And how much, how often, during what time frame, with what frequency, and by whom?
- **Repeat Step 2 until all relevant residential uses are addressed**

Survey Data: Macro Activity Patterns

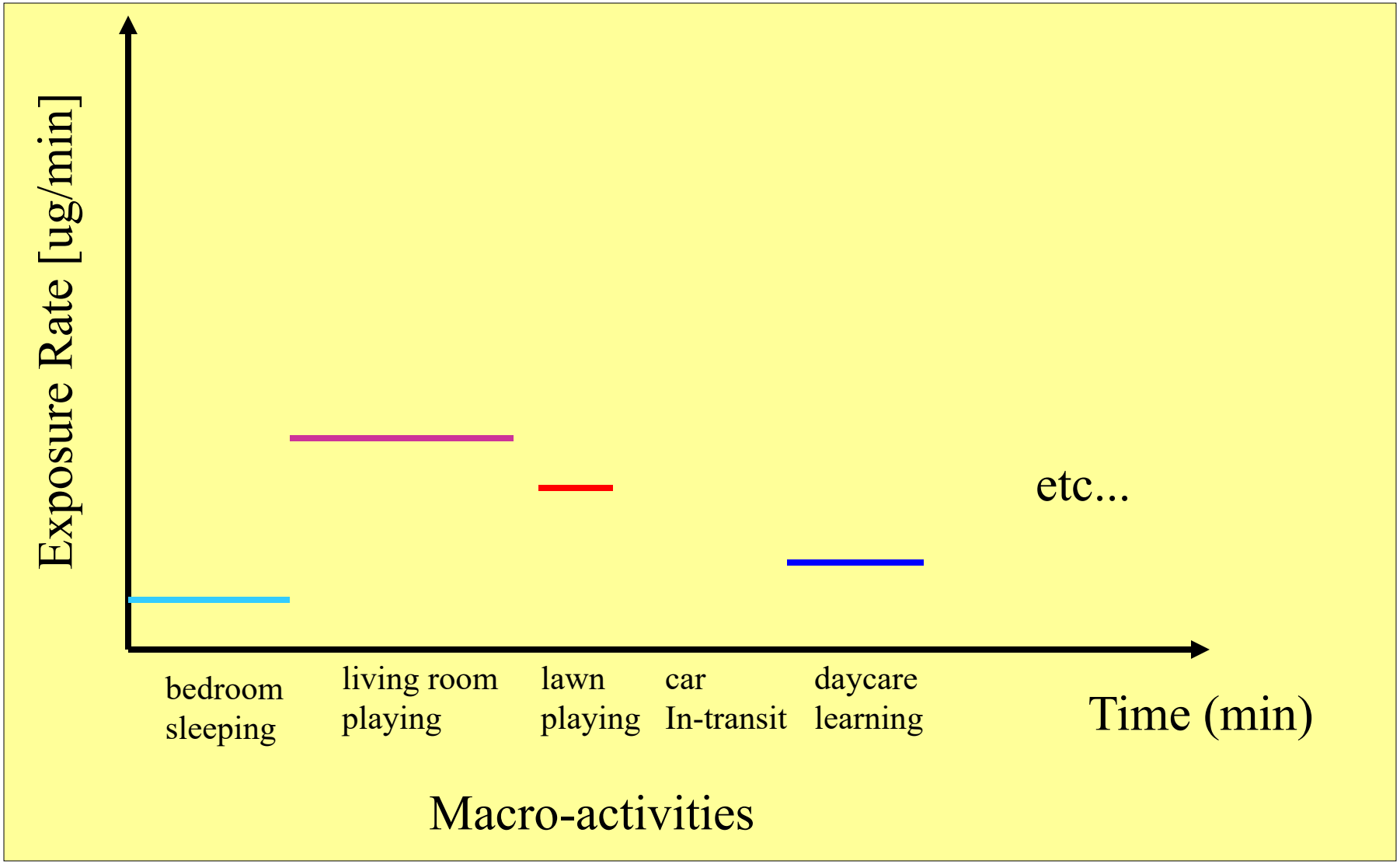
- Co-occurrence is driven by random probabilities (% households being treated)
  - (6% lawn use) x (10% crack and crevice) = 0.6%
- However, once a household is selected, the probability of being on the lawn is 1 because:
  - We used a distribution of time spent on the lawn based only on individuals who were actually on lawns
  - Does not account for individual responses indicating they did not spend time on lawns

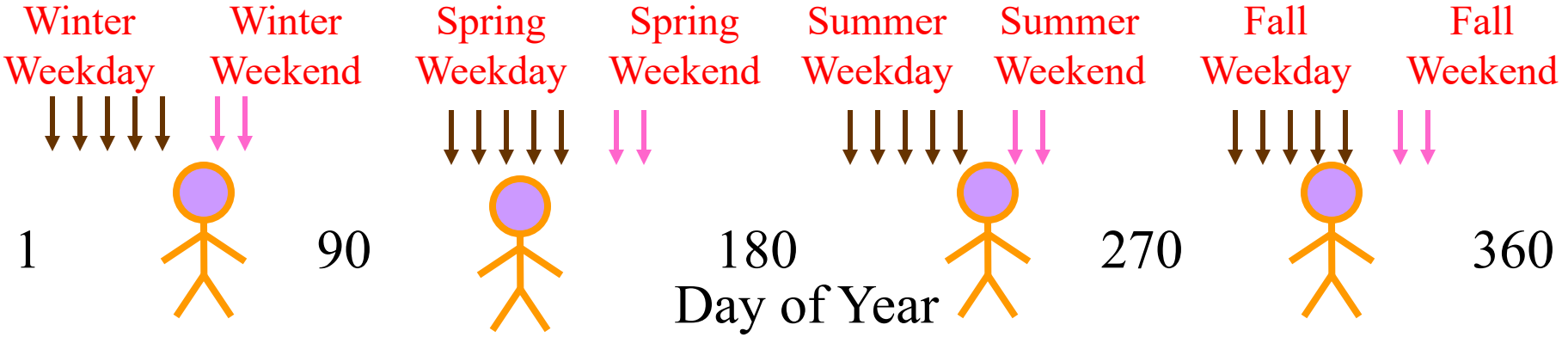
Survey Data: Macro Activity Patterns

- Consolidated Human Activity Database (CHAD) hhtp://www.epa.gov/chadnet1
  - Compilation of pre-existing human activity surveys collected at the national, state and city level
    - Review questionnaires and individual responses
    - Develop daily activity patterns for an individual based on responses to the questionnaires
    - Most surveys are cross-sectional rather than longitudinal

Survey Data: Macro Activity Patterns

- Stochastic Human Exposure and Dose Simulation model - SHEDS
  - Developed by:
    - Valerie Zartarian
    - Jianping Xue
    - Haluk Ozkaynak


Exposure Rate [ug/min]
etc...
bedroom
sleeping
living room
playing
lawn
playing
car
In-transit
daycare
learning
Time (min)
Macro-activities



- **8 CHAD diaries simulate a person's year in specified age-gender cohort**
  - **1 person from each of 4 seasons**
  - **1 person from each of 2 day categories (weekend and weekday)**
- **Fix 5 weekday diaries and 2 weekend diaries**
- **Repeat 7 day activity patterns within each season**

Survey Data: Macro Activity Patterns

- Residential Exposure Joint Venture (REJV)
  - Longitudinal survey data addressing the application pesticides in and around households
    - When and where applications are made
    - Multiple applications made in one day
    - What they wore while making those applications
    - Demographic information (children)

Questions for the SAP on Residential Exposure

Question 1

Historically, the Agency has relied on means (primarily arithmetic or geometric) from residue and exposure studies for key input variables in exposure assessments. The recent development of calendar based models and others having features to incorporate distributions of exposure values has presented the Agency an opportunity to consider using all available data points from existing exposure and residue studies. In the Cumulative Risk Assessment Case study presented to the FIFRA Scientific Advisory Panel in September, 2000, most of the exposure variables were presented as uniform distributions. The exceptions were for variables that are reasonably well established , such as exposure durations taken from the Agency's Exposure Factors Handbook. The data used in the Case Study and in the preliminary CRA, are believed to be from well conducted studies of generally high quality. However, these data sets tend to be small (e.g., n = 10 - 30) and are being used to address wide variety of exposure situations. The uniform distribution appears to be most appropriate for these relatively small data sets because it relies on easily established values such as the minimum and maximum and provides the most conservative estimate of the standard deviation (riskanalal@lyris.pnl.gov).

Question 1 (continued)

Does the Panel have any additional comments or thoughts on OPP's use of the uniform distribution in general or on OPP's selection of the uniform distribution for the specific parameters chosen? What criteria, if any, would the SAP recommend for developing parametric input distributions from available data? Under what circumstances, if any, would it be appropriate to use available data empirically? Does the Panel have any recommendations on how sensitivity analyses could be performed to determine if the assumption of a uniform distribution is responsible for a majority of the risk at the tails of the exposure distribution.

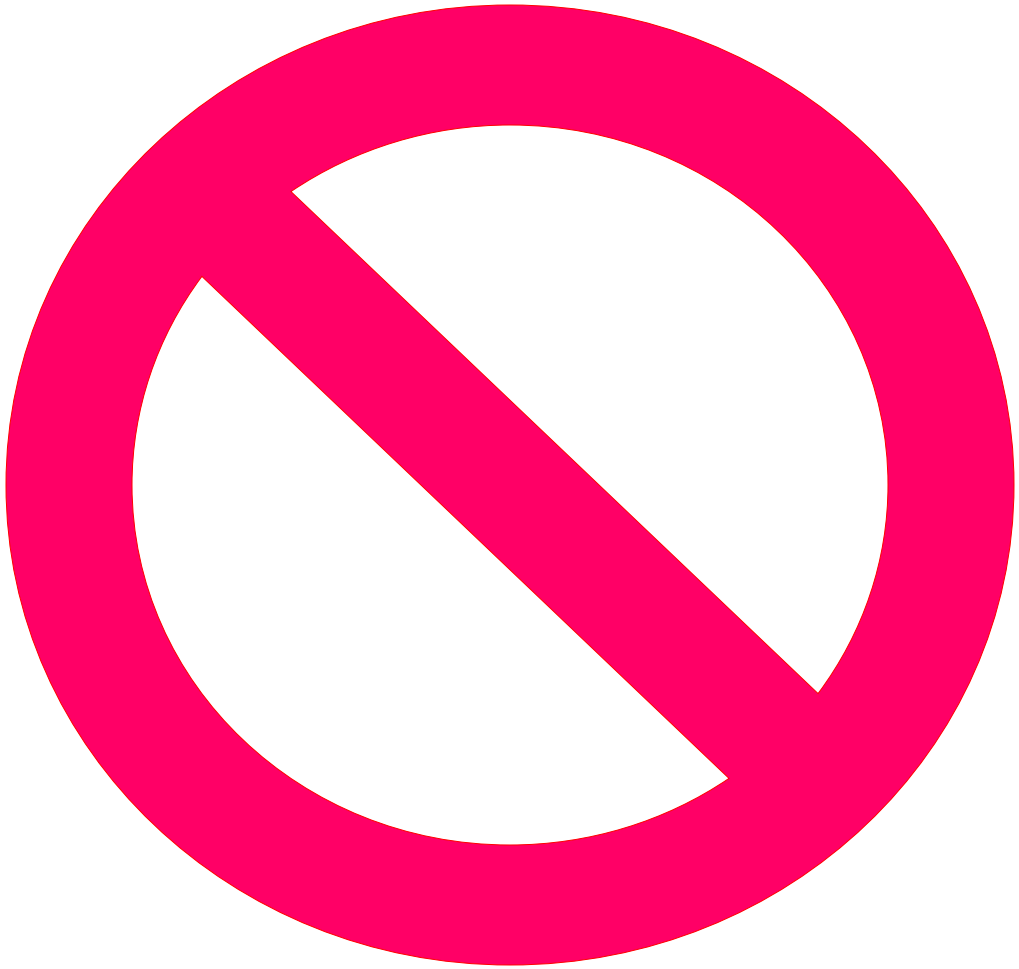
Question 2

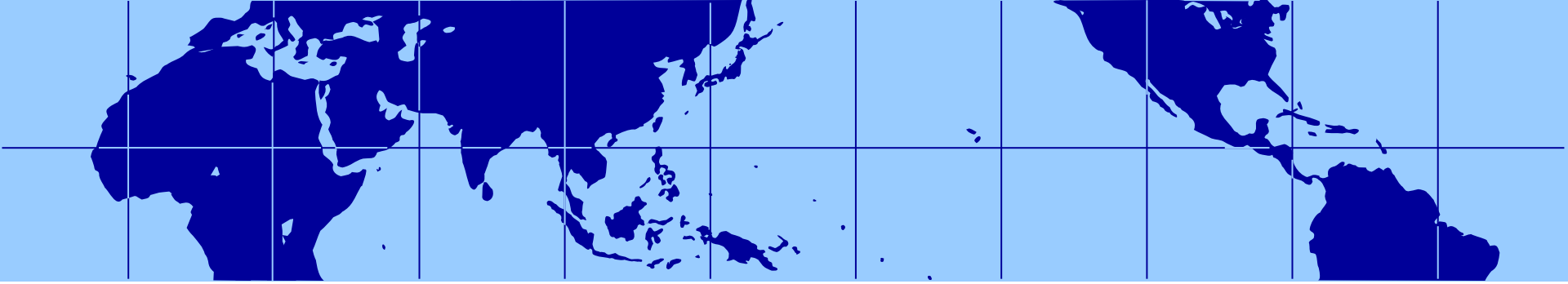
The use of calendar based models also allows exposure assessors to consider exposure from a variety of sources from the same or from different chemicals. Longitudinal survey data such as the National Human Activity Pattern Survey (NHAPS) are available for consideration by HED for use in future assessments. In addition, from a practical standpoint, the use of such survey data ensures combinations of exposure do not come from unrealistic random combinations that current models may produce (e.g., activities adding up more than 24 hours in a day).

Question 2 (continued)

The use of calendar based models provides an opportunity to explore the potential for the co-occurrence of multiple sources of exposures from residential pathways. In the cumulative assessment, OPP used summary statistics from sources such as the Exposure Factors Handbook (EFH) regarding the time spent indoors, time spent on lawns and time spent at other outdoor locations. In the preliminary assessment, we assumed these activities were stochastically independent. OPP is currently evaluating data in the EFH such as data from the National Human Activity Pattern Survey (NHAPS) to determine if it can directly incorporate (i.e., empirically) information on an individual's activity patterns over a full day from this database to account for the likelihood and duration that an individual might be exposed to a pesticide through various activities over the course of a day.

Please comment on whether and how OPP might directly incorporate NHAPS (or similar time use data) into the software to better account for variation in activities across individuals?





SESSION on Risk Characterization

Risk Characterization

David Miller
Chemist (USPHS)
Health Effects Division
Office of Pesticide Programs

Outline

- Summary of Preliminary Results/Findings
- Key Principles for Conducting a CRA
  - Hazard/Exposure Aspects
- Preliminary Cumulative Risk Assessment
- Time Frame Considerations
- Example Exposure Scenarios
- Questions to SAP

Summary of Preliminary Results/ Findings

- In general, consistent exposure/risk patterns across regions
  - Major contributor to risk is indoor residential uses of DDVP
  - Exposure through food is considered to be national and does not vary by region or season
    - performing additional analyses of these results
  - Drinking water and outdoor lawn and garden uses are not a significant contributor to risk

Key Principles for Conducting a Cumulative Risk Assessment

- Time Frame of Toxic Effect
  - What is the time to peak effect?
  - What is the time to recovery?
- Time Frame of Exposure
  - How often does exposure occur?
  - At what levels does exposure occur?
  - What is the exposure duration?
- How are Exposure and Toxicity compared?

Time-Frame Considerations

- September 2001 SAP Meeting considered this issue of how to compare time component of toxicity endpoints and exposure:
  - CRA should ideally compare toxicity endpoints and exposure durations of same time-frame
  - To the extent possible, comparison should take into account the pattern of human exposure

Time-Frame Considerations: Hazard Aspects

- Steady-state/equilibrium ChE Data
  - Point at which continued exposure at the same dose level does not result in further reduction in ChE activity
  - RPFs and PODs based on studies of 21 days or longer of continued dosing of naive animals
    - Represent more stable measures of RPFs and PODs
- Following insult, recovery of ChE inhibition may require days to weeks.

Time-Frame Considerations: Exposure Aspects

- Human exposure patterns to multiple OP pesticides may be single-day(spike) or short term exposures through food, drinking water, and residential uses superimposed upon more or less continuous exposures through food
  - biomonitoring data from NHANES
  - most animal data available to OPP are developed using laboratory animals that were naïve in their exposures to OPs
- Continuous exposures through food might resemble multi-day dosing used in determining BMD_{10}

Preliminary Cumulative Risk Assessment

- PCRA used a BMD_{10} which reflects continual daily dosing for a sufficient period to produce equilibrium response
  - BMD_{10} used in PCRA is based on multi-day animal dosing studies and reflects that multi-day dose required to achieve a steady-state 10% inhibition of cholinesterase

Preliminary Cumulative Risk Assessment

- In the PCRA, OPP developed a distribution of single consecutive day exposures (NOT rolling time frame) and compared this to a steady-state (equilibrium) multi-day BMD_{10}
- Consider "pattern" of exposures looking for ***sustained elevated exposures*** over a period of time
  - Recognize that such sustained elevated exposures at high percentiles are unlikely to reflect the same single individual

Time-Frame Considerations

- DEEM(FCID)/Calendex permits use of a "rolling time frame" approach
  - Exposures to the ***same*** individual are tracked over the time frame of interest and averaged ***for that individual*** over that time-frame.
- SAP considered this issue in previous session of this meeting

Time-Frame Considerations

- While this rolling time frame approach may allow for a better “match” between selected exposure time frames (e.g, 7 days or longer) and the hazard endpoint, OPP is concerned that this may not adequately permit estimates of risk associated with shorter duration exposures
  - e.g., single day (spike) or short-term exposures

Time-Frame Considerations

- While an advantage of a rolling time frame approach is that it better simulates continual (non-naive) exposures and allows us to better match the time frame associated with the toxicological data, result of this "averaging" process may obscure one-day "spike" or elevated short-term exposures

Time-Frame Considerations

- A BMD_{10} associated with a 21 day steady-state response is appropriate for 21 days or more
- If acute (1-day) or short-term (<21 days) exposures are of concern, how might OPP evaluate/compare such exposures with toxicity data which is based on a multi-day BMD_{10}?
  - How does one estimate the effect of different exposure patterns on risk?

Time-Frame Considerations

- Some information is available with respect to how multi-day BMD_{10}s compare to 1-day NOAEL values
  - A rough comparison of BMD10s with NOAELs based on ChE data from single-dose studies reveals good similarity of values
    - Based on limited data set
    - Some exceptions

Example Exposure Scenarios

Discussion

NOTE: The example exposure scenarios will be provided on transparencies

Questions for the SAP on Risk Characterization

Question 1

There are several key principles for conducting a cumulative risk assessment. One such principle concerns the time frame of both the exposure (e.g., What is the exposure duration?) and of the toxic effect (e.g., What are the time to peak effects and the time to recovery?). Both must be adequately characterized prior to performing a cumulative risk assessment so that an individual's exposure is matched with relevant toxicological values in terms of duration. There are several important considerations with respect to the temporal characteristics of the exposures and of the cholinesterase inhibitory effects of organophosphorus pesticides in estimating their cumulative risk.

- There may be single day (spike) or short-term exposures to organophosphorus pesticides via food, nonoccupational/residential uses, and drinking water, as well as more or less continuous exposure via the diet (food).

Question 1 (continued)

- In the Preliminary OP Cumulative Risk Assessment, OPP used relative potency factors and points of departure developed from cholinesterase inhibition in rats exposed to pesticides for 21 days or more. This practice was adopted to reflect cholinesterase inhibition at a point in the treatment schedule at which a steady state had been achieved. OPP elected to use data reflecting a steady state in the interest of producing relative potency factors (RPFs) that are reproducible and reflect less uncertainty due to rapidly changing time-sensitive measures of cholinesterase. In addition, when the compounds are at steady state, the differences in toxicokinetics among the OPs are less likely to impact the assessment.
- OPP has information that indicates that the American population, in general, has some continuous level of exposure to OPs. Biomonitoring data from NHANES suggests that more than 80% of the American public have urinary metabolites indicating possible exposure to OPs.

Question 1 (continued)

- Most animal data available to OPP are developed using laboratory animals that were not previously exposed to OPs. In other words, the laboratory animals used in the toxicology studies were naive in their exposure to OPs. These studies show that OP's can produce cholinesterase inhibition after a single exposure. A rough comparison of the BMD10s derived from female brain rat cholinesterase data from 21 days or longer duration with NOAELs based on cholinesterase data from single-dose studies reveals good similarity of values, with differences rarely exceeding two- to three-fold.
- Animal data suggest that recovery from a single exposure may take days to weeks.

Question 1 (continued)

In light of all these factors, OPP wants to evaluate exposure across the most appropriate time frame(s). In the Preliminary OP Cumulative Risk Assessment, OPP developed a distribution of single consecutive day exposures, considering the pattern of MOEs occurring at a particular percentile of exposure across the calendar year. This approach focuses on exposure to the population of interest as a whole rather than attempting to track the variation in an individual's exposure from various sources of pesticide exposure. As an example, at the 95th percentile of exposure, each day of the year will reflect a 95th percentile exposure for the entire population and not reflect what may be lower, multi-day average exposures for any given individual.

Calendex allows calculation of multi-day, rolling averages of exposure estimates for the individuals within the population. While this may allow for a match between selected exposure time frames (e.g., 7 day or longer) and the hazard endpoint, OPP is concerned that this may not adequately permit estimates of risk associated with shorter duration exposures.

Question 1 (continued)

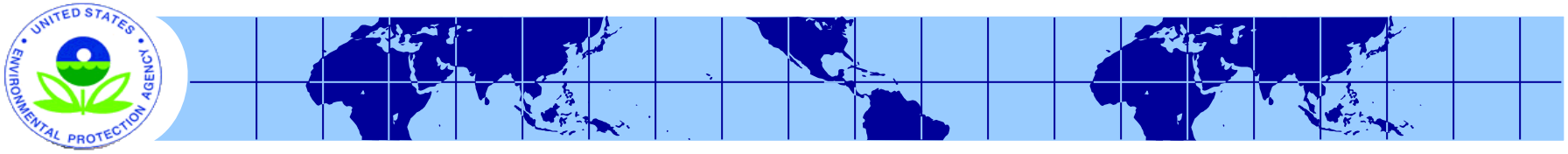
Please comment on how best to evaluate risk, taking into account the temporal characteristics of the hazard endpoint (i.e., cholinesterase inhibition) and the temporal characteristics of the exposure patterns for the food, drinking water, and residential/ nonoccupational pathways, with specific reference to:

- *the pros and cons of various approaches of combining the exposure and hazard time frames to estimate cumulative risk, and*
- *methods to bound or estimate the biases in each approach.*

Question 2

In the Preliminary OP Cumulative Risk Assessment, Section I.H lists a number of potential follow-up activities proposed by OPP. This list is not exhaustive.

Does the Panel recommend any additional follow-up activities or sensitivity analyses beyond those listed? Does the Panel have any thoughts or recommendations about how these additional analyses should be conducted? Which activities should receive the greatest priority?



The End

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FIFRA SCIENTIFIC ADVISORY :
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PANEL (SAP) OPEN MEETING :
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METHODS USED TO CONDUCT A PRELIMINARY CUMULATIVE RISK ASSESSMENT FOR ORGANOPHOSPHATE PESTICIDES

February 5, 2002

[8:30 a.m.]

SHERATON CRYSTAL CITY HOTEL
1800 Jefferson Davis Highway
Arlington, Virginia 22202

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PARTICIPANTS

FIFRA SAP Session Chair

Ronald J. Kendall, Ph.D.

Designated Federal Official

Mr. Paul Lewis

FIFRA Scientific Advisory Panel Members

Herb Needleman, M.D.
Christopher J. Portier, Ph.D.
Stephen M. Roberts, Ph.D.
Mary Anna Thrall, D.V.M

FQPA Science Review Board Members

John Adgate, Ph.D.
William Brimijoin, Ph.D.
Richard Bull, Ph.D.
Rory Conolly, Sc.D.
Patrick Durkin, Ph.D.
Natalie Freeman, Ph.D.
Jean Harry, Ph.D.

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Steven Heeringa, Ph.D.

Ernest McConnell, D.V.M.

Peter MacDonald, D. Phil.

Nu-May Ruby Reed, Ph.D.

Lorenz Rhomberg, Ph.D.

Lauren Zeise, Ph.D.

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DR. KENDALL: Good morning. I'd like to welcome everyone to the February 5, 2002, meeting of the Scientific Advisory Panel to discuss the Cumulative Risk Assessment for Organophosphate Pesticides. My name is Ron Kendall. I'll be chairing the next several days.

And at this point, we would like to introduce all the panel members. We had a few minutes to meet this morning to get organized, to get going. This is going to be a very challenging meeting. The amount of material received to date had been extraordinary. And we appreciate the effort of EPA in moving this process forward and giving us an opportunity to continue to review and contribute where possible.

I'd like to go ahead and introduce the panel members as we do as standard procedure. Dr. Bull, we start with you, and we'll move around the table.

DR. BULL: How much history do you need?

DR. KENDALL: Name, rank, serial number.

DR. BULL: I'm Richard Bull. Washington State University. My area is toxicology.

DR. KENDALL: Please use the microphones. And Dr. Bull, really, the name of area of expertise and affiliation, please.

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DR. BULL: Richard Bull, Washington State University, toxicology.

DR. DURKIN: Pat Durkin, Syracuse Environmental Research Associates. I do pesticide risk assessments primarily for the USDA.

DR. HARRY: Jean Harry, National Institute of Environmental Health Sciences. Research area is in neurotoxicology.

DR. RHOMBERG: Lorenz Rhomberg. Gradient Corporation. I'm also an adjunct professor at The Harvard School of Public Health. And I'm interested in quantitative risk assessment methodology.

DR. CONOLLY: Rory Conolly, CIIT Centers for Health Research in Research Triangle Park, North Carolina. I'm interested in the mechanisms of toxicity that underlie the shape of the dose response curve and the use of biologically based models in risk assessment.

DR. MCCONNELL: Gene McConnell, Toxpath, Raleigh, North Carolina. My area of interest is experimental comparative pathology and toxicology.

DR. BRIMIJOIN: I'm Steve Brimijoin, Department of Pharmacology, Mayo Clinic. I do research on pharmacology and toxicology of cholinesterases.

DR. ROBERTS: Steve Roberts. I'm a toxicologist at the

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University of Florida. I'm a professor with a joint appointment in the College of Medicine and the College of Veterinary Medicine. My interests are in mechanisms of toxicity and, also, in risk assessment.

DR. PORTIER: Chris Portier from the National Institute of Environmental Health Sciences in Research Triangle Park, North Carolina. I direct the environmental toxicology program and sort of direct the national toxicology program. My area of expertise is biostatistics and risk assessment.

DR. ADGATE: John Adgate, University of Minnesota School of Public Health. My expertise is in exposure assessment and risk assessment methods.

DR. FREEMAN: Natalie Freeman, Robert Wood Johnson Medical School and the Environmental and Occupational Health Sciences Institute in Piscataway, New Jersey. My areas of expertise are exposure assessment in the residence and children's exposure.

DR. REED: Nu-May Ruby Reed from California Environmental Protection Agency, Department of Pesticide Regulation. I am a toxicologist doing pesticide risk assessment.

DR. MACDONALD: Peter MacDonald from Mathematics and Statistics at McMaster University in Canada. I have a general expertise in applied statistics and model fitting.

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DR. HEERINGA: Steve Heeringa, the University of Michigan Institute for Social Research. I'm a biostatistican. I direct research operations for the institute there at the University of Michigan.

DR. KENDALL: Thank you. My name is Ron Kendall. Again, I'll be chairing the session today. I serve as chair of the SAP. And I have enjoyed working with this very fine group at the SAP. I'm from Texas Tech University. I'm professor and chairman of the university's Department of Environmental Toxicology. I also serve as director of the university's Institute of Environmental and Human Health.

I wanted to just say a special word of thanks for the staff's efforts to make sure this panel, this very fine panel, gets here okay as coordinated. I thank Larry Dorsey, Shirley Percival, and the rest of the group, Larry's very fine staff, who always do a great job. And it's going to be my pleasure to work with Paul Lewis. Paul and I served for years together. And I turn it over to you, Paul, for any administrative procedures. Thank you.

MR. LEWIS: I think you, Dr. Kendall. Again, it's a pleasure to work with you and for the members of the panel for another meeting with the Scientific Advisory Panel. I would like to welcome the panel members and the public to this important meeting of the FIFRA Scientific Advisory Panel addressing methods used to conduct a

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preliminary cumulative assessment for organophosphate pesticides.

And I, also, want to thank the panel for agreeing to serve at this meeting and for their time preparing for this meeting and the upcoming deliberations that will happen over the next four days. Also, to my colleagues on the EPA staff and my colleagues with the Scientific Advisory Panel for their efforts in preparing for this meeting today and for the reminder of the week.

We have several challenging science issues over the next four days. And we have five sessions that are distributed over that time period that outlines the discussion for the panel that's upon us. We have a full agenda for today and meeting times are approximate. Thus, we may not keep to the exact times as noted due to panel discussions and public comments. And I want to assure adequate time for Agency presentations, public comment, and panel deliberations.

For presenters, panel members, and public commentors, please identify yourselves and speak into the microphones provided since the meeting is recorded. And for panel members, we have distributed copies of overheads to be presented for today. And any public comments that are presented in written form, if we have copies, we'll be sharing them with you also for members of the panel.

In terms of public commentors, for members of the public

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requesting time for public comment, please limit your remarks to five minutes unless prior arrangements have been made. And after completing your comments, we would appreciate that you complete the form that's located at public comments stand next to Dr. Bull to be used to identify yourself. If you can attach a business card that we can include that as part of the public record that would identify yourself and your affiliation.

All background materials, questions posed to the panel by the Agency and other documents related to this SAP meeting are available at docket. And the overheads that will be used for this meeting by the EPA presenters, will be available in the next few days, also on docket. The primary background materials, the agenda, the list of panel members, and the subsequent final report will be available on our docket and also posted on our SAP web site.

My role as a Designated Federal Official for the meeting this week is to serve as liaison between the Agency and the panel. I'm responsible for ensuring provision that the Federal Advisory Committee Act are met. And as a Designated Federal Official, I work with appropriate Agency officials to assure all appropriate ethics regulations are satisfied.

In that capacity, panel members are briefed for provisions of the

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Federal Conflict of Interest Laws. Each participant has filed a Standard Government Ethics Report, commonly known as a Financial Disclosure Report. And I, along with our deputy ethics officer for the Office of Prevention Pesticides and Toxic Substances in consultation with the Office of General Counsel have reviewed the report to ensure all ethics requirements are met.

At conclusion of the meeting, the SAP will prepare a record as response to the questions posed by the Agency, background materials, presentations, and public comments. The report serves as the meeting minutes with be available in our OPs docket and, in addition, posted on the SAP web site in approximately. And we expect the report to be available in approximately 30 to 60 working days.

Thank you, Dr. Kendall, again, for serving as the chair and for the panel members and for the public for participating in today's meeting. I'm looking forward to a very challenging and interesting dialogue over the next four days. Thank you.

DR. KENDALL: Thank you very much, Paul. Next on the agenda, Steven Johnson, the Assistant Administration of the Office of Prevention Pesticides and Toxic Substances was going to be with us this morning. And I understand that he's got a little health problem he's dealing with at home. Ms. Sherry Sterling is here to represent Mr.

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Johnson. And, welcome, Ms. Sterling.

MS. STERLING: Good morning. I'd like to say thank you to all of you panel members. You are veterans so you knew what you were getting into when you joined this panel. So I doubly appreciate what you're doing here.

I'd like to say that I realize that these four days, while they're very intensive, are just the tip of the iceberg. There's the preparation in advance and the report writing afterwards. We appreciate all of that work. This is complex. It's cutting edge and you are really helping us in moving forward on these issues.

So thank you very much. We look forward to the next four days.

DR. KENDALL: Thank you very much. It's my pleasure to introduce Marcia Mulkey, the Director of the Office of Pesticide Programs and from the Office of Prevention Pesticides and Toxic Substances. And, Ms. Mulkey, I can't say enough on behalf of your staff how they have approached this SAP time and time again to move this process forward. I think this group here that's seated is most impressed with the challenge and the opportunity to keep up with your group.

So, again, thank you for being here. This is special when we

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have such high level members of the Agency join us for the opening.

MS. MULKEY: Well, thank you, Mr. Chairman. You've captured a little bit of my enthusiasm about the opportunity to be affiliated with this group of professionals with whom I'm fortunate enough to work.

You are all used to seeing me at beginning of these meetings. I like it that we are used to spending time together at the beginning of these meetings. But I did want to take a few moments to tell you that Steve Johnson who, as you mentioned, is Assistant Administrator for Prevention, Pesticides, and Toxic Substance, was very committed to being part of this particular SAP. And literally, but for bed confinement and doctor's orders, I think Steve would be here this morning not withstanding the discomfort he's also experiencing.

I have Steve's notes for his talking points which is a way of assuring that what I say, assuring me, assuring you, assuring everybody else, assuring Steve, that what I say to kick us off this morning is fully consistent with the kinds of messages that he intended to bring. So I would like to spend a few minutes on those messages. They are not extensive, but they are important for EPA and for our organization.

Starting with thank yous. A special thank you to Ron and to all

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of these panel members for the time you have spent preparing for and will spend as part of this meeting and for the time you have spent at the many previous meetings leading up to this one on the subject matter that has grown into this integrated comprehensive presentation about our approach to the cumulative risk assessment for the organophosphate pesticides.

Your role has indeed been critical. I think you know that, but it does us a lot of good to be able remind you and remind ourselves how important we have found this work that we have done together. You will recognize many of your recommendations surfacing in our adjustments and adaptations in our work as we have gone along. And so it should be know surprise that we are eagerly awaiting an opportunity to engage with you in again when it is so obvious what a difference it has made in our work up until this point.

It's always helpful to us. We understand that you have the benefit of some arms-length distance from the statutory obligations, the statutory time lines, and so forth which govern, in the literal sense, our work. But it is worth reminding all of us that we do have another of the three deadlines set out in the Food Quality Protection Act of 1996 passed back in the last century.

The second deadline is August 3 of 2001 by which we are to

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have completed the next 33 percent of pesticide tolerance reassessment. That means we have to have completed 6,416 of the tolerances in order to be in compliance with our obligation under law. We have been working hard since the day the law passed in order to meet these deadlines. And even more importantly, in order to accomplish the public health protections that go along with assuring that all of the pesticide tolerances of the United States meet the tough new standards of the Food Quality Protection Act.

It's clear we have been as transparent as we know how to about this fact that in order to meet this next deadline, we must have completed all or at least a very substantial portion of the organophosphate tolerances. And because this group operates by a common mechanism, that means we must have considered cumulative risk to have accomplished that.

So not only devising a workable method to assess and consider cumulative risk, but implementing it through the risk assessment, of which you now have before you our preliminary cut, is a critical aspect of meeting this August 3 deadline. In fact, it's an absolutely critical aspect of meeting it.

So we bring this to you today with some sense of urgency, and we share with you that. But we want to make it clear that while we

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are committed to meeting that deadline, we are at least equally committed to doing it in a responsible way. And from our point of view, a responsible way has at least three critical elements: Sound science; transparency, openness, and understandability; and full stakeholder involvement.

While this panel and our engagement with it is an absolutely core piece of our commitment to sound science, as it happens you also play an important role in our commitments to openness and understandability and to our commitment to stakeholder involvement. This is an advisory committee complete with, not only fully public meetings, but input from the public. And that will be an element of this four-day meeting.

So you are not only a pathway through to our statutory obligations, our obligations to the American people under their laws, but to our approach to doing so in a way that we can all hold our heads up about; that is, scientifically sound, open and understandable, and involving all points of view.

With that, I want to mention that we are also looking forward to the part of this meeting that is about the public and it's input. And we, as we expect you, will be listening carefully to the perspectives, to the insights, and to the information and expertise that may be brought to

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bear through public participation.

But I do want to mention that this is not the only opportunity that the public will have to engage with us, nor is it the only opportunity heretofore. But I specifically want to mention that we are conducting an open public comment process relating to this preliminary risk assessment and all of the information connected with it and that comments are due March 8. So all public commentors will have the benefit of this meeting, the benefit of the outcome of this meeting, and some time beyond this meeting in order to complete their public comments.

But I, also, want to take this opportunity to urge everyone in the public to bear the same kind of burdens we have borne of timeliness regarding this process because of the common obligations that we all have under law.

I want to conclude with just a couple personal notes. I intend to spend as much of my time as I can possibly manage to spend in the next four days here with the panel. I want to do that for several reasons. First and foremost, because I'm so pleased and gratified to be part of the EPA team that comes before you today. And I want to stand proudly with them throughout this time.

Secondly, because I learn a great deal. I learn a great deal,

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frankly, from listening from to them again, as well as from hearing the input of the public, hearing the input from the panel members. And I think that that helps me do my part of the responsibilities that's around this more effectively.

And, finally, because we want to show to the public the importance we attach to this and the seriousness that we give to all of the principles I just mentioned: Sound science; openness, understand, ability and transparency.

So I'm very much looking forward to the time here and the proceedings of the next few days. And I anticipate that after it is behind us and we are on to the next step, we will always look back on this as a seminal event in the progress of science in EPA's pesticide program.

DR. KENDALL: Thank you very much. We welcome you here again, Ms. Mulkey. And it is significant when people of your level in the Agency are willing to stay with us and hear the deliberation.

I also thank you for conveying some of the comments from Mr. Johnson. It is very obvious for those on the SAP. We know that the support is there and it continues to be there. And we appreciate his support your support.

Next, I welcome Ms. Margaret Stasikuwski from the Office of

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the Pesticide Programs. Margret, we've seen a lot of you and your team over the last couple years and we welcome you and congratulate you for the progress you're making. I look forward to this deliberation.

MS. STASIKUWSKI: I am pleased to be here at this really important extraordinary meeting, the review of the preliminary cumulative risk assessment for organophosphates. Today I will give some historical perspective on the development of the assessment, briefly go over the agenda, and introduce members of the EPA staff who will make presentations and participate in the discussions.

The next four days are a culmination of five years of extensive work to develop the methods and guidance for conducting cumulative risk assessment. This first slide shows the critical stepping stone documents along the way to our objective of having the first, the final, OP cumulative assessment completed in June of this year.

The first critical step document was guidance issued in January of '99 on identifying pesticide chemicals and other substances that have a common mechanism of toxicity. The final guidance on conducting aggregate exposure and risk assessments across residential, dietary, and drinking water pathways was published in 2001. The draft OP risk assessment you just received was finished

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during the first week of December 2001. And our final generic cumulative guidance was just finalized in January of 2002.

In preparation for this meeting we looked back at how we consulted and sought your advice during the last five years. To get where we are today, we started in 1997 with SAP reviewing our approach to defining common mechanism toxicity for the purpose of conducting cumulative risk assessments. In March of '98, we asked SAP to review our conclusion that organophosphate pesticides form a common mechanism group through their cholinesterase inhibiting activity.

Two years later, OPs asked the SAP to review the validity of the toxicity endpoints that we selected and the approach that we used to calculate relative potency factors.

Last September, we presented to the SAP for comment our refined Preliminary Hazard and Dose Response Assessment for the OP pesticides.

For the exposure assessment, the SAP reviews and consultations covered incremental improvements in our residential exposure assessment methodology and drinking assessment methodology over the period of three years. The big leap forward in our methods took place when OPs proposed to use probabalistic Monte Carlo techniques,

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first, in conducting dietary exposure assessment, then for drink water and residential assessments.

SAP reviewed several software models that were being proposed for use in exposure assessments, DEEM, Calendex, Life Line and CARES.

SAP advised the Agency several times on development of risk assessment methods for aggregating exposures across dietary, drinking water, and residential pathways for single chemicals. In 1998, SAP reviewed our probabilistic assessment methods. Building on aggregate risk assessment methods, OPs took our proposed methodology for cumulative risk assessment to the SAP in 1999.

In December of 2000, we brought to the panel the risk assessment methodology and our case study of 24 organophosphates. When you count this all up, this adds up to 21 reviews by the Science Advisory Panel of our approaches, methods, and case studies. And these all lead directly to our presentations today.

SAP recommendations have been invaluable, and here are just some highlights of their recommendations made in response to the SAP. In the area of hazard and dose response assessment based on SAP recommendations, the Agency is using a refined exponential model for dose response modeling. In the dietary exposure

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assessment, OPs moved to the use of pesticide data program and other monitoring data rather than rely on field studies. OPs is using publicly available data bases and recipes in this assessment.

Based on the recommendations of the SAP, the Agency is using a finer division of age groups in children in this assessment, zero to one year, one to two years, and three to five years. This was possible with the use of the newer CSFII data with a supplemental children's survey of 1998.

In the drinking water assessment area, OPs in our preliminary assessment implemented SAP recommendations to devote resources to surface water impacts to define higher assessment tiers and develop techniques for estimating concentration distributions for probabilistic risk assessments. We adopted the recommendation to conduct regional drinking water risk assessment modeling and to shift focus for monitoring programs to support model development and model evaluation.

In their residential and occupational risk assessments, SAP made some key recommendations regard recommendations regarding frequency of children's hand-to-mouth activity and transferability of pesticide residues from surfaces to hands to mouth.

Based on the recommendations of the SAP, OPs today is using

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uniform distributions for small data sets rather than rely on point estimates in residential assessment.

These are just some of the few, of some of the highlights, of how we implemented SAP recommendations in this assessment.

The next steps over the next 9 to 10 months will be to revise the December 2001 document based on today's deliberations and the public comments that we will receive. And the intended completion date for our assessment is June 2002.

Now, briefly, to go over our agenda. Immediately following these remarks, we have a public comment period that is scheduled to last through lunch and will cover all aspects of our cumulative assessment. This afternoon, Dr. Lowit and Dr. Setzer will present the hazard dose response analysis. This presentation will be followed by a public comment period and a panel discussion.

The panel discussion is scheduled to continue through tomorrow mid-morning. All of the sessions will follow a similar schedule: Presentation, public comment, and panel discussion.

Tomorrow mid-morning, we'll move to the presentation of the food exposure assessment presentation to be made by Dr. Bill Smith. The session on drinking water exposure assessment is scheduled to start tomorrow after and continue through mid-morning Thursday.

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The session will be presented by Mr. Costello and Mr. Nelson Thurman.

Residential and non-occupational exposure assessment will be presented by Mr. Jeff Evans and will proceed from Thursday mid-morning until afternoon break. And then risk characterization to be presented by Mr. Dave Miller. And the session is to scheduled to continue through mid-day Friday.

I'd like to acknowledge that participants -- and these are just a few of the people in EPA who are responsible for preparation of this document. Mr. Kevin Costello, Dr. Vicki Dellarco, Dr. Elizabeth Doyle, Jeff Evans, Anna Lowit, David Miller, Randy Perfetti, Woody Setzer, Bill Smith, and Nelson Thurman. Thank you very much.

DR. KENDALL: Thank you, Margret. That was quite a summary. A lot of memories. In fact, it even forced us to change our management paradigm of the SAP because there were so many meetings that we had to rotate the chair because it was so challenging. And that has actually worked out extremely well. Our permanent panel members have stepped up and have worked with me and we have been able to accommodate this process. A lot of challenging meetings and discussion.

So here we are these years later. And we, at this point are there

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any questions from the Panel for our speakers this morning from EPA? We're right on time. Any clarification? I think we're all just overwhelmed right now just reflecting on this.

We would like move into the public comment period. I have on my agenda here at least five registered.

MR. LEWIS: Right.

DR. KENDALL: We will start in the order I have received them. Jennifer Sass, Dr. Jennifer Sass, on behalf of the Natural Resources Defense Council. If you would come forward. The public commentor microphone is to our right. And we are asking -- first of all, welcome. And we are asking that those that do come forward to present try to limit your remarks --

MR. LEWIS: Five minutes.

DR. KENDALL: -- to five minutes unless other arrangements have been made. And if you anticipate it to be longer, please, approach me or give us some note. We're trying to accommodate everybody. So anyway, we will go ahead and proceed forward. State your name affiliation, please, for the record.

DR. SASS: Thank you. My name is Jennifer Sass. I'm a senior scientist at the National Resources Defense Council. I've made previous arrangements so I have about ten minutes to present.

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And I want to first thank the EPA. I think they've done a tremendous job and a tremendous effort has gone into this both in the science and in the presentation in making it publicly available and making it accessible to the stakeholders in going through the presentations, which at best, are time consuming and at worse must be painful. And I do thank them. It's been a tremendous job.

And also thank the SAP. It is a tremendous commitment of time. It's also a very, very important issue. And it will set the stage for cumulative risk assessment to come by the EPA.

Onto the assessment. I have a couple points. First of all, I think that children have been inadequately considered throughout the risk assessment. NRDC requests that the Scientific Advisory Panel recommend a FQPA factor of at least tenfold be applied to account for the absence of proper developmental testing and for demonstrated neurotoxic effects in the DNT, the developmental neurotoxicity battery of tests where such tests have been done.

Under this point, all toxicology data is derived from adult animals. This data cannot be extrapolated to fetuses, neonates, and juveniles directly. It is an extremely serious omission in this cumulative risk assessment that all toxicological assessments, including dose response determinations, are based solely on adult

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animals, in this case, cholinesterase inhibition of female rat brains with know experimental data from fetuses, neonates, or juveniles.

Considering the impetus of the CRA is the FQPA, which mandates the reevaluation of pesticide exposures with specific attention to the effects on fetuses, infants, and children, it is an obvious omission to disregard the life stages from the tox assessment. The magnitude of this omission, especially in light of the fact that less that half of the organophosphate pesticides have undergone DNT testing as required by the Agency is pervasive through throughout this document and is, therefore, discussed throughout these comments in various lights.

The developmental toxicity testing, the DNT, is still outstanding for a good number of the organophosphate pesticides and this critical data gap makes it impossible to assess the neurotoxic effects to fetuses, infants, and children.

Studies show that the DNT testing is more sensitive and, therefore, more appropriate for assessing and protecting children's health. DNT testing is essential for pesticides, not only as a measure of toxicity to the developing brain and the nervous system but also as an often more sensitive measure of developmental and reproductive effects generally.

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EPA's task force for the 10-times FQPA, recommended that the DNT testing be included as part of the minimum core tox data set for all chemical food use pesticides for which a tolerance would be set. In fact, there is a data call in September 10 for DNT testing on all the OPs, all the organophosphate pesticides.

All of the OPs must be assumed to be developmentally neurotoxic. NRDC believes that the Agency must presume that the developing nervous system is more vulnerable than the adult to neurotoxic insult. NRDC requests that the SAP recommend that a tenfold FQPA factor at least be applied to the OPs to adequately protect fetuses, infants, and children from these neurotoxic chemicals.

Presuming all of the OPs to be developmentally neurotoxic is consistent with current scientific understanding of neurobiology, embryology, and neurotoxicology. A number of individual OP chemicals have been shown to be especially harmful to fetuses, infants, and children even at low doses. This is expected, given that the OPs are designed specifically to disrupt cholinesterase levels thereby affecting synaptogenesis, neuroid outgrowth (inaudible).

Functionally, this has been demonstrated to result in permanent disruptions in learning, memory formation, cognitive ability and behavior.

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For chlorpyrifos, for example, DNT testing which was completed demonstrated evidence of neuropathology and increased vulnerability of fetuses when exposed. Most concerning in these experiments, neuropathology was seen in the neonates at the lowest doses tested. These studies were unable to identify a know effect level in the offspring in the DNT tests.

In that study, structural alterations in brain development which would result in permanent brain disfunction were seen at the lowest doses tested. Similarly, increased sensitivity of young animals compared with adults has been demonstrated with Malathion in studies performed by the registrant.

The organophosphate pesticides are a common mechanism group. They target a common enzyme and they induce a common set of effects, not overlapping but common; and, therefore, by all scientific criteria if any are shown to be phytotoxic, then it should be presumed that all are phytotoxic, particularly in light of the fact we do not have the proper DNT data on a lot of them.

Clearly, the OPs which were rigorously tested using appropriate study designs, such as DNTs were shown to be especially harmful to the developing nervous system.

The NRDC requests that the Science Advisory Panel consider all

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the OPs to be developmentally toxic, both the parent compound and the toxic metabolites.

NRDC believes that any other conclusion is not supported by scientific evidence of phytotoxicity demonstrated in the DNT studies and will not adequately protect fetuses, infants, and children.

The cumulative risk assessment has failed to consider regional effects, behavioral effects, cognitive effects, and learning and memory effects in terms of neurotoxicity. The endpoints of all the tox studies used in this CRA were whole brain cholinesterase activity. This approach ignores regional variability within the brain and responses in different brain regions and masks local perturbations which may be very severe.

NRDC believes that histopathological examination would reveal regionally affected brain areas. Behavioral and cognitive testing including learning and memory tests, reflex tests, and others are key to assessing the key toxic affects of any neurotoxic or phytotoxic chemicals. Most importantly, with any developmentally neurotoxic chemicals, such as the OPs, effects are the result of more than the magnitude of the dose. Rather the effect is dependant on the dose, the duration of effect, in this case, cholinesterase inhibition. How long does the inhibition last, and the stage of the development at the which

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the exposure takes place.

Exposures during key windows of susceptibility during neurodevelopment even at very low doses are most likely to have permanent devastating effects on neurofunction, including behavior and cognition. This was never examined in the current CRA and is a very serious data gap in the understanding of the toxic effects of OPs. In particular, the effects of OPs on fetuses, infants, and children have not been adequately described.

The CRA that we're going to see, the preliminary CRA, did not consider newborns, young children, and teenagers. And NRDC requests of the Scientific Advisory Panel that it recommend including all age groups in the cumulative risk assessment, including zero to 11 months, 6 to 12 years, and 13 to 19 years. This is a very serious omission, and it makes this preliminary cumulative risk assessment unable to comment on an exposure or risk to these absent age groups.

NRDC believes that these omitted age groups are the intended targets of the FQPA. And without consideration of these groups, the requirements of the FQPA have not been met.

Exposure has been underestimated throughout this document. And I think contrary to some of the cover letters that have been going around suggesting that this document is more than adequately

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protective, quite the opposite. There has been an systematic underestimation of exposure and, therefore, risk. And NRDC believes that this is not a public health protective document; rather it's evidence in many ways that exposure and consequent risk have been underestimated. And NRDC details examples and request that the Science Advisory Panel consider this document to be an underestimate of exposure and recommends that EPA amends the cumulative risk assessment appropriately.

Some points that speak to that. The Agency did not consider toxic degradants. This results in an underestimate of exposure. The NRDC requests that the SAP recommend using data on toxic degradates where available, such as some water monitoring and some food data. Where such data is not available, the EPA should estimate exposure and risk based on chemical structure, mobility, degradation rate, and known characteristics of the degradates.

Though EPA has abundant data for dietary exposure to OPs, the PDP and FDA data bases used only include monitoring data for residues of the parent compound. Likewise, toxic degradates and metabolites treatment byproducts were not included in the water assessments. Where metabolites were considered, they were presumed to behave as the parent compound. This is not scientifically

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justifiable. And NRDC believes that the omission of proper consideration of the degradates results in an underestimation of exposure.

Many pesticides, including the OPs, have toxicologically significant metabolites. Malioxone, the bioactivated form of Malathion, inhibits acetocholinesterase about one thousand fold more strongly than Malathion under some tests. Similarly, the dimethoxone, the metabolite of dimethoate is 75 to 100 times more potent than dimethoate in inhibiting acetocholinesterase. This metabolite is found in field crops and food.

The primary degradate of ethoparathion, paraoxone, is five times more easily absorbed than parathion and is 40 to 50 times more toxic. And one of the chief metabolites of chlorpyrifos, thixone (ph), inhibits cholinesterase more strongly than the parent. Although the metabolite appears to be short-lived, the breakdown product, TCP, is more persistent and has been found in the urine of children.

The impact of these metabolites on developing animals, even where short-lived, could conceivably have effects irreversible effects on the nervous system and heightens the need for prudence in carrying out cumulative assessments.

In this cumulative assessment, the Agency did not consider

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violative residues which may underestimate expose. NRDC requests the Scientific Advisory Panel recommend including data on violative exposures. This data is available to the EPA and should be provided and incorporated appropriately.

Violative residues may be either residues detected on foods for which know tolerance is issued or which exceed the tolerance. In either case, they are extremely important and may indicate a wide spread and very dangerous problem. If residues are routinely, seasonally, or even occasionally exceeding the allowable tolerance level, then the public has a right to know and the CRA must consider these real-world residues.

It is unacceptable for the Agency to disregard these data based on actual monitoring as simply being outliers without providing evidence that they are flatly incorrect or of inconsequential health impact.

If these violative residues are the result of spray drift, of illegal applications, of machinery residues, then, again, they must be considered indicative of widespread exposure and a contributor to cumulative OP risk. In any case, the Agency must provide the data as to the frequency, spatial and temporal pattern, if any exists, and magnitude of the violations.

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NRDC considers the absence of this monitoring data in the CRA to be a data gap and likely results in an underestimate of exposure.

The Agency did not consider some of the organophosphate pesticides. NRDC asks that the Scientific Advisory Panel request that omissions of OPs be considered and or else be considered an underestimate of exposure in this cumulative risk assessment.

In this preliminary CRA, the Agency has excluded from consideration all chemicals and all chemical uses which have been cancelled, voluntarily withdrawn, or phased out. In some cases, we have concerns that the phase out periods are long, four to five years. And the possibility that these phase-out periods may be extended is of concern to us.

In addition, chemicals which only have public health uses have been excluded. Again the risk to the fetus, the infants, and to the child to the developing nervous system depends on the time of exposure during development and not only the dose.

NRDC recommends that the EPA in the water assessment be based on all available data of use rates, of use patterns, and monitoring data so that the cumulative risk assessment will adequately capture the populations at highest risk.

The water model used for the preliminary CRA plots the

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distribution of daily residues over multiple years and plots multiple sites rather than high exposure sites. Know point estimates were considered. This is a major departure from the individual risk assessments where point estimates were used to capture the 99.9th percentile.

Ignoring peak estimates leads to a very severe underestimation of risk and ignores the potentially devastating effects of exposure of OPs even at very low doses and even short durations on the developing nervous system.

The CRA further underestimates risk by presuming typical use rates and typical use patterns. This is a departure from the individual risk assessment which assessed exposures based on maximum allowable label rates and maximum allowable use patterns. This is a more conservative approach. While still ignoring exposures which exceed allowable limits, it at least attempts to protect those people who suffer the allowable high-end exposure. The CRA makes know so attempt.

The final output of the CRA water assessment reflects the typical or average use pattern which, although describing the majority of the calendar days, does not describe the majority of the risk.

Finally, we think that the CRA ignores the most vulnerable

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populations. The effects of exposures which may be at low possibility but high risk impact are excluded from the CRA. Use of the central estimate, the benchmark dose, or BMD10, will estimate risk unacceptably. Use of the BMD01 is more protective and is supported by the data.

NRDC requests that the Scientific Advisory Panel recommend using the BMD01 rather than the BMD10 to adequately protect all populations. The point of departure in each chemical's dose response curve was determined to be the BMD10. The benchmark dose for cholinesterase activity was reduced by 10 percent. The use of the BMD10, a central estimate rather than its lower limit, ignores risk for those who are most sensitive to cholinesterase perturbations such as fetuses, infants, and children for whom changes less than 10 percent or sustained changes may induce permanent alterations in cytoarchitecture of the nervous system.

The Agency has never performed a proper evaluation of the subtle sustained or neuroregional effects of OP exposure either in the adult or in the developing nervous system. Thus, NRDC believes that the choice of a central estimate which the Agency's own data indicate is higher than the know ALs for oral, dermal, and inhalation exposure routes, is a potentially large underestimate of risk. In fact, the

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BMD10 is a full threefold higher than the dermal NOAEL. And NRDC believes that the use of a lower limit, BMD01, is more acceptable as a point of departure estimate and would better reflect the low dose exposure scenarios and thus be more health protective.

Very importantly, the Agency has measured the magnitude but not the duration of the OP exposure. And NRDC requests that the Scientific Advisory Panel recommend including data on duration of cholinesterase inhibition in addition to magnitude to more accurately capture the toxic effects of OP exposure. To measure the full toxic potency of any chemical, including the OPs, it is necessary to measure the effects of sustained duration of exposure. This has not been done in the Agency's model of toxic effects.

While the animal toxicological studies considered the magnitude of cholinesterase inhibition at each dose, there is know consideration of the duration of the inhibition. Without any attempt to capture the sustained inhibition of cholinesterase activity, this model is inadequate and will likely underestimate risk.

NRDC encourages the Agency to pursue a truly expanded model which will describe not only the magnitude but also the duration of enzyme inhibition at each dose. This will surely prove extremely in evaluating the full toxic effect of OP poisoning and will be especially

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important in describing the sensitivity of the developing nervous system to acute and sustained perturbations of cholinesterase activity.

Very importantly, farm children are especially vulnerable to pesticide exposure and are not adequately considered in this cumulative risk assessment. NRDC requests that the Scientific Advisory Panel recommend to the EPA that farm children comprise an especially vulnerable population and their exposure to OPs must be considered in the CRA where data is available.

Children who live on our near farms are at risk of airborne pesticide drift when they spend any time outdoors, and numerous data gathered and published reveals this to be true.

The current CRA model does not account for the leftover food effect. And NRDC requests that the Scientific Advisory Panel recommend that the EPA evaluate the overlap of peak residues which are likely to be seasonal with peak eating patterns which are also likely to be seasonal, such as eating fresh fruit shortly after pesticide applications.

These data are viable available to the EPA and should be considered. These very real exposure patterns are not random and they are likely to indicate high exposures. Of further concern, they are likely to be especially particularly concerning for young children

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whose eating patterns are likely to correlate with seasonal fruit availability.

NRDC requests that the Scientific Advisory Panel recommend to the EPA that the cumulative risk assessment be based on periods of known exposure peaks such as shortly after pesticide application. In the current CRA, these data are not recorded or considered. The current CRA does not focus on the days when pesticides are actually applied.

And, finally, the NRDC believes that a nonproprietary model should be used on all risk assessments now and in the future. And we recognize the uncertainty and potential bias inherent in any model. And we request that the SAP recommend that assessments are done with the following safeguards.

Number one, that each risk assessment be performed as two or more models to begin to document model variability and model bias if it exists. Number two, each risk assessment should be performed using a nonproprietary model as one of those models in addition to any other models. And, number three, the need for uncertainty factors is required in calculating a margin of safety when probabilistic risk assessment has been done. Thank you.

DR. KENDALL: Thank you. Any clarification, questions from

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the panel? Dr. Roberts.

DR. ROBERTS: Yes. Thank you, Dr. Sass. You raised many points obviously. I just wanted to ask you about two of them.

Does your organization have or are you aware of any synthesis of information that exist currently on OPs in terms of DNT testing versus adult cholinesterase as an endpoint? You've made the point that maybe by not considering effects, neurodevelopmental effects, that the wrong endpoint is being used. I think it would be very helpful for the panel, or at least helpful for me, to see a summary of the evidence, the data that exists, comparing those endpoints and the doses for various OPs to judge whether or not this is speculation or whether or not -- or to what extent data exists that support a difference.

DR. SASS: Probably the best thing out there is a paper that is still in a draft stage; although, it was a 1999 paper by Susan Makris who is a scientist with the EPA. And she compared about 12, I think, different pesticides, including some of the OPs and DNT testing with different batteries of tests that the EPA uses including subchronic. I think there was the normal neurotox, a subchronic. There is about five different tests that she compared including DNT and compared the know ALs and low ALs that resulted from these different tests and

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including maternal and juvenile susceptibilities.

DR. ROBERTS: If that could be made available to the panel, I think that would be very helpful.

DR. SASS: Is that available on the web site or know, considering the paper by Susan Makris? It's an EPA paper. It's put out by the OPP. Okay. I can bring a copy.

DR. ROBERTS: Same sort of thing on the regional versus whole brain cholinesterase point. Some sort of synthesis or summary of what data exists however limited it might be that would suggest using whole brain might underestimate regional effects would be, I think, also helpful.

DR. SASS: Thank you.

DR. BRIMIJOIN: Actually, I have some direct knowledge of that particular issue. That's one of the points of interest in my research for the past 10 years. And I would say just a rough summary that there isn't a lot of regional variability. I would challenge what we just heard. There is some.

DR. KENDALL: Dr. Portier.

DR. PORTIER: Dr. Sass, thank you for making a number of points. I counted, I think, about 21. But I had a few questions. The violative exposures issue is one that's fairly interesting that I hadn't

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thought about before. Do we have data on violative exposes? How often does it occur? And any idea how often it has been missed?

DR. SASS: I would answer, number one, apparently the EPA has that data and as a carrot member that has been following this all along, it's been requested by both me and the Adam Goldberg at CU. The EPA has said that they would provide that data for us. It hasn't been done yet. I know they have because they say they have it.

Chuck Benbrook has submitted comments that will be read by Adam Goldberg of Consumers Union later this morning; and he has done some estimates of that based on what he's been able to gather and suggests that in some cases it could as high as 10 percent in terms of above where these 10 percent of the exposures; it would add 10 percent to what we know. He has some charts that I can bring that I have. I think the best would be probably be to get it from the EPA.

DR. PORTIER: Well, I look forward to his comments. Mr. Chairman, if you would like to give EPA a chance to respond at this point.

DR. KENDALL: I am -- I am --

DR. PORTIER: That will be fine because I have several other points.

DR. KENDALL: Okay. Would EPA like to respond to that

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particular point?

MS. MULKEY: I think what I might work best is for us, as we go through our presentation, where we have -- for example, this issue comes up in the choice of which of the PDP data we used. And so if we can keep track and rather than trying to do point by point, maybe as we roll out our presentation. Because I think there will be a number of points that the other public commentors make, also, that relate to a range of issues. So if you think that's workable, we'll try to keep track and do that. I mean, if there's some clarification we can offer that's particularly --

DR. KENDALL: I accept your suggestion. I think that would be best. Dr. Portier, any further points for clarification.

DR. PORTIER: Several. Phase-out chemicals. The comment made that some of the phase-out chemicals will be as long as five years in phase out. Is that a statement of fact or not? It's something I think we should consider in looking at this over all risk assessment. Any comment on that?

MS. MULKEY: Most of the phase outs are shorter than that. And I don't know that any of the ones that involved applications for food go that far. But some of the residential phase outs are in that range. So we'll try to be specific about that when we talk about what's

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excluded as we go through our presentation.

DR. PORTIER: And then another question, again, for clarification on my part with Agency. The use of peak estimates. Dr. Sass implied that the use of peak estimates are common for other risk assessment, other risk assessments rather than the more average issues looked at here. And my question to the Agency is: That my understanding of use of peak estimates and maximum allowable use rates is more for a screening-level risk assessment than his, which I gather, is much more of a finalized risk assessment; is that correct?

MS. MULKEY: That's correct.

DR. PORTIER: And I believe that's all my questions.

DR. KENDALL: Thank you. Dr. Bull.

DR. BULL: Thank you for the points you raised. I had a couple of questions. I just didn't quite hear. Were you suggesting that the FQPA factor be applied available even when data is available or only when data is not available on the children's issue. I was a little confused by it.

DR. SASS: Right. Either when data is not available, we should presume, based on data from other OPs, that they're neurotoxic. Or when there is data available that show that the juveniles are more susceptible. If there is data to show otherwise, that that certainly

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should stand definitely.

DR. BULL: The other issue I'm intrigued by as well that you brought up and it relates to what your calling violative, but it's not really violative kinds of things in the usual application of chemicals to crops and so forth. That's spills. And if there is ever an issue in the drinking water circumstance with these kinds of compounds, it relates more to spills. And I was going to bring up the issue if there has been any attempt to address how frequently that might occur. I'm not sure that it should affect any standards that are apply to applications.

But it's more likely, you know, you have a compound in commerce that's a solvent a pesticide or whatever, every once in a while it ends in up in a reservoir somehow. And those are the kinds of things I'd be more concerned about in the drinking water than the average kind of input. And I just don't know how, if there's a basis for getting at that kind of frequency.

DR. SASS: I would ask the EPA if they have a water monitoring data on that.

MS. MULKEY: Again, if we could try to fit that into our presentation on water.

DR. KENDALL: I agree. Let's proceed. Dr. Portier.

DR. PORTIER: This does bring up another issue for me as I

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think about the comments I want to write down since I will miss the last two days and get some of them read before the panel.

None of the questions on the risk characterization actually ask us about the 10X safety factor and whether you want a comment on that. I won't ask you to give me guidance on that, since I'll use my own guidance on whether to tell you what I think about that. My question is will we be seeing a final version of this for comment at some later point at which point we will at least see whether you've decided to use 10X or not and then can comment on it. Do you know?

MS. MULKEY: We are working through the issue of how to analyze the 10X in the context of cumulative risk assessment and, also, the question of what kind of peer review, public participation, is appropriate. So we don't right now have a definitive time line and plan of action on that.

I will mention we have had out for extensive public process the approach for the individual chemical 10X analysis. And we expect to have our revised or final paper on that within this month. We also expect to put out for comment an approach to 10X in the context of cumulative risk assessments. That's a generic one not an application to the OPs. And that we're going to put that out for public comment in this month.

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So that's been sort of the first waive is to sort through our articulation of the generic approach and then we'll be working through initially internally how we analyze that with reference to the organophosphates. Obviously, issues of uncertainty and sensitivity are the key elements of that. And there are many things in what we're consulting with this panel about that go to these questions. So there's no question that this consultation will inform our work on that, although we have not identified a very specific question relating to the FQPA safety factor.

DR. PORTIER: Thanks.

DR. KENDALL: Any further points? Okay. Thank you very much, Dr. Sass. We will continue on. We have three presenters speaking on behalf of Food Quality Protection Act Implementation Working Group, Mr. Botts, Mr. Driver, and Mr. Zabik. They've requested 45 minutes for the three of them, what I assume to be an integrated presentation or separate. Can you do it in 45 minutes?

MR. BOTTS: Hopefully, we will do it in 45 minutes.

DR. KENDALL: Are you Mr. Botts?

MR. BOTTS: I'm Mr. Botts.

DR. KENDALL: Thank you. Welcome. State your name and affiliation for the record, please.

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MR. BOTTS: My name is Daniel Botts. I work for the Florida Fruit and Vegetable Association. And my real job, I direct the Enviornmental and Pest Management division of that organization which is a grower organization representing the fresh fruit and vegetable industry in Florida.

One of my unpaid jobs, among many, is being the vice chairman of the Implementation Working Group which was created after FQPA passed to provide a coordinated input into the process as the Agency moved forward to the aggregate risk exposure assessment to the cumulative exposure process to final decisions. Hopefully, it will meet the time schedules that are proposed in the law so we don't have to go through other issues associated with that process.

That bit of personal background is to provide some input on why we're here today and what we wanted to do. We did submit a series of written comments that were, hopefully, distributed to the SAP to address a lot of issues. And rather than go through those specifically today, not only are the two persons that are going to join me this morning going to make presentations, but some of those other issues will be covered in the panels appropriate to the topic matter as they go forward. And we appreciate the SAP allowing us to split those comments up, to be able to make them directly to those panels that

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will be dealing with those issues.

Just in the way of general comments, I would like to echo my sentiments and more personal as both a member of the food safety advisory committee, the track committee, and the carrot committee among others. And my other unpaid job with EPA I have been involved since 1996 and looking forward to the day that we get to the point of a cumulative exposure assessment.

If somebody had asked me as a nontechnical person whether it would be possible to do what the Agency has put on the table today, I would have said it was impossible. Just knowing the little bit that I do about pesticides application, having been involved in commercial agriculture prior to going to work for the Association.

I think the cumulative assessment in the preliminary mode that's in front of us represents a significant achievement by the Agency. But having said that, there are further refinements that need to be made to the document if we're accurately going to reflect the exposures that are produced by the use, not only in agriculture, but other uses of pesticides that are out there.

To echo some of Jennifer's comments relative to the transparency of the issue, the Agency has gone a long way towards making the process totally transparent. I would suggest that I think

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I've been to 80 percent of those 24 SAP meetings and other processes brought forward by the Agency to try to get to the point where we are today. And in my other life, in my real job, I'm supposed to translate that to my membership who are actually out there doing the work of applying pesticides.

And transparency, also, has an understanding component and just listening to the discussion so far and other scientific advisory panels, there's a translation to get it down to the level of understanding where my grower membership will understand the need for regulation of crop-management tools that they've been using for the last 40 years with the expectation that their use of their products had not created a problem.

From that standpoint, if we do lead to regulatory action against those products, it needs to be communicated in a manner that's understandable so when we explain it to the growers at the farm levels, they understand why they are being asked to modify longstanding agricultural practices.

The most apparent issues associated with this cumulative assessment, if you go to the CD-ROM and pull down all the data files behind the written text to look at what's there, it becomes readily apparent that this is a data-intensive process. One of my concerns

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since day one has been is the appropriate data available to be able to do the type of thing we're asked to do in a cumulative assessment; and then to follow on to that from the data that is out there, are we using it appropriately. Are we looking at it in the right manner, are we taking the information that's there and utilizing it into the models and tools in the most appropriate manner.

Our written comments to the SAP, which were circulated, reflect a small level of frustration in that they are preliminary pending the results of the review of this comment will be writing extensive comments relative for the March 8 comment period to capture both what's discussed today and other issues that are being brought forward through our own internal review process. And would I hope that both the Agency and the SAP would take those comments them in the spirit that they were given. They're meant to be constructive and in a manner of continuing a dialogue with the Agency to ensure that, as we move forward to making the final discussions, we're doing it in the best possible way.

Having said that and the major points, the general points, in relation to the preliminary OP exposure assessment that you had you before you, there's some general overriding questions that I have to answer to my membership. And these are my words not necessarily the

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reflection of the IWG. But it builds upon their comments.

First of all, does a preliminary OP cumulative assessment utilize the existing data in the appropriate manner. I've got to be able to tell my membership it does and understand how you got to the points that you reached.

Are the methods used appropriate to support the risk endpoints identified? If we're looking at brain cholinesterase level and using different acute endpoints to look at what drives the risk equation, if this is appropriate, how do I explain that to my membership.

And probably the last and most important to my membership, because we're the people that use these products, we are the people who are exposed both occupationally and through our field interactions and often times through being on the farm with the products as they're used, is the assessment appropriately conservative to be protective without overstating risk to the point of taking our tools away from us unnecessarily.

Having given you that general background, what I'd like to do is bring the rest of the group up that's going to be making presentations on behalf of IWG. The first will be Dr. Jeffrey Driver from Infoscientific.com, Inc., followed by Dr. Jack Zabik from Dow AgroSciences. The other participants in the process are identified on

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your agendas and will come forward during the appropriate panel.

I would be happy to answer any questions, but I assume I'm not going to get nearly the technical questions that Jennifer got.

DR. KENDALL: Mr. Botts, I'm assuming that you were part of working group that developed the January 31, 2002, comments to the panel here on behalf the Food Quality Protection Act Implementation Working Group; is that correct?

MR. BOTTS: Those are the ones that we submitted on behalf of the IWG; right.

DR. KENDALL: Okay. And then the next several speakers will build on this document.

MR. BOTTS: Will build on that document, yes, sir.

DR. KENDALL: I was particularly impressed in my review of it with your summary. And I'm assuming that your additional speakers will elucidate how you came to the summary recommendations.

MR. BOTTS: I assume so.

DR. KENDALL: Any further points of clarification for Mr. Botts? Thank you, sir.

Mr. Driver. Welcome. Please state your name and affiliation for the record.

DR. DRIVER: Yes. My name is Dr. Jeffrey Driver. I am a

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toxicologist by training with Infoscientific.com. We've been serving as a consultant to a variety of industry groups over the years, and I'm happy to be back for yet another presentation.

DR. KENDALL: Welcome.

DR. DRIVER: The presentation, you have a handout. I'm shifting gears a little bit so if you could just be patient with us. I'm focusing in on the residential component of the cumulative risk assessment. Some of the comments that I will make will be overarching in terms of statistical issues and other issues applicable really to dietary and drinking water as well in the overall assessment.

My comments focus on the residential and the role of one particular group, the Residential Exposure Joint Venture, the REJV, in providing critical information for doing scientifically based credible, if you will, calendar-based modeling of residential product use and exposures.

The REJV is conducting a 12-month, a temporal product use survey. This is a representative survey instrument across the United States. Thousands of U.S. households involved. It is a diary instrument that people use to record, literally, each pesticide product they use during the course of each day of each month for 12 months.

Obviously, that's an ambitious effort to maintain an adequate

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sample size of participants for a 12-month period. There's a nationally recognized survey firm, NFO, a worldwide group who is conducting the survey. They have experience with temporal survey instruments.

The records that people are keeping in these diaries provide some very important critical inputs into the residential component of the modeling effort that EPA has put forth. This includes things such as the site of application, the method of application used, the frequency and timing of the use. Again, since we're doing temporal, calendar-based modeling, obviously, time is a critical element. As we said before in previous presentations, time, space, and demographics are three categories that we want to maintain consistency across individuals and within individuals in these simulations.

This survey is designed specifically for probabilistic calendar-based modeling. In my opinion, and that of the REJV, it's really required, in fact, for calendar-based modeling in the same way that CSFII you have to have some fundamental survey instrument to do dietary or drinking water. CSFII has been serving that purpose, albeit with some limitations, again with two or three diaries. But here we have an opportunity to have a 12-month diary profile for a statistically representative sample of individuals.

The survey started -- we had to go through a pilot process,

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obviously. That was a three-month pilot. We started the did definitive survey in May of last year. We currently have May and June data sets that have been processed and are data based and we have an ongoing dialogue with EPA, CAL EPA Department of Pesticides Regulations, and Health Canada, regarding the results of those months that we have. So the data are coming in month by month.

Just to give you an overview of where these data fit in specifically. One of the key aspects of any residential assessment is focusing in, especially if you want to be more realistic is focusing in on which products people actually use. So when people record this diary, or fill out the diary, the key index is the EPA registration number. They record the EPA registration number of the product they're using as well as the product name. So they give us a way to check in case there's an incorrect entry for the registration number.

Obviously, with that information, you can then link it to other data bases that give you the active ingredient information, label instructions, et cetera.

The treatment interval. When you use a product, based on efficacy of the product, pest pressures that you're dealing with, obviously people may use a similar product frequently throughout the course of the year. It differs by geographic region and pest pressures

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that are indicative of different regions, and the conditions that support pest populations. So that treatment interval when you think of calendar-based modeling again is very, very important.

Household-related information, what exposure scenario does it fit into. You're applying it to a lawn or ornaments or pets, et cetera. That information is captured in the survey. Obviously, getting an idea of the proportion of user versus nonuser of products in the U.S., whether it's a professional or consumer-applied product.

The use-related information. You can just go up to the right top there, Jack, and click the stop button, the left top. My apologies.

Use-related information. You can see on the slide. Demographics. Obviously, you want to understand the geographic location, age, gender, information about the household's presence or absence of children, entire profile of the household members. I had mentioned method of application. That's key, particularly, looking at applicator exposures, seasonality of the use, day of week. There are differential probabilities we find with weekend and weekday use with different product use or categories.

The next bullet is very important. I'll hammer on this a couple more times. Co-occurrence of product use. When you start looking at upper percentiles of these output distributions for cumulative risk

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assessments, aggregate assessments, you start and you need to drill down and figure out what's going on. You find out that people are using more than one product not surprisingly. And while that can occur, you need to associate a realistic probability with the co-occurrence of use. And this survey estimate gives you an empirical basis to derive that probability.

The annual number of uses. That's another input that goes into this product use event allocation across the market share. Obviously, you want to accurately represent the proportion of people using the products and who those people are.

The current status. As I mentioned, the definitive survey was initiated in May of 2001. Diary results are being reported monthly, processed monthly. The May results involved greater than 14,000 pesticide applications from greater than 6,000 U.S. households. Data files are from compatible for use in CARES by the REJV member companies.

Next slide. If you could look at your handout it would probably be more meaningful than this Powerpoint. This gives you an idea of just some of the data fields that we have access to that we can process. If you look at the top, obviously, each person has an NFO ID number on the top. Starting with demographics, this example happened to be a

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white female from Michigan and some associated information.

Under that is the initial inventory that this household had in place in their home when they started participating in the survey. These are the products they had in their garage and their closets, et cetera.

Then you have this application section. Obviously, they are recording the month, the day. This co-occurrence is our derivation. You can see there were three co-occurring events, if you will. There were three situations, three days. This happens to be July, August, and September. Three occurrences where more than one product was use. We know exactly which products they there, where they applied them. We can attached the associated method of application, label rates, et cetera, to derive expose estimates for this household.

This give you a feeling for the kind of information that the survey provides.

And that is my last slide. Jack Zabik will now follow-up with some work that we're doing with the CARE software that takes information like the REJV is eventually obviously is an ongoing survey. But the CARES software, we're hoping to use as a constructive tool to provide EPA and put on a cumulative risk assessment.

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DR. KENDALL: Any points of clarification? Dr. McConnell.

DR. MCCONNELL: I have one quick one here. I was fascinated by your presentation. I have one question. If I were asked to do something like this, I would find it incredible task just with all the other work I have to do. How do you get people to do this? What is the incentive? How do you get them the on that 11th month to be as careful as they were the first month?

DR. DRIVER: There are a variety of features to the survey instrument. First of all, there's a screening process. By the way, there's know incentive. This is a voluntary process, believe it or not. The National Family Opinion Worldwide Group has decades of experience of doing these types of surveys. They have North America's largest pre-recruited panel of survey participants. So they have a large sort of standing group of people who, in concept, will agree participate in surveys of different durations, different purposes, et cetera. There's know monetary incentive here.

What they do, obviously, is select a statistically representative sample of these people through a screening process. We're focusing on pesticide users I should point out. You don't want to waste people's time for 12 months of the year if they really are not users of pesticides. There are some quantitative definitions of what we use to

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define a user versus a nonuser.

You also, obviously, want to make sure your survey can differentiate. Are there any demographic or statistical differences between users and nonusers to make sure that you've picked people that are representative or that you know why they're different from nonusers.

Anyway, the process is the own person's interest in this subject, if you will, biases, not withstanding perhaps. But again NFO representatives have done this. They really have what they feel are statistically representative samples. What you do is you have to over sample dramatically at the beginning of a survey like this. You might start out with 15,000 house holds. At the end of a 12-month period, you may end up with only 300 who have finished all 12 months.

However, partial month or partial year people, you know, people who complete surveys, still valuable data there. If you've completed say 9 of 12 months or if you've completed maybe 3 of 12 during a high pesticide use season, you still want to look at those data and glean whatever value you can.

But what we do want for the calendar-based modeling is a static sample of a representative number of households at the end of 12 months. So you have to do some dramatic over-sampling.

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DR. KENDALL: Thank you.

DR. DRIVER: That's why it's very expensive.

DR. KENDALL: Dr. Portier.

DR. PORTIER: I sincerely hope you don't get a 99-percent dropout rate. That would be catastrophic in terms of the actual data.

I applaud the survey and the idea of doing a survey. But let me get to the practical matter at hand. What does this have any bearing on our discussions about EPA's cumulative risk assessment? You haven't shown me any examples of the real analysis of the first few months of the data. Are we going to see that?

Do any of those data violate or support any of the assumptions EPA has done? Will we see some of that?

DR. DRIVER: Well, you know, it's a timing issue quite frankly. The survey was initiated in May. Obviously, we have two-months worth of data so far. The answer is, yes, we will be sharing the information with EPA and hopefully the panel, examples with the panel. We hope that might happen at the next meeting. For us maybe at the end of April beginning of May. I think it's a timing issue.

We're trying to bring these data to bear as quickly as possible for EPA's August deadlines. There are just logistical issues in doing that.

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Do we think the data are applicable? Yes, we do. We've been looking OP use that we have months for, data for rather, in May and June. We do see use of disulfoton, other compounds. So we can start to look at how the frequency of use reported and the products that are being used compared to EPA's market share estimates and the frequency.

We haven't been able to figure out exactly how EPA's assessment is estimating use across the year. We need to figure that out. And then we'll be able to use these data, hopefully, to validate or evaluate the predictions. But we're working on it. It's work in progress.

DR. KENDALL: Dr. Freeman.

DR. FREEMAN: Jeff, I was wondering whether the people who were doing the survey have it written in Spanish to reach the Spanish-speaking population.

DR. DRIVER: The Hispanic population. NFO is definitely sensitive to that issue. My understanding there is a multilingual opportunity there. I'd have to get back to you on that particular. I know the issue came up originally. I think the only demographic strata that may be underrepresented for reasons that it is in the U.S. census and other groups, might be the Hispanics and African Americans in

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certain socioeconomic strata. But I can get you a response to that later.

DR. FREEMAN: Yes. The other thing on the demographics, particularly, in terms of the cumulative risk assessment that we're dealing with now, did they, also, collect the age of the children in households?

DR. DRIVER: That's correct. Yes, age and gender.

DR. KENDALL: Dr. Herringa.

DR. HEERINGA: Yes. Thank you very much. It caught my attention definitely when you started talking about population-based collection here. I have several questions.

Has NFO provide you a sample design document or a study protocol description that you could share with the members of the panel?

DR. DRIVER: I certainly will make that request.

DR. HEERINGA: I think that will be very, very helpful. The second question I had, and I think you've answered and that is: From their large prerecruited panel, which has some selectivity in it already, they have sort of stratified through a screening process intensified the sampling of people who have some propensity to use pesticides.

Is there any oversampling of farm communities, farmers, farm

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families, orchard growers, greenhouse operators?

DR. DRIVER: Good question. We considered that issue. There are monetary restraints in dealing with the survey. Our goal was initially to try and be representative on various criteria: age, gender, geographic region. There are several others. But, again, getting at higher use subpopulations, we considered that but it was cost prohibitive. We figured that was a likely follow-up opportunity for individuals or other groups to sponsor surveys that focused in on those.

DR. HEERINGA: Also, if you haven't done it already with NFO, I encourage you to preserve the results of this screening.

DR. DRIVER: Yes, we have.

DR. HEERINGA: That is your only link back to the population-based activity use patterns and other data sources like human activity use pattern survey.

DR. DRIVER: That's a very good point.

DR. HEERINGA: It's going to be quite critical here because you're obviously concentrating these uses in fairly small segment of the population. It's very important, but it's concentrated.

DR. DRIVER: Very good point. And, in fact, we are doing that.

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DR. KENDALL: Dr. Adgate.

DR. ADGATE: Do you know if you can use this with your own model? Is the data going to be formatted in such a way that it will be fairly easy to get this into CALENDEX as well?

DR. DRIVER: The REJV, that we're dealing with is proprietary at this point. The future of it... I think you're pointing out a very good suggestion, and I certainly agree with it. It's not my data to choose to provide it to other parties. So I think it's a good idea.

In my view, I think a survey of this type, this type of survey instrument really in the future should be conducted with Federal money in an analogous way that we're doing the CSFII. I think there's an opportunity here. If we're going to be doing calendar modeling in the future, why shouldn't be we collecting some type of survey data for residential product use in the same way we look at dietary. And that would perhaps make things publicly available in a totally transparent way.

DR. KENDALL: Very good. Dr. Bull.

DR. BULL: Thank you. Interesting project. I had one real quick question that related to some things brought up a minute ago. I notice in your list here you have a lot of products that are not OPs.

DR. DRIVER: Oh, yeah, in that example.

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DR. BULL: Yeah. And the data base is apparently more useful than just OPs as well. What about these phased-out products? Are they, also, captured in here?

DR. DRIVER: You bring up a couple of interesting point. What about phased-out products? What about new AIs and their products in the future? We've contemplated that. That's part of the ongoing dialogue with EPA, CAL EPA, Health Canada.

With phased-out, with both categories, our current thinking is that we would use relevant substitutes, surrogate products, that are in the data base.

Well, let me qualify first. The phased-out products in the context of the cumulative risk assessment, they're not included, diazinon, chlorpyrifos. There are some phased-out or already removed actives that are not included in EPA's cumulative risk assessment. We wouldn't necessarily use those products unless there were substitutions. If there were other OPs that could be credibly substituted for those products's uses, then we would pick surrogates for that purpose. And the same way with new AIs. You pick surrogates that exist.

DR. BULL: I'm mostly concerned about the fact that if there's any place that the phase-outs are going to have a longer life than they

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will in open commerce is in somebody's garage.

DR. DRIVER: That's a point to bring up.

DR. BULL: I've know people that have things that have been banned 25 or 30 years ago still in their garage. And it should be part of a cumulative risk assessment. My question is: Are you collecting that kind of data in these inventories for each household? If you've got that, then you've got --

DR. DRIVER: Yeah. The inventories reflect what's really there. So you do find phased-out products. I think again, you know, all modeling should be as simple as possible but no simpler. You do have to prioritize what you include in these cumulative risk assessments. I mean, in a way, you could argue this type of accounting system would give you a more accurate -- you know, you could use the inventory as is and do some great empirically based modeling and that's fine.

There are, also, practical reasons why you have to narrow down the universe of products and labels that are registered for these types of assessments. That's kind of a practical reality, I guess.

DR. KENDALL: Any further points of clarification? Can we move forward? Thank you, Dr. Driver.

DR. DRIVER: Thank you.

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DR. KENDALL: Very much. Dr. Zabik, welcome.

DR. ZABIK: Jack Zabik. AgroSciences on behalf of the IWG and SSPA. I want to thank the SAP and EPA for a chance to comment. What we're here today is to give an update on where we're at with an OP case study that we're conducting using the industry CARES cumulative risk model. Go to the next slide, Joe.

And I'll share credit with those who are really doing the work on this. And I have to say that we really look at this as building upon EPA's tremendous effort. And perhaps it would be most appropriate to go back to some of the slides shown earlier of all the EPA folks that have been involved in putting together this assessment because we're really building and refining on what they already done, which is a tremendous effort.

What we planned to do with this case study is, first, a national dietary assessment. We'll first go through, or actually are in the process of going through, and rerunning the assessment with the EPA inputs. Then we're going to go back and refine these inputs using processing information which we feel is more appropriate. Also, there was a number of crops that were included that did not have tolerances for us so we'll go back and refine based on that.

With residential, given timing, et cetera, we're going to focus in

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on Region 12. Region 12 represents Florida. And we're going to look at all 9 OPs used in this region. And we think this is a good region because of the intensive use down there. It's year round. Many use patterns are incorporate here.

This simulation will be based on refines inputs. We'll correct for some errors in label application rates, some scenarios that don't really exist, nonregistered uses, and also hit co-occurrence probabilities.

The methodology for CARES in this assessment will to be use a reference population which is a sample of the U.S. census. We use statistics to match to other key data bases such as CSFII.

The CARES dietary module based on 365-day profile of the consumption derived from CSFII on temporal and demography matching criteria such as age, gender, et cetera.

The CARES residential module will include product use event allocation that allows for co-occurrence probabilities and, particularly, incorporation of the data that Jeff just discussed, the REJV survey data which gives us really good longitudinal understanding.

The 365-day profiles maintain geographic, demographic. And temporal specificity. And one thing we think is really key with this

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assessment is output analysis which includes both contribution and sensitivity.

Some of the software features that we think are key is the modular design. It makes it easy to adapt and expand to accommodate new methodologies or new situations required for an assessment. This includes things that we think are very important such as moving averages, being able to easily correct errors and, also, using alternative data sources such as REJV.

The data base engine for this allows for input and output data file management, so you can see what type of data you're asking and how it's being used, and has import export features.

This case study which is well underway is going to be submitted to the EPA by the March 8 deadline. And, then, it's anticipated that the CARES Version 1 software will also be submitted to EPA in March for SAP review in April and May.

One of the areas we really want to look at this morning is the whole issue of contribution analysis. If we look at this example of EPA output which is for Region 12 for children, it gives MOE result and methamidophos equivalents. And one of the key problems we find with this is not being able to determine what the key drivers are to this assessment. And, of course, without the key drivers, it's very difficult

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to make risk mitigation decisions.

If we go to an example of the CARES output, shown here is an output across all percentiles by dose. We can, also, do exposure. And the key point here is you can look across the entire percentile range and then pick the percent you're interested in and drill down from there to determine what the key drivers are.

And this is important from two aspects. One is from a QA. aspect. Obviously, you want to be able to determine if there's any unrealistic scenarios driving the assessment. For instance, if you're adding up exposures and the exposures add up to more than 24 hours for a day, then you need to be aware of that. Also, it's obviously, key to be able to drill down for risk management decisions.

If we look at the next slide, this is really focusing in on a narrower band of percentiles. Again, this is looking at dose. But we could look at exposure for the different routes. And from here, you can pick a very narrow slice of the percentile to drill down even farther.

And this is really a top-level contribution look. And here you can see that we're looking at the percent contribution either by chemical, source, or route. And this the capability of this program allow us to drill down even farther. For instance, with residential,

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we'll be able to drill down to what scenarios may be driving the assessment, what compounds might be driving the residential assessment, or other co-occurrence issues.

Likewise, with dietary, you'll be able to look at what specific commodities are driving the assessment or if there is a particular consumption pattern that is driving the assessment.

That really wraps up what I have to present this morning. I would like to make everyone aware that there is a web site you can look at for more information on CARES. It's alfacares.org. And as you know, there are some additional attachments that we provided to give more information on CARES.

I would like to thank you everyone for their time, and I'd be happy to answer questions or at least divvy them out to key people.

DR. KENDALL: Any questions for Dr. Zabik? Dr. McConnell.

DR. MCCONNELL: I have one question. I applaud you for instigating this exercise. But I wonder how I am to use it in my exercise this week. It's all in the future. What is in it this for me today?

DR. ZABIK: I guess this gets back to something Jeff commented on, which is timing. We have been moving we very rapidly to get the software finalized and out and get this case study

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completed. The software will be available later this year. It's publicly available. And we're working to that extent to get it out. And the case study, we'll put into the docket by March 8. It really comes down to a timing thing. Obviously, we would like to have it out right now.

DR. KENDALL: Dr. Driver, you need to use the microphone.

DR. DRIVER: We're thinking that what we can hopeful do is present the CARE software, this will be the end of April, some of the panel members may not be at that particular meeting. But we will be able to share the results of the case study at that time. It's a race against time for all of us.

DR. KENDALL: Thank you. Dr. Roberts.

DR. ROBERTS: A quick question. On your case study, in terms of your ability to incorporate your REJV data, you have two months of data; is that what you're plugging in or one month or how are you going to get this? I'm wondering how you're to get this just in a couple of months.

DR. ZABIK: Yeah. I think in that case we're going to, because of timing considerations, we're going to give a specific example of how the REJV data can be very helpful but it won't be totally incorporated into this assessment. And that is both a timing and, also, this whole issue of proprietary.

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DR. DRIVER: One of the aspects of the CARE software is to take the major survey data bases that are used statistically match them. Our reference population in CARES is a statistical sample of the U.S. census. Based on demographically criteria, we match those individuals to the individuals in the CSFII. Our goal is to also similarly match people to the REJV survey participants.

For purposes of EPAs decision-making, what we're hoping we can help with -- you know, summer months are peak-use seasons for some of the OPs. So we will be able to look, I think, some good examples as Jack mentioned.

DR. KENDALL: Dr. Zabik, you were, also, part of the Food Quality Protection Act Implementation Working Group.

DR. ZABIK: Yes.

DR. KENDALL: And you were part of development of the document dated January 31, 2002.

DR. ZABIK: Parts of it.

DR. KENDALL: I'd like to read this for the panel. The first sentence in the summary, "EPA has made tremendous progress along a difficult road into uncharted territory as it has developed the methodology for cumulative risk assessment and applied if to the organophosphate pesticides." Do you stand by that statement, Dr.

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Zabik?

DR. ZABIK: Yeah, I think it has been a tremendous effort.

DR. KENDALL: The final sentence in that summary is, in quotes, "The sound methodology developed here provides the firm foundation for policy decisions yet to be made." Do you stand by that statement, Dr. Zabik?

DR. ZABIK: Having not wrote that statement specifically. I mean I'll give my opinion. I think that this has been a tremendous effort. But I think there are clear areas for refinement. And this is what we're trying provide with the CARES case study is looking at some of both the errors that have been made in the assessment and, also, some methodology issues and refine that and move forward and build upon what has already been done by the EPA.

DR. KENDALL: Excellent. I commend you. I'd like to one additional question. What is the level of interaction with the Agency as you're developing this case study? Is it high? Medium? Low?

DR. ZABIK: I'd say high and very good.

DR. KENDALL: Excellent, excellent. I thank you. Dr. Portier. No? Go ahead.

DR. PORTIER: Two questions. Is the CARES software, even though being public available, is source code going to be available?

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DR. ZABIK: I think I'll refer that to my good friend, Jeff.

DR. DRIVER: All of the source code, the code associated with the methodology, will be available. They are third-party proprietary tools that get used in these software packages. We don't have access to the code. These are some things like graphing features and the underlying data base engine. Just like with Microsoft Access, you're not going to have access to all of the source codes. So it's not all 100-percent available, period.

DR. PORTIER: But the third-party software that are available are all general tools software like data base management, like graphics, like statistical analysis tools.

DR. DRIVER: Yeah. Everything except the data base management engine is a proprietary too. Again, I don't see that prohibitive in any means. What's real important is the code associated with the actual algorithms and the methodology to use to transform any data and estimate the output as well as the Monte Carlo sampling schemes, random number generation.

DR. PORTIER: In one of your bullets you pointed out that the CARES residential module includes a product use event allocation procedure that allows for co-occurrence probabilities. Can you give me some idea about what you mean by co-occurrence probabilities and

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how you're using them in this module, especially for the example that was just shown?

DR. DRIVER: Well, if you think about a 365-day profile that you're trying to create for each individual in a given subpopulation or the overall population, obviously, there are probabilities associated with the likelihood that an individual will use a product to treat their lawn and on the same day, any given day during the year, also use a second product to treat another site, for example, ornamentals or to use the same products on multiple sites. You might mix up a batch, treat your ornamentals, your lawn.

So that's what we mean by co-occurrence, using the same product on multiple sites, using multiple products on multiple sites. Those are the things we're trying to get at. Because, obviously, you're again, trying to reach credible estimates of exposure, particularly at the upper percentiles. And I think now the 99.9 is highly controversial in the sense that we don't have robust data to support these extreme percentiles. And if we can't do contribution and sensitivity analysis to get at issues like co-occurrence, we can't make credible decision. I think we've got to be careful about.

So what I mean by co-occurrence is something someone using, again, multiple products for multiple products on the same day or the

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same product for multiple sites on the same day. You need a survey instrument to derive the probability of that.

DR. PORTIER: So your co-occurrence probabilities are not, in fact, longitudinal; they are in fact co-occurrence probabilities on a single day times...

DR. DRIVER: That's correct. Except you're maintaining -- you can create a probability profile for an individual across time. So --

DR. PORTIER: I'm curious --

DR. DRIVER: -- you do get a temporal structure.

DR. PORTIER: -- longitudinal co-dependence -- co-occurrence probabilities. Do you -- have you used them in the example we're looking at here?

DR. DRIVER: No. No, we haven't.

DR. PORTIER: And if you did, how would you do it?

DR. DRIVER: We haven't yet. And as I told you, you know, this is race against time if you will. We're developing the methodology, working through case studies where we have used it. I have not shared at this presentation.

DR. KENDALL: Thank you, Dr. Driver. Thank you, Dr. Zabik. We really appreciate your comments. Mr. Botts, I just wanted to tell you, sir, when you sat down, you said you and your group would

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achieve your goal in 45 minutes. And you have indeed done that, sir, and I thank you for doing what you said you were going to do.

At this point, we're right on scheduled. We will take a break for 15 minutes and reconvene at 10:45.

[Break taken.]

DR. KENDALL: Okay, we will reconvene the meeting. We are in our public discussion period. And the next registered speaker is Adam Goldberg. Mr. Goldberg.

MR. GOLDBERG: Good morning. My name is Adam Goldberg, and I am a policy analyst with Consumers Union. These comments are submitted on behalf of Consumers Union and the Institute for Environment and Agriculture. And as was eluded to earlier, much of the credit belongs to Dr. Charles Benbrook for the comments.

We have, also, submitted them in written form. But I'm sure you haven't received them yet from the EPA staff. The written comments contain additional information beyond what I'm going to present today. And they are much more expansive.

DR. KENDALL: Very good.

MR. GOLDBERG: Members of this Panel know all to well that it has been a long road to the this point -- your review of a near-final cumulative organophosphate risk assessment methodology is now

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nearly final. This is your 12th meeting focusing just on the OP CRA and or the selection of an appropriate toxicological endpoint for the OP CRA. We appreciate your efforts and your durability.

While the Agency has not been able to accommodate all your suggestions and requests for more elaborate analytical approaches, they have responded well in our judgment to the most important technical recommendations and suggestions regarding how to assure that the outcome of the future OP CRA is based on the soundest possible scientific methods and data.

A measure of the major progress made by EPA over the last five years is reflected in the narrow scope of most of the questions you have been asked to address during this meeting. At last, the end is in sight for the phase of the process, leading to a point we wish to emphasize. It is time for EPA to move from the methodology development phase cumulative OP risk assessment process. It is time run the numbers and to progress to the risk mitigation phase.

We applaud for the OP risk mitigation actions taken thus far. Likewise, some OP registrants deserve recognition for putting public health before profits by voluntarily agreeing to phase out high risk residential and urban uses. But more needs to be done as is abundantly clear from a review of the results of the December 2001 Cumulative

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OP Assessment.

Accordingly, we hope that your report will both provide guidance to the Agency regarding where and how it can further improve the technical foundation OP-CRAs while also stressing that the underlying methodology and data bases are sound and will support refined assessments of the relative contribution of risk from various OP crop combinations.

I'd like to briefly touch on the role of BMDs in setting the size OP risk cup. Our written comments are more expansive on this point.

Much will be said during this meeting on the Agency's proposed estimates in uses of benchmark doses. Without doubt, the last remaining critical science policy judgment EPA must make before moving to the risk mitigation phase is determining what level of exposure for children is consistent with a reasonable certainty of no harm, the basic standard imposed by the FQPA as EPA reviews existing and sets new tolerances.

This is a cautious and health protective standard. It is stricter than the benefit risk balancing standard driving EPA decision-making before August 1996. Note the standard calls for a reasonable certainty of no harm, not some level but heretofore acceptable level of harm.

Based on past Agency actions and current FQPA science

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policies, as case could be made for three approaches in establishing the size of the cumulative OP risk cup and/or minimally acceptable MOEs.

One, the acute population adjusted dose of methamidophos, the reference chemical. Two, the benchmark dose for methamidophos used in establishing relative potency factors along with a standard 100 fold safety factor plus an additional FQPA safety factor. Three, a weight-of-the-evidence approach taking into account all data and knowledge of methamidophos toxicity including both its acute cholinesterase impacts and developmental impacts to the extent they are known.

The second approach was used in the analysis reported in the December 2001 methodology report, although no decision has been made regarding the need for an FQPA safety factor. Hence, the results in the December 2001 report reflect OP-CRA outcomes as if EPA decided no additional FQPA safety factor is needed. This is an extremely unlikely outcome.

We urge the SAP in the report following this meeting to offer the Agency its recommendations regarding whether and how BMDs should be used in establishing the minimum MOE that the Agency should insist upon for the child at the 99.9th level of exposure. The

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SAP will no doubt get another opportunity to review and comment on the approach EPA ultimately chooses to follow.

But in the interest of reaching closure and avoiding further delay in reaching the risk mitigation phase, we hope you will speak to this critical issue in this round of review and comment.

I'd like to discuss relative potency factors for a moment. We have supported the Agency's continued refinements in its establishment of RPFs and considered the current BMD approach to be a major step forward. We understand why over the last two years the SAP has urged the Agency to move in this direction and hope the SAP is pleased now with the Agency's basis for setting RPFs.

Industry scientists have argued and may again assert during this meeting, that a 10-percent inhibition brain cholinesterase function is hardly distinguishable from natural variation or from background levels. They instead will likely argue for a BMD20 reflecting a 20-percent inhibition of cholinesterase function instead of 10 percent.

If the purpose of BMDs is just to establish relative potency factors, it would make sense for the Agency to chose a point along the lower end of the calculated BMD dose response curve for each OP that is as statistically robust as possible, hence minimizing the chances of error in the magnitude of RPFs.

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Accordingly, the Agency should make a determination of whether the confidence limits around RPFs would be significantly narrower if base on the BMD20 as opposed to BMD10. We doubt that moving to a BMD20 from a BMD10 would affect statistical reliability very much. Plus, even if the Agency made the change it will mater little in final RPFs. Indeed, the Agency could even calculate an average RPF based on several points long the BMD curve. The results would be very similar to BMD10 or BMD20 approach.

While it might be defensible to use a BMD20 in setting RPFs, EPA cannot say with a straight face to the American public that a 20-percent inhibition of brain functions represents quote "no harm." It is even difficult to make this case with BMDs based on a 10-percent inhibition. And EPA should seriously consider a lower limit as has been advocated earlier by NRDC.

I'd like to turn, now, to the PDP. In CU's extensive analysis of dietary risks based on the same PDP data supporting EPAs OP-CRA, we have consistently found that just a few food pesticide combinations account for the largest share of risk. EPA sensitivity analysis lends strong further support to the conclusion that relatively few food pesticide combinations are true risk drivers and that regulatory actions targeting them can eliminate most OP dietary risk while leaving largely

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unaffected the majority of OP food crop uses.

To estimate the degree of OP risk reduction achieved through implementation of the FQPA, EPA should also complete and publish an official FQPA OP baseline assessment of risk reflecting the frequency and residues found in food in the mid 1999s.

EPA decided to exclude from it's most recent OP-CRA all illegal residues found in food by the PDP as was discussed earlier during the comment period. CU has analyzed the share of total OP risk accounted for by illegal residues in PDP data through 1999. We concluded that illegal residues account for a little over five percent of total risk.

If EPA were to include these residues in future OP-CRAs, we would expect a comparable approximate 5 percent increase of risk levels across the exposure distribution. Put simply, we believe that excluding illegal residues from the OP-CRA is bad science and inconsistent with the clear language of the statute and we'd be happy to discuss at some other point, individually or collectively, the data that we've gathered on illegal residues through PDP data if it would help the members of the SAP.

Thank you for the opportunity to provide these comments. We look forward to your report and forth coming applications of the

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Agency's cumulative OP risk assessment methodology.

DR. KENDALL: Thank you, sir. Any points of clarification from the Panel?

DR. BRIMIJOIN: I have a question, although I hate revealing ignorance in public. I think I've got to get clear on this and maybe somebody else does as well.

It seems to me that there are two ways to use benchmark dose data. And one is just for comparing the relative potency, the relative toxicity, of a number of different compounds. The other is the regulatory decision about what is a starting point or what is a safe level.

DR. KENDALL: Right.

DR. BRIMIJOIN: It seems to me that these two points are being grossly confused in the current discussions, both the comments we heard earlier this morning from Dr. Sass and the present ones. If that's not a confusion, if both of these individuals are correct that in going to a central measure of toxicity like BMD10 or BMD50, even, we are, in fact, recommending that this is not a harmful level of exposure and that this would be a good point, a safe dose, to regulate from.

If that's correct, that needs to be made clear to me and everyone

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right now. If it's simply a matter of deciding whether compound A is 3.5 or 4.7 times more potent that compound B, then the decision should be made where do we have the best dose response date, where can we make the tightest analysis. And we don't need to pick particularly low dose just to make people feel comfortable that, oh, we're picking a dose that's nearly safe.

DR. KENDALL: Right. Good point. Mr. Goldberg, would you to address that point or question?

MR. GOLDBERG: Well, as one of the previous commentors said, I'd love to be able to turn this to somebody who is a little more knowledgeable than me. So I'd like to ask Jennifer to address this.

DR. BRIMIJOIN: Actually, I think somebody from EPA ought to comment on this.

DR. KENDALL: I am going to ask EPA would they like to respond. Margret?

MS. STASIKUWSKI: Yes, I will ask Dr. Vicki Dellarco to respond to the question.

DR. KENDALL: Thank you. Dr. Dellarco.

DR. DELLARCO: We've had a lot of discussions about the benchmark response level that we might use for this class of common mechanism chemicals. When we first went to the SAP back in 2000,

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September 2000, we had to use the ED50 as some of you who were there remember that. And then when we went back and we got Dr. Setzer involved in the modeling, we brought forth the concept of using a slope scaling factor, the M value. And there was a lot of discussion at the September 2001 meeting about the use of M for looking at -- and I'm talking about potency right now, comparing potency. Or maybe going down and using a benchmark 10.

And I believe there's some written comments about using a benchmark 10 to compare potency, and we decided it was the best way to go because of the issues of parallel dose response relationships. So we wanted to go as low as we could reliably to estimate potency in an empirical range of observation. And this, also, happens to be the same benchmark response that we'll use for the point of departure.

That doesn't mean that will always be the case. But for every cumulative assessment that we do, the benchmark response we might use to compare potency may be very different from the point of departure. And in this case it is. There's been a lot of discussion and thought on this.

Do you have anything to add, Anna or Woody?

DR. KENDALL: Dr. Bull, I think you're first.

DR. BULL: This is just a point of clarification and don't

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necessarily need to have an answer right now. But I'm a little confused by this issues we're addressing in cumulative risk assessment by compounds that have common mechanisms and then dealing the FQPA factor which is adjusting for some effect on development. And maybe somebody can educate me as to whether cholinesterase inhibition always leads to developmental delay or some compounds that are organophosphate pesticides also have developmental toxicities because I don't see how you combine those two, if, in fact, the mechanisms for developmental toxicity and cholinesterase inhibition are not related. And there are certainly possibilities of that occurring.

So if someone can tell me that every cholinesterase inhibitor at some level of cholinesterase inhibition causes developmental delays or other reproductive toxicities, I'd be really tickles to know that. But I don't know that off the bat.

DR. KENDALL: Dr. Harry, do you want speak to that briefly? This point keeps coming up. We've been challenged this morning -- Dr. Dellarco, do you want to comment. Dr. Durkin, I have not forgotten you.

DR. DELLARCO: Usually about the sensitivity or susceptibility to this class of pesticides has come up this morning twice. And the issue about the children's safety factor, the FQPA 10X fault factor

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that's under the law. And we will be conducting a separate analysis, pulling together. We are currently pulling together data on cholinesterase inhibition that's been conducted with in utero exposures as well as postnatal exposures. And we will be looking at that and comparing it to the adult data that Woody will be discussing today.

And so the analysis that you'll hear today about looking at relative potency and the point of departure is focused on the adult animal studies. But we will have to do this analysis. And as Marsha indicated and Margret pointed out, we've taken a very careful step-wise approach to get to where we are at today in laying down guidance documents and tools.

And as Marsha pointed out, we will be putting out our final guidance for how you make a decision about a kid's safety in looking at the issue of sensitive and susceptibility in single chemical assessment. That should come out soon. And following that, we will have separate guidance on how you do this in a cumulative assessment where you're focused on a common effect and common mechanism. And we'll put that out for public comment.

So there is some literature on this. And some of these OPs do show some sensitivity. That's been published. And some of them don't. So we're going to have to look at this in total and see what it

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means in respect to the group.

With respect to the susceptibility, I believe that's the issue you raised: What kind of effects can you get in terms of developmental delays and effects on cognitive function? We don't really know. And Dr. Brimijoin can probably speak to this because I believe he's done some work. But Acetocholinesterase is an important neuromodulator during development. It is an important mechanism to look at when you're looking at sensitivity and susceptibility.

DR. KENDALL: Dr. Harry?

DR. HARRY: I think you answered a number of the questions in which the framework to consider in what we're talking about this week. And I think when a number of the comments came up about referencing to the developmental neurotox guideline tests, the answer of saying, one, this is focused on the adult; and, two, that to look for the components for the children's susceptibility is the next step. We need to remember that framework as we're going through today.

I think you're going find it very difficult when you start trying to do this in developmental. One of them is going to be there is a good amount of effort and a good amount of data on the adult. We still have to come in -- I still come in with a question of what's adverse. And you're going to have that even more when you get

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developmentally. We're not going to have that data in the developmental. We're going to have made an awful lot of assumptions based upon the adult data. And I think you're going to need a lot more data and understanding of the basic biology of that to be able to truly make these different.

The other caution I would raise in there of automatically assuming that the developing animal is more sensitive than the adult based upon the two testing guidelines is that your developmental neurotox guidelines are much more intensive than the adults are. You deal with a cognitive functioning. I don't know how much you have on organophosphate on the adult on cognitive functioning or learning component. But you do have that in the developmental.

And you have a number of other components of the developmental that we're sort of still waiting on data on for some validation of those. And that's what was brought up with the Makris Study that 13 chemicals have been triggered. It was still in question about how much more sensitive that testing guideline really was for picking things up.

So you got a lot of other things involved in that developmental aspect that you're going to have to work out before you even get to this point on it. Just to raise a caution on that.

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DR. DELLARCO: Let me just since you mentioned the Makris Paper and that came up this morning. That paper wasn't really intended to look this issue sensitivity and susceptibilities to OPs. And although it was mentioned that the Panel may want to look at it, we'll be more than happy to provide it to you. But it's not really going to get at the heart of the issues on this.

DR. KENDALL: Very well. Dr. Durkin.

DR. DURKIN: Just briefly, there was a point made about the two uses of the benchmark dose; one is point of departure; the other for relative potency. And I think I heard Vicki say that in some cases you may use something like an ED40 or whatever for relative potency and an ED10 or ED1 for a point of departure.

The one thing I think you have to keep in mind with the OPs and any extrapolation of this method to other chemicals. If you have a dose response function or a class of them where potency is constant across doses as in what you had originally done with probative analysis, then it doesn't really matter where you measure the potency, although the variability of the relative potency can vary.

With the OPs, especially the kinds of much more complex model that you have now, relative potency in that sense is no longer a meaningful term. Relative potency will vary with dose. So for the

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OPs, I think you are in a situation that once you decide on your benchmark dose, be it an ED10 or ED1 or whatever, that is indeed the dose or the response level that you have to use to define relative potency. So that at least within the context of your point of departure, relative potency is indeed the ratio of equitoxic doses. And as long that isn't violated, you're going to be fine.

But I think you have to be a little careful about talking about using some other region of the dose response curve for the kind of model you have now, even though your confidence intervals might be narrower, that measure of relative potency would not be appropriate for the point of departure that you may have selected.

DR. KENDALL: Good point. Any further points of clarification for Mr. Goldberg. Thank you. Thank you, sir. Dr. Portier.

DR. PORTIER: Just to make it clear that we've had two sort of disjoint comments about the use of relative potencies and the point of departure. And I want to make sure when we get into the Panel discussion, we get back to this because I may or may not agree to either one of the two.

DR. KENDALL: I intend to do that.

DR. PORTIER: I think that's something we have to discuss.

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DR. KENDALL: We intend to do that. I didn't it's appropriate to do that resolve that right here. It's on the table. I think we understand.

We've have had one additional presenter that would like to approach the Panel. Ray McAllister.

MR. MCALLISTER: My name is Ray McAllister. I am the vice president for Science and Regulatory Affairs for Croplife America. In my work with the Implementation Working Group, it was my responsibility to coordinate the assembly of the written comments which we submitted to you. And I felt it was important to take just a few moments and respond to Dr. Kendall's question earlier on the summary statements and those comments.

He asked specifically about the final statement, "Sound methodology developed here provides the firm foundation for policy decisions yet to be made." Our comments were assembled quickly. And even when you have the opportunity for a lot of people to review, it's not unheard of that someone else reads it and finds a different way to interpret it.

What we intend by that statement is that the sound methodology that comes out of the cumulative risk assessment process that is being developed now must provide a firm technical foundation for policy

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decisions yet to be made. The development of sound methodology is the responsibility of EPA as well as a number of other contributors including in a large part this Panel that the Agency has consulted and also the stakeholders who are involved in providing the data that goes into the risk assessment and who are involved in helping the Agency with interpretations of that information. And that was our intention with that statement.

DR. KENDALL: Very well. Any points of clarification for Mr. McAllister? Thank you, sir.

At this point, are there any other persons desiring to approach the Panel in the public comment period? We allocated an extraordinary amount of time to try to accommodate this. And I was concerned in the early phase of this because I didn't know if we could get through it, but we've moved very quickly.

DR. TOBIAS: Abraham Tobias with Adventis Cropscience.

DR. KENDALL: Welcome.

DR. TOBIAS: In the discussions earlier there were questions asked whether there were data concerning spouse and children on the farm. I'd like to remind the Panel, and maybe to inform the Panel that under Croplife America and several companies within that organization we are running a study. This is a companion to the NCI study which is

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looking at cancer risk for the farmer, their spouse and children. We have done a study. We are in the final stages of completing that study where we will get to the issue of what children and spouses are being exposed to.

From our preliminary study, range finding study, we're not finding much exposure to those subpopulations. And I think our final study will bear out that information and will give the Agency much more information on that front to be able to say that the exposure is very, very minimal or nonexistent. I just wanted to bring up to the Panel that we will be coming up to the table with more data.

DR. KENDALL: Excellent. Is this regional based or national based?

DR. TOBIAS: It's paralleling the study that is run by NCI which was done in Iowa and South Carolina. Excuse me. North Carolina. We mimicked that study, and we mimicked the questionnaires, the epidemiology aspect. If you're going to get into the epidemiology questions, I'm the wrong cowboy to answer those question. So I can't answer those.

DR. KENDALL: We thank you, though, for updating us, Dr. Tobias. Dr. Portier. Just a minute, Dr. Tobias. Do you have a question for him?

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DR. PORTIER: Yes.

DR. KENDALL: Dr. Tobias, can you reapproach the microphone. We have Dr. Portier with a question.

DR. PORTIER: First of all, I'll play nice, Chris. I'll point out that the pesticide study is both NCI and NIEHS just to make sure everybody hears that.

DR. TOBIAS: I apologize. I didn't meat to slight you or anybody else. And it is part of EPA, too. I better apologize to them for making that error.

DR. PORTIER: More importantly, do you have any preliminary data to show us now?

DR. TOBIAS: We're in the final.

DR. PORTIER: Actually look at quantitative numbers and make --

DR. TOBIAS: Yes. We're in the final stages of doing the QA aspects on a lot of these numbers. And plus checking our field checks and everything else so that before we come out with some preliminary information that we, at least, are on a solid basis from the analytical point of view. So we will be ready to give some preliminary information out on that shortly. I can't promise you what date or time.

Let me just plead a little ignorance. I haven't been in touch to

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that for the last month due to some personal things, so I have to bring myself up on to speed on a lot of the issues that we're working with that right now. I am the treasurer for that group, and they do want me to sign some checks. So I will figure out a lot of things.

DR. PORTIER: So in terms of our debate this week there's nothing for us to look at.

DR. TOBIAS: I can try to get you what we did in the preliminary study, our range finding study. And I think we may have some data from the first year of the study because it was a two-year event. We looked at it over two years. And we wanted spatial and temporal issues on the study. So, yeah, I may be able to get some information to you. But I wanted to make sure the Panel did know that and Agency will get that information.

DR. KENDALL: Thank you very much. Dr. Conolly.

DR. CONOLLY: I guess this is a question for the chair as much as anything. We've heard a number of presentations this morning about I think very important studies that are underway, collecting data, which obviously could impact cumulative risk assessment for organophosphates. And we've also heard question about whether information is available in a way that actually let's us usefully evaluate the assessment that the Agency's presented to us or will be presenting

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to us over the next couple days.

What I may be looking for is a bit of guidance here about what our job is. You know, in risk assessment, those of you who have looked at the cancer guidelines recently, for example, it's carefully laid out there how there are default approaches to risk assessment which can be carried on with minimal data sets and much more complicated approaches that require rich data.

And I think we seem to be faced with a similar situation here where we have a methodology that can go forward with currently available data and alternative approaches that will require much richer data sets and which might not be doable today, might be doable in a year, or two years or five years.

I think it's important that this group be clear on what it is we're here to evaluate today. Is it sort of this richness that might be pursuable in the future or looking just at what's on the table today and, you know, what the Agency has to work with today?

DR. KENDALL: I'd like to ask Ms. Stasikuwski to respond to that. Margaret.

MS. STASIKUWSKI: Yes. In my presentation, I described our obligations under FQPA. And we are discussing today the preliminary risk assessment that we need to finalize in the summer of 2002. So we

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are discussing that which you have reviewed, and that's the crux of the discussions this week.

DR. KENDALL: What I see happening, Dr. Conolly, there additional projects underway that can contribute to, additionally validate, and make this whole process more robust I believe. So, again, this is a continuum we're working on. Yet the Agency has certain time lines they've got to respond to and I think our job is to continue to offer and contribute to the acceleration of their efforts to bring the preliminary cumulative risk assessment to the table. And I think they're doing it.

I'd like to ask the EPA -- at this point, this will close the public comment period. And I'd like to ask, and we are ahead of schedule. And we're significantly ahead of schedule. So I'd like to ask the EPA, would you like to procedure with your introductory comments from Dr. Lowit or would you like to go ahead and take our break.

MS. STASIKUWSKI: Just consulting Anna. Are we ready?

DR. KENDALL: The Chair would like to take our break at 12 noon, therefore, we have 45 minutes. Would you like to engage us for the next 45 minutes?

MS. STASIKUWSKI: We're just consulting on time.

DR. LOWIT: We might run a little long but too much longer

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than 12.

DR. KENDALL: Would you like to proceed or we could reconvene at 1. I'm a little reluctant to reconvene. I think a lot of people, Dr. McConnell questioned the point of view of start at 1. I'm afraid people may be traveling in to see the dialogue beginning at 1:30. I would like to ask if you can start and I would like to stop at 12 noon.

DR. SETZER: Well, actually, my only concern was that at 12 noon I might have 10 minutes left and a couple of three slides.

DR. KENDALL: Okay. Then let's do it. Dr. Portier.

DR. PORTIER: I'm going to propose differently in that because this is such an important topic and because people may actually be traveling here at 1 o'clock, not only to hear public comments, not only to hear the Panel, but also to hear EPA's comments on what they have done in their defense of this. I would move unless we have more public commentors or a specific topic we want to discuss now about the approach we are going to take to reviewing this that we close this session until 1 o'clock as stated in the calendar.

DR. KENDALL: It's 1:30. I would --

DR. PORTIER: I know it puts us potentially in a tight spot this afternoon. But, again, this is a very complicated risk assessment, it covers a number of issues, and I'm a little bit concerned about us

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moving too quickly on it.

MR. LEWIS: I think just managing the time, I'd like to comment. I'd really like to see us use the extra hour we have because we do have a tight agenda. And we have notified everyone that this is a flexible schedule, that with the complexity of the issues being discussed and the public commenters that they have to be prepared that it might be 1:30; it might be 1 o'clock; it might be 12 o'clock; it might be earlier.

So I understand your issue, but I've also very concerned that we do have the time. And I think we're going to need if today, so I'd like for us to try to use it. Thank you.

DR. KENDALL: All right. Let's proceed, EPA, and we will reconvene at 1:30. Let's go ahead. That way we will attempt to address Dr. Portier's point of view of people traveling in if they can't get here until 1:30. Let's go ahead and try to move there are your presentation. Is this okay, Margret?

MS. STASIKUWSKI: Yes, we're ready.

DR. KENDALL: Very good. Thank you. Let's proceed.

DR. LOWIT: As we look at time, I'll try to go quickly so I can concentrate on what Dr. Setzer is going to talk about. I'll reiterate the same appreciation to the Panel that you heard and will hear in the next

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few days.

In 1999 the Agency released a document identifying the organophosphates a common mechanism. And, subsequently, we have concentrated on the inhibition acetocholinesterase as the endpoint for the cumulative risk assessment.

The hazard and dose response portion of the assessment has been to the Science Advisory Panel now three times. The first time in September of 2000, followed roughly one year later with a preliminary hazard and dose response assessment, which we'll call the July Document. And what we'll discuss today is the revised preliminary hazard dose response assessment which we'll call the December document.

The hazard and dose response assessment includes 29 OPs that have exposure through either food, water, and/or residential and ongoing as a determination of roles of potency for 3 more: chlorethoxyphos, profenofos, and phostebupirim. Just to remind everyone, to put it in context, we are using the relative tox potency method where each chemical is compared to an index chemical and we are using methamidophos as the index and exposure equivalents as you'll hear in the next few day, of the index chemical are combined in the assessment.

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The toxicity data used in the assessment come from oral, dermal, and inhalation studies tested in rats of subchronic and chronic exposure, and the exact same data in the July Document was, also, used in December. And just for reference, the electronic data set of all the oral cholinesterase data and not only the brain compartment but the plasma and red blood compartments is available on the internet.

We're going to concentrate in the next hour or 45 minutes on four key major refinements. One was the relative potency factors used in the preliminary assessment, the method for combining the cholinesterase data molding of the low dose region of the dose response curve, and also the measure used as a potency determination.

In the July Document, male red blood cell cholinesterase was proposed as the end point. Red blood cell cholinesterase inhibition will continue to be an appropriate endpoint for risk assessment. But RBC was selected primarily based on the availability of a large data base and our ability to consider time course information. And the males were selected over the females for not a very good reason.

In the December Document, the female relative potency factor is based on female brain cholinesterase inhibition were used. And why was the brain used? All though red blood cell cholinesterase is an appropriate end point for risk assessment, the confidence limits on the

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potency estimates for brain were much tighter than those of red blood cell. Also the brain is target tissue for OPs.

Why were the females selected over the males? The sexes were equally sensitive for most of the OPs with the exception of roughly five for which the females were more sensitive. And this is my rode map sign to turn it over to Dr. Woody Setzer who will discuss the methods used.

DR. SETZER: Good morning. I thought I was going to be saying good afternoon.

In this talk I want to do essentially four things not with equal weight. First of all, I want to review the methods that were used in the July draft and bring you up to speed and remind you what we did before and what you all commented on and talk, briefly, about the issues that were raised in the September meeting that we addressed in this analysis and tell you that how we addresses those issues; and, finally, since release of the December Document, I've done work since then and I'll talk about that as it's appropriate during the discussion.

Overall, the SAP supported the approach that we used. In particular, they were happy with the exponential model using multiple studies and time points. And I was happy to see accommodation for using open source software package to do the analysis to facilitate the

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communication and oneness of the analysis.

It was recommended that we look further at the low-dose end of the dose response curve in response in part of some commentors at that meeting. And there's a comprehensive list of all the comments in the cumulative risk assessment available at the web site indicated there.

Just to remind you, in the July Document, which the September SAP commented on, was based on a dose response model expressed here. It was essentially an exponential model with a modification to allow us to estimate an horizontal asymptote. And we were using what we've been calling the dose-scaling factor as a measure of potency in that analysis.

In July, we followed a strategy. We have multiple data sets. And so you've got to figure out how you're going to get a single estimate out of multiple data sets for a given chemical. In July we estimated a value of potency for each individual data set and then used a statistical approach to nested to essentially a sort of a population model to nested data to estimate an overall mean potency.

And the point of this slide here is to indicate that what we have are sort of major studies with individual data sets nested within those studies, and then what we're trying to do is estimate an average

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potency, sort of an average of those studies.

Finally, to estimate the parameters for the model in the July Document, we used an approached called generalized least squares. We assumed the constant coefficient of variation. What that means is variance, within group variance, was presumed to vary according to square of the mean. This is a sort of situation where scientists like log transform their data or when they express variability, they like to talk about coefficients of variation instead of standards deviations.

That's a common. That's a common sort of structure to find for these biochemical data and that was the weighting scheme we used in that analysis.

Also used a sequential approach to fitting. And the reason for this was it wasn't always possible to estimate all the parameters to the data. And, also, we found that occasionally we didn't get -- we weren't able to describe the data with the model given.

The first step was to fit the full model to all the data. And then if we didn't get convergence or estimates to all the parameters or the fit was inadequate, we would repeat the following process. First, set the parameter that quantified the horizontal asymptote to zero, refit to the data set. If it still doesn't work, drop the highest dose and keep going until you run out of doses or you get a good model.

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Here are some problems and issues from the September SAP report. First of all, the approach we used to estimating the horizontal asymptote could result in bias estimates. Remember, we're setting B to zero if something doesn't work right. It turns out that N is sensitive to that estimate of B. So if we base our potency estimate on N and set B to zero, you're potentially introducing some bias.

It was suspected that the weight function used underestimated the variance at low doses and overestimated at high doses. So we needed to revisit that decision.

And, finally, the dose response curves for some chemicals appeared to have a shoulder at low doses; in other words, it didn't drop straight down like an exponential model but was more horizontal for a range of doses before the curve steepened. And we wanted to try to address that.

The changes I want to talk about today. First of all, we changed the way the models were expressed in terms of the parameters. We reparameterized the model. It's essentially the same model we're using; we're just expressing it in terms of different parameters that make the model a little bit easier to estimate.

Secondly, use the reciprocal of the benchmark doses as a measure of potency instead of m as recommended by the SAP. That

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has several benefits. One of them is that the benchmark dose turns out to be substantially less sensitive to the estimate of the horizontal asymptote than is the potency. So we're winners there.

And, finally, rather than fit a model to each individual data set and then combine estimates, we combine the data sets and then fit what's called a nonlinear mixed effects method -- and I'll talk about what that means before I stop talking anyway -- to estimate that model.

One of the problems -- the issue of setting B to zero and then going from there, it was one of the probably two potential sources of the bias in the last estimate that we could relatively easily address. One of the changes we made in this analysis is to use a profile likelihood approach to estimate a value of B that's consistent with the data when we can't estimate is jointly with the other parameters.

The goal there is to identify a value of the horizontal asymptote, well, like I said, consistent with the data. It's plausible. And then condition the analysis on that value.

One of the consequences of adopting of strategy of fitting models to a number of data sets was we have more dose levels available and it's a bit more possible to develop a model to describe the low dose shape of the curve.

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We also changed the weight function. We set the weights to be proportional to the mean value and not the squares of the mean value. That seems to improve the sort of the scatter of the residuals plots. And I'll talk about the more when I give dose-specific detail.

Okay. Let's go through the models, the various forms of this simple model. At the top, I show you the July model we started off with. It's perhaps easiest to understand this first reprioritization in terms of the units involved. This first model we have parameter B and a parameter A. Both of them are in terms of response units. And, actually, partially in response to some confusion that happened among the discussion in the September SAP, it made sense to reparameterize the model to pull out one parameter that contained units in terms of response units, factor that parameter out, and A then has always been the background or the control estimate of the control cholinesterase activity level.

And then there's this parameter P sub B which is a fraction that ranges between zero and one. Makes it a fraction. Which is just this ratio B over A. So instead of estimating B and A, we're estimating A and the ratio of B over A. Same model, just a different approach.

And then, finely, and this is something that I've done since the December release. This looks much more complicated, but it's not

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really. It's just algebraically more complicated. We have, again, the same model but instead of using the slope parameter m, scale parameter m, we reparameterized the model in terms of benchmark dose. And in all the calculations, we've set benchmark response level to correspond to a 10 percent reduction in mean cholinesterase activity.

The main advantage of this is that the estimate of B and D, as we said before, tends to be substantially less dependent on the estimate P sub B. So when we do estimates with this model, we're somewhat more stable numerically.

Advantages of the current model, more stable estimation. And it, also, simplifies computation of the benchmark doses and standard errors since it happens in one computation instead of two.

And just to keep me honest, the parameters we actually estimated were the log of the parameter A, the log of the benchmark dose, and this logistic transform of P. Those are mainly to assure during the estimation process the parameter values stay legal because the software that I was using doesn't allow to put bounds on the parameter estimates correctly. At least not easily.

The model fitting. We use the approach called nonlinear mixed effects models. This is really a rubric for a whole suite of different

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approaches to dealing with population models. The particular approach I used the is codified in a function N, L, and E in the software package R. It's based on an approached developed by Doug Bates and his coworkers. And Doug Bates -- well, who is also the author of the software package.

Essentially, the approach is this. For each parameter that we're estimating, we assume that there is a separate mean value. And in our case, for example, for the background level, we assume there is separate mean value for each sex by unit combination.

Let me digress for a second. What I mean by that is not all our studies used the same units for measuring cholinesterase activity. And it's not always obvious that you can just do a simple conversion to get from one unit to the other because they imply somewhat different methods for measuring cholinesterase activity. It made more sense to keep those sort of separate approaches separated out. And then we estimated a separate value for B and for the log benchmark dose for each sex.

Superimposed on that, we have multiple studies for the same chemical and multiple data sets for each study. And we treat the parameters. We treat each of those sort of individuals levels of the nesting, as if they had their own mean parameter level and they vary

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around. So for example, the mean value for the studies varies around the overall population mean level and the mean level for the individual data sets vary among the mean level for the study. And this is, essentially in somewhat nontechnical language, this is the approach that LME uses.

And, finally, as I said, before, we've used weights based on presuming that the error variances were proportional to means. This is determined empirically. It seemed to work better. It seemed to describe the variation better than did the previous weight function.

We still had problems with getting --

DR. KENDALL: One moment. Dr. Portier.

DR. PORTIER: Simply a question of process for this. Again, this is a fairly complicated analysis that we're looking at and Dr. Setzer is about to go from the description of the model to the description of the methods used to estimate parameters in the model. And I'm wondering if this is maybe not a good point to stop and have questions for Dr. Setzer before he goes onto, again, more complicated and other issues or not and whether my colleagues feel that is a good idea or not.

DR. KENDALL: Dr. Heeringa.

DR. HEERINGA: Just a very quick clarification to this point.

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In terms of random effects in the nonlinear mixed model, you're effectively nesting data sets within studies.

DR. SETZER: That's correct.

DR. HEERINGA: So you've got a nested random error term there. Okay. Just as a little bit of background for me in terms of the numbers of observations we could typically find at each of these levels of nesting at any given data set for a study would have multiple dosing. Would it have replications at each dosing?

DR. SETZER: I'm sorry. There were probably slides from the previous presentation I should have included here. Each individual data set is a complete dose response study. It would be typically three, four occasionally five or more doses at each dose group. You'd have anywhere from 4 to 10 animals. And actually the data reported to us are in terms of means and standard deviations from those studies.

DR. HEERINGA: Means and standard deviations across animals for each dose level.

DR. SETZER: That is correct.

DR. HEERINGA: And then separate data sets for each study if they replicated it.

DR. SETZER: I'm sorry. Yeah, right. The separate data sets normally correspond to different durations of exposure.

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DR. HEERINGA: I see. Thank you.

DR. SETZER: So the study would have been, for example, potentially a chronic study, the number of animals that have gone on study. There would have been serial sacrifices during that. We're talking about brain cholinesterase here so the same animal can't be observed twice.

DR. HEERINGA: Thank you very much.

DR. KENDALL: Thank you. Dr. McConnell.

DR. MCCONNELL: As I understand this, you have multiple data sets and you combine them in your analysis. Do you have minimum criteria, or do you have criteria to say this data set is good enough to use? Or do you take any data set and, because there are some numbers there, you use it?

Where I'm heading is that in any area of science we all know that some data sets are better than other data sets. In fact you might, in looking at five or six data sets, find one of them to be particularly outstanding, one of them to be minimally acceptable. Are all five of those from the minimally acceptable to the outstanding one given equal weight in your analysis?

DR. SETZER: I suppose that's a difficult question to answer completely. Probably the answer is no for two different reasons.

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There was some filtering that went on before we even looked at the data. And we talked about this for the September meeting, that there were minimal standards in terms of adherence to the standards in terms of performance of study and being able to extract the relevant information from the study in a believable way. There were minimal criteria that the study had to ask before I even saw the data.

Secondly, in terms of the actual sort of statistics, one criterion for quality of a study is sort of how tight the data would be for a given dose level. And in general, a study where the data are quite variable will be weighted in a not a very obvious way but be weighted less in the final estimate of the mean than would be a study that had a much tighter estimate of the same value.

So there is some weighting going on based on data quality to the extent it's expressed in terms of a sort of variance and things like that.

DR. MCCONNELL: I think I understand.

DR. KENDALL: Any further points of clarification that really can be held to the completion of the presentation, you think we need to do it now. I mean, Dr. Portier made a good point. If there is a clear need to get definition as to the methodology versus the process, you know, let's do it. If not, let's proceed.

Okay. Dr. Portier.

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DR. PORTIER: I promise. I only have two questions. The first one has to deal with the simple model versus the broader model. Obviously, the broader model, if I'm looking at my notes, goes to infinity effectively converges to the simpler model. Is that --

DR. SETZER: That's the model we've called the expanded model. That's right.

DR. PORTER: Well, as S goes to infinity or as D goes to zero. That's where they become collinear is either at infinity or zero. There's no way to tell the difference.

DR. SETZER: Yes. Well, yeah, effectively, it's the same model. Yeah.

DR. PORTIER: And you've done a number of conversions from arithmetic numbers to log transform parameter estimates, those of which will affect, obviously, not only the parameter estimates themselves but any variance estimates that you put on those parameters. Specifically I'm interested in the parameter PB and its inability to assume a value of zero when you do a log transform to estimate PB. When you go into the estimation phase, we you tell us how you dealt with that issue specifically? It pertains to the other parameters as well, but PB bothers me a bit.

DR. SETZER: Yeah, it's true. We can't get zero, but we can

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we can get something very small. And, in fact, I haven't done anything special with that to deal with the possibility that P sub B can get very small.

DR. PORTIER: In your convergence criteria, then you have a minimal value in essence of PB that convergence is going to stop on, or log PB, negative value in log PB, upon which it will stop then because obviously negative infinity is something the computer can handle easily.

DR. SETZER: That's right. It sort of runs out at 10 to the minus something, 320th or something like that.

DR. PORTIER: Thanks.

DR. KENDALL: Dr. McDonald, could it hold to later? Dr. Harry, is it necessary to proceed now with your question? Dr. Rhomberg.

DR. HARRY: No, it can wait.

DR. KENDALL: Excellent. Proceed, Dr. Setzer.

DR. SETZER: When we couldn't get estimates for all the parameters, we proceeded in this order. Of course, first, we fit the full model using sex-specific values for B and random effects for B. Next step, since we'd already observed that it was pretty common for B to be similar between the sexes, to try single value with B with

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random use with B.

The next step would have if that, again, didn't converge, try sex-specific values for B but no random effects. And, finally, to try to estimate a single value with B with no random effects. And then if all those failed, we'd use an approach I'm going to describe in a minute to identify sex-specific value of B that were consistent with the data and then estimate the other parameters given those sex-specific values.

I'll say that, in this estimation process, we only basically only approaches one, two -- they're not numbered here. But the first one, the second one, and the last one actually ended up being used. If we couldn't get estimates even for a single value of B with random effects, none of the other approaches worked either.

So in those cases where we can't estimate a value of P sub B, and it's just under half of the chemicals where this happens, how do we do it? The basic approach is to use the fact that we can calculate a likelihood for the model on the given data and identify values of P sub B that are consistent with the data by trying different values of P sub B, estimating the other parameters, and calculating the likelihood of the result, and then finding that value of P that is on the maximum of that surface or at least is consistent with the maximum of the surface in cases where the surface is very flat.

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Just in review, the log likelihood is a measure of the degree to which the data supported a particular parameter. This approach I'm describing is generally called is "Profile Likelihood." It's most commonly for calculating confidence levels for a parameter. And the rest of that slide just goes what I already said.

In detail, we set this parameter P sub B. Remember, there is a separate value for males and females. This is really two parameters. We're fixed in turn to each point on an 11 by 11 grid ranging from .001 to .999.

At each point for each of those values of P sub B for males and females, we fixed the value to an point and then estimate the rest of the remaining parameters, calculate the log likelihood, and plot it on a grid. And to aid visualization, values were linearly interpolated between grid points. We selected the grid point with the largest log likelihood as the value of P sub B that we used for the estimate of the other parameters.

Here's a graph of one of those plots. In this particular case, the highest value is down here in the lower corner. We can see that as we progress from bright yellow to -- yellow, my wife corrects me -- as we go from the bright yellowed to red, the surface is dropping off. I'm using the intervals here are based on minus 2 times the difference of

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log likelihood between the maximum value and the interpolated points here. So these sort of roughly corresponds to confidence intervals, confidence contours for the parameter if we were estimating it. Red would then correspond to values that are significant at .95, or .05, whichever way you count it.

Furthermore, we identified grid points that aren't -- not only aren't significantly different from the maximum value by open circles, the remainders are pluses indicate that they are significant.

Missing points indicate models that for some reason didn't converge. So there are a few up in there here, and there are a bunch out here.

One thing we can get at is to what extent -- what is important to know is since we're not jointly estimating our parameters with the horizontal asymptote parameters with the other parameters, it's important to know something about the sensitivity. How much would our estimate of benchmark dose change if we picked a different value.

So basically on the same kind of grid we plotted the profile likelihood plot, plot benchmark dose then this is fraction of the value at the selected point. And this is something that is not in the December draft, but was something I've done since December.

So we plot contours, again, plot contours like we did the

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likelihood plots. And in the figure I'm about to show you, the smallest, contour that's closest to the estimate, corresponds to a plus or mine 25 percent in change in benchmark dose.

Okay. And again this is the same chemical we saw before or we saw the profile likelihood before, and we can see that, basically, we -- well, within 25 percent, the same estimate of benchmark dose regardless of what value we chose. For the male benchmark dose, over a wide range of estimates of B, we don't get a change.

I want to move on to the expanded model that Dr. Portier was talking about. Some of the data sets looked like there was a low dose shoulder. And the approached we used in the July draft, there generally weren't enough doses to actually examine that. One of the advantages of aggregating the data sets is that it allows to us build a somewhat more complicated model to look at that.

One of the explanations for this low-dose shoulder is existence of saturable metabolic clearance of the parent compound. The approach I used here is a little bit different from sort of a standard statistical approach, was to build a submodel which was inspired by this mechanism -- and I want to emphasize the word inspired -- to the basic model which would create that low-dose shoulder. And the point part was to keep the model simple. We don't have the data to

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parameterize a real biologically based dose response model for these chemicals. Nevertheless, we have some information to allow us to use some biological ideas to develop a model shape.

The approach is to build a very simple PBPK model. This is useful conceptually, not for the parameterization but to get a sense of the shape of the submodel we're going to use. This model has two compartments, a liver and everything else. We're sending oral dosing. One hundred percent of the oral dose goes into the portal circulations so it goes into the liver for metabolism.

And then there are venous and arterial circulation. And we only considered saturable metabolic clearance of the parent compound and first order of renal clearance.

It turns out when you write down the differential equations for this model, they are simple enough you can solve explicitly for steady state.

Now, you can write down now then, if you assume dose is the administered dose rate, and you describe the concentration in the rest of the body part of that compartment of that model as I dose or internal dose, this is the steady state. It's in constant dosing. And you get these two parameters, S and D, which are these functions of the pharmacokinetic parameters.

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In principle, if we had the information and particularly what we don't have are metabolic information -- sorry -- metabolism information and measure of renal clearance, we could have used the biological parameters to parameterize this.

Instead we treat this model as an empirical model and estimate S and D as empirical parameters just like the others. So the way we use this model then is to compose the two models. We have the internal dose model, which describes internal dose in terms as a function of administered dose. And then we use the basic model, the exponential model we've been talking about, that describes the relationship between internal dose and the response, the cholinesterase activity.

To show you what this looks like.

The dotted lines show the shape of this internal dose model for different values of S and for one value of D. The names come if D from displacement because it acts like a displacement of this internal dose model. S describes the shape. Where S is very small you get a very dog-legged like shape, as S gets larger you get a more smooth shape.

All of these curves will eventually converge to a shape that's parallel to the internal dose equals external dose line. One thing that S does is control the rate of convergence of that actual model to that

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parallel line.

If you combine this model with the basic model, you get dose response shapes that look like this. And this what we actually see when you compare the data. Again, when S is very small, you get an almost threshold-like model, although this isn't really a threshold. It's a smooth curve.

As S gets larger, you have a more smoother curve. And finally, as S gets relatively large -- as we talked about before, as S gets large without bound, you can converge to the basic model.

That's also true as D gets small, as you can see, if you slide this dotted line back towards the origin you get closer -- as D is zero you, in fact, do get the basic model. The rate of convergence depends on the actual value of S that's happening.

It's currently difficult to estimate parameters in this model using the NLME function. And I don't understand why and that's something working on right now. But we can still estimate values of S and D fairly well by, again, using the reasonable profile likelihood approach that we described for P sub B.

The main consequence of doing things this way is that it makes it somewhat more difficult to get reliable estimates of the confidence levels for the benchmark dose since they don't take into account

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estimating S and D in the process. And that's why I want to keep working on doing it the other way.

I have to fess up here. Due to some programming errors in the analysis before the December draft, we were only able to calculate the profile likelihood plot for a small number of chemicals; and those were wrong. And the main consequence of the programming errors was -- actually, the subsequent analysis where we actually then estimate D, for example, for the chemicals, those, I believe, were correct. So the main consequence of this was to limit the number of chemicals which benchmark doses could be calculated using the expand model.

Right now we've got profile likelihood for all 29 chemicals. And 17 of those 29 chemicals, the fit for the expanded model is significantly improved over the basic model. And there's a list of the chemicals for which that's true.

Here's an example profile likelihood estimate surface for S and D for bensulide. The scale is the same. So these are probability steps going down. The actual scales for S and D depend on the dose scale used. So if the largest dose in the study is very small, these will range over a small range; if these are very large, these will range over a much larger range.

And some dose response plots. I'm afraid these don't show up

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very well I have to learn to use wider lines when I make these graphs. These were a little bit busy and hard to see. So let's go through some of them.

The individual points are individual dose means from individual data sets. So this is essentially every individual dose mean in all the data sets plotted versus dose. For the same in this case in bensulide, there was only one set of units used so all the data are on one graph.

The solid lines are the dose responses that correspond to the population mean parameters values for all the parameters. The colors indicate values for males and for females; blue indicates male; red indicates females. The dotted lines indicate mean values for each individual study.

So in this case, it looks like there were two studies, to two separate studies, for bensulide with somewhat different background levels so you get these separated values.

And then what you don't see on this graph is with each individual study may have multiple data sets. You can sort of see the values, the doses sort of piling up here at discrete dose levels. And when we look at residuals in a minute, you'll see that.

This is the basic model. You can see that it's an exponential model. It just drops. For the expanded model, you see the shoulder

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that, adding the expanded model, the internal dose model adds to the dose response curve.

Residual plots on the left side are the residuals are the basic model; on the right side are residuals from the expanded model. What you see here is an excess of positive residuals down around 10 percent. What we're plotting here is the residuals from the model fit. That is the difference between the actual observed mean and the model-predicted mean for each individual data set -- this is the particular mean for each individual data set -- scaled by its predicted standard error, plotted against the fraction of inhibition predicted by the model.

We see that in the basic model at around 10 percent, which is where we want to put our benchmark dose, we are overestimating the degree of inhibition. And that's consistent with the graphs I showed you before with the shoulder.

If we move to the model with low dose curvature with the expanded model, we see that the residuals are more uniformly or more evenly scattered around this horizontal line that indicates zero. So basically what that means is we're over-predicting about as often as we're under-predicting, which is sort of when we're looking.

This is just a slide of the table of the chemicals and the relative

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potency factors, I think, from the December draft of the document and points of departure.

Summary. In summary, we attempted to address SAP recommendations; and we believe we've improved benchmark-dose calculations. We've used profile likelihood to estimate the horizontal asymptotes results which gives us a value that's consistent with the data. That's superior to sort of assuming that it's zero.

By switching to benchmark dose, our measure of -- is our basis for calculating relative potency. We have a measure that's less sensitive to our estimated horizontal asymptote than was the slope factor that we were using before. And by changing the weight function, we've improved somewhat the quality of the estimate we've done.

We've reparameterized the basic model to improve the stability of the estimator. This allows -- essentially what that means is we have convergence more often and it's easier to get convergence when you do get it.

By estimating parameters for combined data sets, we can introduce a slightly more complicated model that describes the low-dose shoulder of the dose response. And that, in fact, does give us -- it improves the fit to the data and improves the benchmark dose

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estimate at least for quite a number of chemicals.

And that so should be all. Yes, that's it.

DR. KENDALL: Thank you very much for that informative presentation. Any quick questions from the Panel? Otherwise -- okay. Dr. Durkin.

DR. DURKIN: Woody, very, very quick. I'm a little dense.

DR. SETZER: No, you're not.

DR. DURKIN: You did, prior to combining studies, everything was scaled -- correct? -- scaled for the differences in the background risk response rates among the studies the way you reparametarized it.

DR. SETZER: Well, actually, yes or no. The parameterization of the model sort of does that by estimating -- we have not explicitly scaled it in the sense of going through and dividing by the background for that particular data set.

What we do have is a multiplier for the model for each data set that sort of takes that into account. That's what the random of both the --

DR. DURKIN: That's one of the random --

DR. SETZER: Well, there's actually a fixed effect because we -- there's a fixed effect that affects sex and units, and there's a random effect term that affects data sets and studies; yeah.

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DR. DURKIN: That explains that figure for me. Thanks.

DR. SETZER: Thanks.

DR. KENDALL: Dr. Roberts.

DR. ROBERTS: Just a quick question. Are you proposing to go forward with the benchmark doses based on the expanded model for all of the chemicals or for some of them with the expanded model and some of them with the basic model?

DR. SETZER: Certainly -- this is probably a policy decision that I'm not really supposed to make. But I would think that, certainly, in those cases where the expanded model describes the data substantially better than did the basic model, that's where the benchmark dose would come from.

The question -- the only issues would be in situations where there's not really a lot of evidence to support the expanded mode over the basic model for a given data set.

DR. ROBERTS: Is there any down side from a technical standpoint just using the expanded model for the complete data set for all of the OPs?

DR. SETZER: I'm trying to balance, sort of model uncertainty parameters versus uncertainty in parameter estimation in this. But, basically, what happens is as you estimate more parameters in a model

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like this, you sort of increase the confidence intervals on the parameters you've estimated. You generally want to use simpler models if you can.

On the other hand, you can introduce some bias by not having the right model. And so that's the tradeoff you're trying to balance.

DR. KENDALL: For the Panel, I have four or five people that want to ask questions. If I do so, it will take another half an hour. I would propose, if there's something quick that Dr. Setzer needs to address, let's do that versus let's get into the depth of discussion that I think you really want to engage when we have a chance to reconvene.

So if there is any clarification -- Dr. Rhomberg, your hand was up. Is there a clarification from you needed?

DR. RHOMBERG: it's a clarification.

DR. KENDALL: Then let's do that.

DR. RHOMBERG: I'll state it. And if we want to defer it, I will defer the answer.

DR. KENDALL: Okay. Go ahead.

DR. RHOMBERG: What my question is about S and D in the expanded model. In the December document, not only did you have to use profile likelihood a lot of the time, but you even had difficulty with that in that you had a hard time in finding a spot on the surface

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where there was really clear differentiation. And I think you solved that by setting S very small and then estimating D.

You didn't mention that problem now. Has that gone away with the fixes you made to the calculations?

DR. SETZER: I wish. No, but what I'm trying to do now is trying to understand better why I'm having that trouble. What I would do, if we can't get -- I mean, it has not gone away. That's probably the easiest way to answer that right now. And if you want more, we can talk more about it.

DR. KENDALL: Dr. Conolly.

DR. CONOLLY: I'll keep it brief, also.

DR. KENDALL: Please.

DR. CONOLLY: Woody, the expanded model, you said, I think, was motivated by knowledge that OP clearances are determined by saturable processes, carboxyesterases (ph), and things like that. And the question I've got for you -- and we can go into that in more depth later if it's a long answer -- is just whether you feel the validity or enthusiasm of using the expanded model in the assessment is really dependant on that interpretation because I might challenge you that biological interpretation of the model, not necessarily on the application of the model.

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DR. SETZER: That's fine. And I would -- no, it's not dependant on that. In fact, I tried to emphasize that. But that's for asking because I get to say it again.

No, that's why I used the word "inspired" by that idea. Basically, what we're looking for, what seemed seems to characterize the belief or the information that we have is that we expect there to be some sort -- it's -- I'm going to get myself into a more complicated explanation than I want.

No. It's essentially an empirical model that allows us to modify the dose response shape in a way that focuses on the low-dose end as opposed, for example, adding polynomials or putting a power on dose which would effect the entire dose range.

DR. MCCONNELL: I think calling it an empirical modeling is probably the safest way to go forward.

DR. SETZER: That's right.

DR. KENDALL: Dr. Harry.

DR. HARRY: I'll wait.

DR. KENDALL: Dr. MacDonald.

DR. MACDONALD: Yeah, I've got two questions and I think they have short answers.

One is do you think what you had problems getting the fit to

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work that could be the result of combining contradictory data sets?

DR. SETZER: For one chemical, that might be the case. But, generally, no, I don't think so.

DR. MACDONALD: And, also, you raised a very good issue about the confidence intervals getting wider when you start fitting more things. I'm not sure everyone appreciates the importance of that. But it really makes me worry about anything that's going to be based on confidence intervals like BMDL because you can always just make more assumptions your confidence intervals get tighter and everybody feels better.

DR. SETZER: Yeah, that's actually one of the problems; isn't it. Yeah.

DR. KENDALL: Dr. Portier.

DR. PORTIER: I'm not going to let you rush me, Mr. Chairman. I have a lot of questions concerning things that are not in the write-up about the procedures that I want to be sure I understand rather than assuming I understand what they are. Hopefully, it won't take more than about 10 minutes; but I have a number of questions that I have to ask.

DR. KENDALL: Sounds to me that that might be best engaged when we reconvene, Chris.

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DR. PORTIER: It's up to you. These are all clarification issues. They are not any further discussion of the other issues. This is one of my concerns was that we would rush through this very important aspect of this presentation. A lot of what's done is going to be dependent on this. So if we're going rush to get my comments in now, yes, I would prefer to put them off. But if not, I would prefer to do them now since the topic is fresh in everyone's mind. I will let you decide that.

DR. RHOMBERG: Comments?

DR. KENDALL: Dr. Rhomberg.

DR. RHOMBERG: Once we get to that point, I'm sure I will have a lot of comments and questions as well that are also, at least on the cusp between things that are clarifications and that are discussions. If you start asking yours, I'm probably going to feel like asking mine.

DR. KENDALL: See, that's what I'm worried about. My druthers were to cut it off completely after the presentation by Woody, but I didn't. I think we did a good job to trying to get a few of these issues on the table. But I appreciate your honesty. If you've got multiple ones, what I'm afraid is you will get into it, others are going to get into it. We're substantially ahead of schedule now.

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DR. RHOMBERG: I don't just want to agree that I don't want to rush the issue, and I think that saying we don't want to rush the issue is a very important point that Chris made.

DR. KENDALL: And because of that, I'd say it's very difficult -- and one of the things I've found it is very difficult for people to get out and get back in an hour. If I had a few more minutes -- I'm going to reconvene precisely at 1:30. Okay. In that way, you got a few more minutes than an hour to get back here because I'm going to start at 1:30. Dr. Portier, will you bear with me?

DR. PORTIER: I'd be happy to. That's great.

DR. KENDALL: We will close this morning session and reconvene at 1:30 p.m. Thank you.

[Lunch recess was taken.]

DR. KENDALL: This will reconvene the FIFRA Advisory Panel. We concluded with an very excellent presentation by EPA in our morning session. And now we have the questions for the SAP on Hazards and Relative Potency Factors. I would like to have those questions posed.

I know there are some clarifications, additional discussion, related to your presentation. Let's go ahead and present the questions, and then we'll proceed forward with the clarification, then move into

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the questions. Thank you.

Go ahead. And let's present the first question. Just the first one only.

DR. LOWIT: In September 2001, the FIFRA SAP made some specific recommendations to the Agency concerning refinements of its dose response analysis of cholinesterase on organophosphates. Some of these include the deviation of the adjustment factors "B" and the modification for use of "B"; a formal analysis of the residues; minor revision to the Agency OP-CRA Assessment Program including the revision of calculations of the goodness of fit statistic and deletion on the p- and t-values PND; consideration of the appropriate measures of relative potency; expression of the inhalation exposure in the same units as the oral doses and adjustment for actual treatment durations; consideration of the impact of individual animal data instead of summary information; and derivation of oral doses from the all dietary intake rates.

Part B of the same question. You are asked to comment on how to address the recommendations.

DR. KENDALL: Okay.

DR. LOWIT: Part B of the same question. Several of these issues were addressed by the application of the nonlinear mixed effect

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for combining cholinesterase data. In addition, EPA utilized the profile likelihood method for estimating horizontal asymptotes when they could not be estimated jointly with the other parameters. And we're, also, asking you to comment on the use of these statistical procedures and the dose responses.

DR. KENDALL: Okay. Thank you very much. As we concluded the morning session, Dr. Portier, you had two questions that you wanted some time to address. Dr. Rhomberg, also, has some points. Why don't you proceed.

DR. PORTIER: I didn't say two. I said 10 minutes of questions.

DR. KENDALL: Two questions for 10 minutes or 10 minutes for two questions?

DR. PORTIER: I think it's 10 questions for one minute each. Just, again, these are all clarifications questions, I hope.

In page five of the write up, you basically describe what you did last time. And in page 9, you describe what you're doing now in terms of full data sets versus data sets. You didn't come in on the dilution of doses issue. Is there no dilution of dose groups in the current analysis?

DR. SETZER: That's correct.

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DR. PORTIER: In the previous version you had average parameter values for each study and then average values for each OP across studies and each time across studies and everything like that. I just want to be clear that I'm understanding what you're doing now. When you analyzed all the data, it is literally for an OP all the data sets; is that correct?

DR. SETZER: That's correct.

DR. PORTIER: And then there's one potency factor that comes off for an OP from that calculation;

DR. SETZER: That's correct.

DR. PORTIER: Which is the grand mean in some sense.

DR. SETZER: In some sense, yes.

DR. PORTIER: You discussed steady state in loss terms in this overall analysis. And I didn't see anything in here -- and correct me if it is in here -- describing half-lifes in male rats, female rats.

DR. SETZER: No.

DR. PORTIER: Or humans. Half lives of the OPs in the animals or in the humans to discuss, to verify, your assumption about a 21-day steady state value.

DR. SETZER: The steady state value we're talking about doesn't refer -- it refers to cholinesterase activity not to whatever

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tissue-specific levels of the OP. So it's an empirically determined value. Actually, it's the same thing we talked about in the September meeting, the cholinesterase, the inhibition stabilize around 21 days.

DR. PORTIER: But there's no formal analysis anywhere in here that verifies that statement about the steady state nature of cholinesterase inhibition under constant exposure for 21 days.

DR. SETZER: Other than the analysis we presented in September, there's no new analysis.

DR. PORTIER: On page 7, let me go back to my notes here. Oh, yes. On page 7, the top of the page in terms of points of departure, you say the BMD10 was selected at the effect level for point of departure because this level is generally at or near the limit of sensitivity for discerning the statistically significant decrease in cholinesterase activity across the blood and brain compartments and is a response level close to the background cholinesterase.

My question was: Were there any evaluations done of other BMDs instead of 10 percent, 5 percent, 1 percent to compare against this?

DR. SETZER: No.

DR. PORTIER: And you discuss about them being close to the limit of statistical significance. Did you take any view of looking at

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the co-efficient of variations in the sense of the BMD10 in variances and looking at what that looks like.

DR. SETZER: You mean looking at how the confidence level would change as we change the response level? No, we haven't.

DR. PORTIER: Okay. I assume, and maybe I'm assuming wrong, that all of the error distributions in the model are normal.

DR. SETZER: They're assumed to be normal; that's correct.

DR. PORTIER: Was any sensitivity analysis done for this?

DR. SETZER: No.

DR. PORTIER: I'm assuming no log transformation was made on the Y-response variable to see the cholinesterase levels?

DR. SETZER: That's correct. The data we modeled were on the original scale.

DR. PORTIER: I'll make a comment. This is sort of an off-the-cuff comment. But if any revised version, I would have preferred to have seen a standard statistical presentation of the expected value of Y is or a Y is this plus error structure and then break out of the error structure for me so I could understand the nesting of the error structure better. That would have been very useful.

Again, I want to verify that in the likelihood-based procedure

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you are using, you are actually using a normal likelihood and not the sum of squared errors.

DR. SETZER: In the particular procedure we're using, which is has been called conditional linearized, it's an approximate log likelihood -- it's an approximation based on some linearizations based on a normal likelihood, yes. On a normal likelihood approach for all.

DR. PORTIER: The error terms. The error terms are proffering into --

DR. SETZER: That's correct.

DR. PORTIER: -- into the normal distribution.

In looking at your starting points or calculation what you called the profile likelihood, I assume that for each point in the grid you have shown me that surface that you were showing me that maximization was done for all the other parameters under at fixed B value.

DR. SETZER: That's correct. With this caveat. Optimization was done. Remember this is a -- this is not an exact maximum likelihood procedure because it's based on a linearized likelihood. But, yes, for all the other parameters were estimated using the procedure conditional on the value of the fixed value from the P sub B, or the S and Ds, depending on the ones you're talking about.

DR. PORTIER: Okay. In looking at the actual format of the

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model under varying studies, varying sex, varying species, varying times of observation, I was a little lost as to how these effects were entered into there. I'll tell what I assume the effects, how they were entered into there. For each study you had a variable for background adjustment to the grand mean of background and each of those variables had their own distribution from which they were derived. Was it a mean structure cross? What exactly are you doing with that one.

DR. SETZER: Okay. You have the basic model in terms -- if you're talking about the basic model. We have a parameter that indicates that qualifies the background. We had horizontal asymptotes in the benchmark dose. We fit a model in which there's a separate grand mean, fixed grand mean, for the background values for the cross of sex and unit in which cholinesterase is measure because we studies where different units were used. And the units indicate different methodologies. It's just sort of rescaleing the units to the right answer in dealing with the different units.

And then a separate grand mean for sexes for the horizontal asymptotes and benchmark dose. Then the variances model, for each of those three parameters, is a considered the sum of that main effect. And two random variables each with mean zero and their own

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variances. One random effect for among study availability and one among data sets that study variability. That's if we're counting, that means six random parameters and six variances to be estimated. We assume to be independent, but there just aren't enough data to estimate covariances among those variables. So it's essentially the co-variances measures is diagonal.

DR. PORTIER: That confused me, then, about one of your plots. I thought I had understood that is what you had done. Then I don't understand how you got the plot -- let's see if I can find the one I'm talking about -- dose response shape at low doses.

DR. SETZER: Yeah.

DR. PORTIER: It was the one that had three plots on it with the grand mean plot. This is from his presentation. A grand mean plot and a plot above and a plot below.

DR. SETZER: It might be 42.

DR. SETZER: It says --

DR. PORTIER: My slides are not in color, so I'm -- it was definitely toward the end. Three or four or five slides back from the summary.

DR. SETZER: There.

DR. PORTIER: This is the one. I'm a little bit confused about

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how you get the different backgrounds for the different models if it's a random effect to tie it down for a particular study.

DR. SETZER: For each study and, indeed, for each data set within study, you get kind of a -- well, you can get a maximum model estimate for the mean value for the parameter for that study or data set. What I've shown on these plots, the solid curves correspond to the grand means to the dose response curves corresponds to the grand means. The dashed curves correspond to those response curves for the study specific value which would be the grand mean plus the estimate of the particular random effect for that study and so forth.

And I only did it one level of nesting down because it would get too confusing to do it...

DR. PORTIER: Okay. That's good. I understand that now. Again, I didn't get into the code of R and sit down and look at it, I just wanted make sure that the NMLE methodology cannot do constrained parameter estimation.

DR. SETZER: That's correct.

DR. PORTIER: Which is why you did all the log transforms.

DR. SETZER: That's correct.

DR. PORTIER: Page 19, you describe the likelihood ration test. It's at the bottom of the page, significance of the fit based upon

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the additional bigger model. Do you see where I am?

DR. SETZER: Yeah. I see where you are.

DR. PORTIER: I'm curious about the degrees of freedom for this likelihood ratio test. What were you using?

DR. SETZER: Two.

DR. PORTIER: Two. Even so though the model sort of collapses, when you send either one of the parameters to its boundary value, it brings you back to the basic model.

DR. SETZER: That's a good point.

DR. PORTIER: You're still using two.

DR. SETZER: I'm still using two.

DR. PORTIER: That's probably not bad or good. I'm trying to make sure I clearly understand everything.

Finally, the steady state solution off of the PBPK model that you're using. I didn't sit down and do it myself, but I need some degree of assurance in looking at this. It didn't appear to me that that type of PPBK model should have had a point of discontinuity in it which, obviously, the steady state solution does have a point of discontinuity in it.

I wanted to make sure there weren't assumptions that I didn't see that went into that model in terms of how it would react or how it

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would work. Continuous, the PBPK model itself is a continuous time, continuous dose system of augmenting differential equations. Even in steady state, I don't see how hat would lead to a nonsmooth response. And yet you got this minus S which is clearly a point of discontinuity.

DR. SETZER: Can we go to the next slide?

DR. PORTIER: There your solution for I dose introduces a break point in the dose response curve which I didn't see in the system itself. And since I didn't have the LDs in front of me, I couldn't.

Are you absolutely certain of what you did.

DR. SETZER: Yeah. Never ask me if I'm absolutely certain of everything, Chris. However, I'm reasonably certain that this solves that system. That's the result of actually -- I mean I cheated. I used MAPLE which is no guarantee that it's right. Although given -- nor done by hand.

Actually, in a sense, that may not be that important. We're not trying to claim that this is. In fact that's the wrong pharmacokinetic model in some sense anyway. The point is to use a sort of simple conceptual model to help you derive a mathematical expression to use in a dose response model that would have the characteristics that I wanted which would cause that shoulder at low doses and have that sort of localized at the low rate it occurred; and localize that to a

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greater or lesser degree, which I contend this curve does; although, computationally, it may be a bit of a problem.

Singularly, I'm talking about S and D, if you're going to drop at all, they have to be positive in that model.

DR. PORTIER: I agree.

DR. SETZER: So where's the point of discontinuity that you're talking about?

DR. PORTIER: My concern is for dose less than

DR. SETZER: I see what you mean. But there's a trick there in that positive square root. It turns out that when dose is less than S, the thing under the positive square root of that under that radical cancels it out. So if dose less than S or less than D essentially, you get a flat line, horizontal line.

DR. PORTIER: That's my point. That implies that for dose less than S --

DR. SETZER: You can get perfect metabolism much in the first pass.

DR. PORTIER: Exactly, that the steady state solution is a zero steady state.

DR. SETZER: That's a good point.

DR. PORTIER: Which in the early DEEMS I find difficult to

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understand. That's all. I hope it wasn't more than 10 minutes.

DR. KENDALL: Very well. Aren't you glad we waited, Dr. Portier?

DR. PORTIER: I'm glad. Dr. Rhomberg.

DR. RHOMBERG: The reason I was raising my hand earlier was I was wondering if this last question didn't actually have something to do with the question I asked just before the break about the actual estimation of values for S and D If you choose a really small value for S, I think it is, and then putting it at the edge of your space of values that you've tried and then optimized D, I think that makes for a very sharp effect so that the curve are actually curves. I don't know if Chris was reacting to the equation here for the singularity or for the actual pictures of the curves.

For my part, the same question arose, but it was looking at the curves that actually seem to be dead flat and then there seems to be actually a little break there and start to go down. I ascribe to the fact that by making S very small and D very large, you were basically making some very sharp kind of rectangular -- although it's continuous on a microscale. It looks like it's a break on the scale that you were plotting out.

Is that a reasonable explanation of that effect?

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DR. SETZER: The reason and -- in the December draft the motive for fixing S as a particular value was that when we looked at the profile likelihood response dose for chemicals we actually got something out. It actually looked like, for each of those chemicals, the maximum -- the likelihood was actually for a very, very small value of S.

And so what we were doing was essentially analogous of what I've done the estimating P sub Bs. If I can't explain the majority, use the profile likelihood to give me a plausible value for one of the parameters and estimate the other one.

But it's true. That for a very small values of S, I showed that on the graph, too. I talked about this curve. That as S gets small, the curve looks more and more like a sort of a classical threshold model. And to some extent, that was an artifact of some programming error. Those figures were wrong.

DR. RHOMBERG: The figure that you showed this time. And I should remember which slide number it is now. The one that actually shows the curves with the shoulder. And in this case, the one you showed today behaving much rounder and more nicely behaved.

DR. SETZER: Yes, sir.

DR. RHOMBERG: Is that typical of the way they looked or is

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that atypical?

DR. SETZER: It's not atypical. There's a variety of shapes from barely discerning a shoulder to all the way to something that looks like the curve we showed before.

DR. RHOMBERG: Okay. I guess Dr. Portier asked a lot of the questions I was going to ask. But there's one part that you started on and didn't quite finish. And that is I guess the way I would rephrase it is choice of starting values for some of these cases where you are now doing profile likelihood.

And I'm not sure I quite follow the explanation in the text about where you got the starting values from for the parameters that you're now reoptmizing when you're doing S and D And in particular, what happens when -- I guess now in this version, you no longer have the case of setting B to zero, but you do have cases where you had to do tricks to estimate B even in the basic model. Where does the starting value for B come from, then, when you're considering the expanded model.

DR. SETZER: Yeah. Well, we start in the expanded model. We start essentially with the basic model that we ended up with. So whatever effects we estimated or probably didn't estimate in the basic model we start there. So if we had to fix B and used profile likelihood

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as the basis model to fix it, the I kept B fixed at that value. If B was estimated in the previous model, it continues to be estimated and so forth. If it's estimated that B varies B's allowed to vary. If B was fixed, at this point there's no effort to sort of reinsert essentially do a three-dimensional profile likelihood or four-dimensional profile likelihood to determine the sort of the best combination of S, D, and P sub B for that.

DR. RHOMBERG: I guess you could be forgiven for that. I guess what I was wondering the degree to which -- these things can draft such that B that you get. So to the degree that B interacts with S and D, could it be that when you add S and D into the equation, you no longer have the problem that B needs to be fixed the way it had to before with the basic model; or has that situation not arise?

DR. SETZER: Basically, that's possible. But I don't think that's going to happen.

DR. RHOMBERG: All right.

DR. SETZER: Because of some efforts I made at trying, I thought of that and tried to sort of refit things but unsuccessfully so far.

DR. RHOMBERG: I have one other clarification question and that is on the different units. I'll confess to not knowing exactly how

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they assays run. I understand why you did them differently. These are not things you can convert back and forth because they are actually different methodologies that might be measuring somewhat difference things and not just measuring units. That's what you were saying earlier; right?

DR. SETZER: That's correct.

DR. RHOMBERG: Can you at least say that these measures ought to be sort of linearly related to one another? I guess the one I'm worried about is the Delta pH which since pH is on a log scale, in a sense implicitly log transforming results for one thing and that's not being done for some of the other things. Does that cause any issue?

DR. SETZER: That's a good point about log Delta's pH. There are, in fact, some published conversions between pH method for cholinesterase activity and one of the other methods. They turn out to be linear transformations nonzero intercept. One of the approaches, I think for rats, that intercept is quite small. It's not sufficient you have a linear transformation for that to work. I think it needs to be a pure scale transformation.

The intercept, at least, I think for rats for one of that is the intercept is quite small relative to the magnitude is the a product of the slope. It's approximately right.

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DR. RHOMBERG: So it's not a practical issue, you don't think.

DR. SETZER: I don't think it's a practical issue.

DR. RHOMBERG: Thank you.

DR. KENDALL: Thank Dr. Rhomberg. Any others want some clarification? Dr. Harry.

DR. HARRY: Of the last question where you were talking about the different types. And what I was concerned about, and I saw how you were handling the different types of assays to bring them back to some sort of comparison. But while you think about the data, did you take into consideration why you had a prescreen to say good studies that you wanted to look at, was there a component point that took into consideration the differential sensitivity of these different assays?

We have different ways of looking at things. Have different assays been looked at different to say their levels of sensitivity. I'm concerned about that -- getting down to the really low dose. In some of these assays, they may not, in and of themselves, have the sensitivity to pick up accurately small changes. So you might be missing something. Was there any way of weighing that or anything?

DR. SETZER: I'm wondering if you're not asking the question that was asked a littler earlier but in a different way.

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If the differential sensitivity is you expect there to be a bias at the low-dose end and a mean value to get it out. Or is it that you expect the variances to grow as you get down to low-dose ends so that there is just a lot of noise down there and you can't -- if you're doing calibration for NOAELs or something, you don't have a lot of sensitivity to see significant differences.

If it's the latter situation, I think the weighting we've done sort of accounts for that. Basically, the data sets were larger variances will contribute less to the overall mean estimate. If it's the former where there's a bias, a real bias, it gets more pronounced as inhibition gets smaller.

I certainly haven't adjusted for that mathematically. Whether in the screening process for studies, that was taken into account. I'd have to get somebody else to answer.

DR. HARRY: This particular question is more on the bias. On the first component of it on maybe the bias rather than the variability. Because if you are outside or below the ability of an assay to truly detect change because of the sensitivity of the assay, and that may also come into play as you're getting new technology to pick it up. So we have a lot of data across a large sensitive assay to pick it up. So it's not so much the variability, but you may see no changes detectable

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coming in you're going to have to deal with that. I was just wondering if anyone had taken that into consideration.

DR. SETZER: I haven't mathematically.

DR. BRIMIJOIN: We're talking about the low end of an inhibition curve not the low end of a activity curve. So where an assay would be perfectly good in this zone.

DR. HARRY: But it may be misleading.

DR. BRIMIJOIN: So it really does come back to the question not of sensitivity of the assay but precision.

DR. SETZER: Correct.

DR. BRIMIJOIN: It's folded into the measure the variances.

DR. SETZER: Thank you.

DR. KENDALL: Any further comments to that question or issue? Dr. Portier.

Did you want to say anything Dr. Lowit? Did you want to say anything to this? Okay. I think we got that at least resolved.

Next clarification issue, Dr. Portier.

DR. PORTIER: Yeah. I'd forgotten to pick that one from my list, but I remember what it is. We didn't hear any discussion or presentation on the CELs for the acute tox studies and the comparison of them against benchmark doses. And there's some points in there

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about these models couldn't be fit to those data. Will we get a presentation on that?

DR. LOWIT: We're going to hold the discussion on the different time frames and all the hazard conditions that come along with that until Friday when we discuss with you the last question which is scheduled for Friday in terms of the appropriate time frame for exposure and all the hazard and exposure issues that go into that.

DR. PORTIER: But I'm more interested in questions pertaining to why the dose response analysis was not done with those data is more my question along these lines. There were some statements made that you could not fit model to those data. Yet when I look at that those, data I see five or six dose points. And I'm curious about whether we will get a presentation on that. Or my comments on this first question, I think I should comment on that.

DR. LOWIT: At present time, the acute data in the table that I think you're referring to has not been through any dose response analysis. Those are NOAELs and LOAELs pulled directly out of study reports of data evaluation records and staff toxicology not from the actual study reports themselves.

DR. KENDALL: Any further points?

DR. PERFETTI: Dr. Portier, one thing was referring to

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inhalation and the dermal study, a lot of times you may have had more than one dose, several doses; but you only have one time point which, if you model some of those like we did using the original model, you get very, very wide confidence limits. So I mean you're talking about BMDs in the same compartment range from .02 to .12. So it's -- I mean you could do it, but I'm not sure it would be any more accurate than just the CELs.

DR. PORTIER: If I might respond. My comments will reflect when we go to 1A the fact that those large confidences bounds or my lack of confidence in a estimate of BMD10 should in fact reflect on our lack of confidence NOAEL, LOAEL, or any type of dose response assessment from those type data. And it's an indication of a lack of consistent information more than it is an indication of the failure on the regression procedure to give you a descent answer.

DR. KENDALL: Dr. Heeringa.

DR. HEERINGA: A question, Dr. Seltzer.

In your presentation this morning you commented that in several cases that you felt that you may actually be working with a data series. I looked at some of the fits within the model. I don't know whether that's changed in a result of your reanalysis. But it really looked to like you had two different profiles going. It's not just so much a

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random effect.

Did you look at this? Did you ever exclude any data series as potentially outliers or poor calibrated or to accept all this, incorporate all the available studies, and treat differences as just the time and effects of population average value?

DR. SETZER: Yes, that's what did. I haven't tried excluding.

DR. HEERINGA: No revisiting. I just looked at the Pomnet (ph) and really in my mind draws two different curves not a random batch.

DR. SETZER: That might be a reasonable thing to do, yes.

DR. KENDALL: Okay. This will close our clarification discussion subsequent to Dr. Setzer's presentation. And now proceeding, the question has been proposed, at least, 1A and B. And proceeding that question I will open it to public comments. If there are any public comments at this time? Are there any public comments?

We have one listed, a Ken Pastoor.

DR. PASTOOR: Good afternoon. My name is Tim Pastoor. I'm with Syngenta Crop Protection and also participate in the IWG.

A couple of comments that we would like to make I think are pertinent in light of both what EPA has already done and I think the information that you're going to be grappling with in the couple of

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days to come here.

First of all, I think what we want to do is make sure you understand very clearly that what was done here is a tremendous amount of effort with a very difficult problem. And I think the EPA, Anna Lowit, and Woody Setzer need to be congratulated for the effort that they put into this. It's a tremendous amount of work that was done. I think it's done in a substantial a scientifically credible fashion.

The best way to go about the risk assessment is obviously pick the best endpoint. Use that endpoint that best represents risk characterization. And I think in this kind of situation, they've done a marvelous job of coming up with the proper endpoint, which is female rat brain, representing the dose response characterization, and I think probably the best methodology that you can get, recognizing at the same time that our interpretations of these kinds of data are going to evolve with time. And as we look at these issues as we go forward, there may be different kinds of interpretations. But the work that was done here was probably as well done as you could expect to be done.

One issue we would like to bring up and make sure that the Panel is well aware of the upcoming issues around this is that the BMD10 that was used to establish the relative potency factors was very well done. But it brings into question in the course of the week

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when you're looking at the time frames of expression for the risk characterization, the time frames have to match up.

In other words, the BMD10 that we have listed here is based on 21-, 28-day studies, intermediate or chronic studies as some people refer to them. However, when you look at the dietary or residential exposure scenarios, they tend to be short-term exposures if not acute. One day there's a concatenation of acute exposures. So even though we're not we're not dealing with this right now, what we do want to do is apprize you and make sure you understand that will be an issue that I think needs to be very carefully considered by the Panel. Because when you come to the risk characterization process, it would be a numerator and did denominator that have to represent the same time frame for the risk characterization.

So we are very pleased with the effort that the EPA has put into this. The individuals that have been involved in this have done an remarkable job. But we want to make sure that you understand that there is still some things that need to be carefully considered as well.

DR. KENDALL: Thank you, Dr. Pastoor. Any questions form the Panel for him? Thank you very much, sir.

Any further public comments? Okay. Then we'll move into the questions which have been posed. The first one, please comment on

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how the Agency addressed the recommendations listed above. We've structured responsibility within the panel, and all of us will contribute. Dr. Brimijoin, would you lead off, please?

DR. BRIMIJOIN: Well, I'm just going to try to moderate this discussion. So we're dealing with Question 1A, which they have divide into seven separate subtopics. And I guess our primary responsibility is to address each of these subtopics and perhaps anything else relevant of this general issue.

DR. KENDALL: The main thing is -

DR. BRIMIJOIN: THE main thing is get the answers to the question.

DR. KENDALL: I think the Agency would desire our feedback on the recommendations we gave them previously.

DR. BRIMIJOIN: Right. So now I have not prepared a point-by-point response to this. In fact, what I would like to do is be the official designated discussion on this Question 1A, myself, Patrick Durkin, Rory Conolly and Eugene McConnell.

The first point the EPA would like to know is our response to its requirements in the dose response analysis, in particular, regarding the derivation of the adjustment Factor B and modification of the decision tree for use in B.

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And as I understand it, we are talking about the combined total approaching the final equilibrium level of inhibition at high dose scenario. And this was something which, at the time of the September meeting which I did not participate in, evidently, there were a number of sort of ad hoc solutions in place to deal with this issue.

But the document that we've received and the testimony we've had today from EPA, suggests that this is now been folded into this more sophisticated exponential and expanded exponential data.

So I would like to invite any of my panel members here who would care to comment further on that. Dr. Conolly, for example.

DR. CONOLLY: I don't think I have a lot to add beyond comments that were made this morning about the expanded model. From a biological perspective it makes sense, I think, to have a model that has a shoulder-like behavior. And since I was originally a biologist before I was a modeler, I am happy to see things like that. I'll stop at this point.

DR. BRIMIJOIN: Dr. McConnell. Dr. Durkin.

DR. DURKIN: All of my comments, other than just to commend the Agency for much of what hey have done. I think they're responded to us extremely well. Only on one of the seven issues, and that is the use of individual animal data. And I don't know whether you want to

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do that now or just save it.

DR. BRIMIJOIN: Actually, let's reserve that for just a moment. But, in fact, maybe we may be able collapse this discussion, at least among this primary discussants, and always like a comment from anyone else including the other modelers, especially the other modeling people on the SAP.

But so the next question would be as effectively all but the draw of the questions here appear to the appropriateness to adjustments to the model. So, actually, I'd like to know if any of the Panel members are dissatisfied with the treatment of B with the analysis of the residuals. That was a pointed issue in September.

And we've been provided with some graphs that do a person with a sort of typical pharmacologist appreciation for modeling to indicate that it's possible to get fits to these data sets which leave points scattered randomly about the lines as evidence of lack of bias.

We have revisions to the approaches to calculating the goodness of fit statistics. We may want some more discussion on this point of the appropriate measure of relative potency. I think that takes us out of the modeling realm and beginning to impinge on biology and regulation.

So then the first three points, are there any further comments

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from anyone on the panel? Dr. Portier.

DR. PORTIER: On all three of these points, I think the EPA has responded as exactly as asked by this Panel from the meeting in September. I commend them on that. I'll note that you might find later I'm not happy with what we asked you to do. That's a whole other issue because seeing it tells you something else. But I want to make you clear that they have addressed exactly what we asked them to address, especially in the handling of the residuals and the change in the test.

DR. BRIMIJOIN: That's how it appeared to me. Let's turn to the appropriate measure of relative potency. I guess, there were two subissues which is the selection of BMD10 as a point of departure and as to whether that does or does not lead to a compromise in the safety factor that's built into the regulatory decision.

And I guess maybe the other subquestion would be about the comparative effects levels when you're dealing with the cases where it's difficult, if not impossible, to calculate a BMD10.

So we already had some discussion of the BMD10 this morning. I think I now understand that this is being used in fact in two ways. And it is being used first as a way of calculating relative potency, but also that selection is likely to drive the estimate of a reference dose

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and safety factors.

So, Dr. Conolly, I think you have some insight into these matters.

DR. CONOLLY: Very little. I appreciated the discussion this morning on the two ways to look at the BMD. One to compare relative potency and then the other. And I hadn't considered the other. In fact, I'm looking at it to establish an reference dose.

My own view was if you want to compare the potency of one chemical to another, you picked the best place on the curve to do that. And I know you've given that a lot of thought and you've come up with a BM10, which I guess is okay based on when I heard. But I really can't comment other than that other than you spent a lot more time on this than I have. And if think that is the best way of comparing chemical A to B to C accurately, then I have to go along with you. And that's should be the object. I think the primary objective should be that for the exercise you're trying to do. The other should come much later in your procedures. Is that clear?

DR. SETZER: I think so, yes.

DR. BRIMIJOIN: I think so yes. Pass it down to the fellow.

DR. MCCONNELL: I think the spirit of my comment is much the same of Genes. You know, I think that basically the Agency has

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done a good job with a difficult problem. Since as I mentioned earlier, my background is originally in biology and I'm very interested is mechanisms and I spend a lot of time pharmacokinetic mechanisms and pharmacodynamic mechanisms to some extent. And then you realize the complexity of the mechanisms of organophosphate, pharmacokinetics and pharmacodynamics and interactions and so on, you know, to bring out of all of that complexity a workable methodology for assessing cumulative risk is a challenging problem. And you've done this as reasonably as anybody could do it.

I have to say that from sort of a mechanistic biological perspective, I think that what we're doing here is a bit like looking at a basket of fruit that's got, say, an apple, a banana, and then an orange in it and then talking about an average fruit. It's not clear exactly what the means in the real world. But I don't know how to do it better without getting much more complex data sets and much more sophisticated models.

Again, maybe, on the other end of the axis from the -- approach, do it more mechanistically based approach. So it might not sound like it, but this actually is my vote of support for the way relative potency is calculated here.

DR. BRIMIJOIN: Dr. Durkin.

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DR. DURKIN: In terms of your approach, other than the comments that I made earlier, I do have a concern that the effect level where you measured the relative potency given the kind of dose response that we have here has to be at the same response level that you would use for your benchmark dose. And you have done that and I have absolutely now quarrel.

If we were reviewing with red blood cell or plasma of cholinesterase, the 10 percent wouldn't even get my attention. That we're applying to brain cholinesterase, it does get my attention. That's not a criticism. I hadn't thought through that prior to coming down the well. And the only thing that I think I would ask for in the document itself is perhaps a little bit more of a biological discussion about if you are going to stick with a 10-percent depression of brain cholinesterase as your point of departure, somewhat of a discussion about what the clinical significance of that might be.

If it was plasma and red blood cells, I think it would almost be trivial. Brain bothers me a little bit more. But in terms of how you used and defined the relative potency, I have absolutely no quarrel.

DR. KENDALL: Dr. Rhomberg.

DR. RHOMBERG: Well, I think you set out the reasons for using the BMD10 very clearly. And I agree with them. I think that the

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points were well taken.

I would like to say, though, that I was really sorry to see the reliance on M go away, the shape factor or slope or scale factor, whatever you call it, because that really did reflect the kind of equivalence across compounds that you are relying on for the whole rationale for the whole process. I understand why you had to do that. You had to do that because of the phenomenon of the shoulder. And I suppose, also, for the phenomenon for somewhat confusing calling B here, this. Refers to B in the July document, and that's different from B today which is the logit of PB if am I understanding it correctly.

DR. SETZER: That's right.

DR. RHOMBERG: So I understand why you had to abandon M because it doesn't work any more. But that's very pretty serious that it doesn't work any more. Because that under mines the whole rationale for dose addativity and looking at these things and using any relative potency no matter how well-considered and how well done as a way of adding up doses that are well below the BMD 10 level as ways of getting up towards some degree towards the BMD10 when they're acting together. And I'm not sure what exactly I would do about that.

I think I'm sort of with Rory Conolly here and saying, I don't know how exactly we could do it differently. But I think it's

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something that is really of concern and it has to be aired the fact that now that you have dose response curves of different shapes, the very method that you're doing all this comparative potency in order to be able to carry out sort of has a twist on it and it doesn't really hold any more. I think you're sort of and doing it anyway and hoping that it will being close enough.

In view of that and in view of the seriousness of it, I think it would be really be important to try to rescue the notion of a the M factor as a way of looking at relative potency. Perhaps now doing it not in terms of administered dose, but doing it in terms of some kind of internal dose. The trouble is that you have some phenomena that are probably pharmacokinetic and really are not about the mechanism of action of action affecting the shapes of your dose response curves here.

Because you're only -- you're doing everything in terms of administered doses, you have to try to capture those effects in the dose response curve incorrectly and sort of incorrectly ascribing them to things that are really about the mechanism of action this point that you're trying to get descriptions of it as you're trying to capture in those dose response curves.

If you could split those things apart and say you got some

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pharmacokinetic things that going on, if we can take care of them separately and then look at once you get some internal dose measures, even if they are empirical and crude, rather than the sophisticated PBPK ones, maybe you can rescue the common shape of the inhibition curve issue which would put you on a much sounder footing and lets you go ahead with the rest of the analysis.

DR. CONOLLY: I would like to say the same to that other than I think discussion needs to start.

DR. RHOMBERG: I would like to underscore Dr. Rhomberg's comments. I share his concerns about dose response analysis for that standpoint although I'm not as optimistic that M can be rescued, at least not in the time frame you have to work with.

On page 1B56 is where you talk about relationships among the dose response curves and acknowledge that they're not going to be parallel for some pretty good biological reasons. And I think that's why we talked about this in previous SAP meetings. Expecting them all to have nice parallel dose response curves is a problem and not realistic given the perhaps the pharmacodynamic and certainly pharmacokinetic.

Also on that section of the document there's sort of a discussion. I was a little bit concerned because the discussion talks

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about, sort of deals with this by saying, well, we really think that addativity is probably a reasonable default and assumption for these sort of mixing -- versus the importance of parallelism and dose response curves. I think you're probably right. I haven't seen compelling evidence that there is a significant interaction at which it need to be factored into your risk assessment. So I think you're probably correct in assuming no interaction which would apply addativity.

The question is how you add. And the method selected was the relative toxic potency approach, as Lorenz pointed out, depends upon parallelism and dose response curves depending on where that doesn't exist. So the potency is going to be different depending upon where on the dose response curve you pick to establish that.

And I was one of the folks that sort of argued at the last meeting for BMD10 as opposed to some other -- because it's at the low end of the dose response curve. And it's probably from a practical standpoint about the best that you can do.

But having said that, of course, we're really mostly concerned with exposure that are going to be occurring at one 100th of a BMD10. And that's where the relative potency really matters for the purposes of this cumulative risk assessment. And I don't know that

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you have any way to estimate what that BMD.

But I think it needs, as Lorenz says, I think it needs to be dealt with more candidly in the assessment. And this is a potential problem ... fundamental assumption that underlies the approach that we're using in this cumulative risk assessment. And you know, we think that that's a problem for whatever reason or do some kind of analysis that really talks about how this would effect the...

DR. KENDALL: Dr. Portier.

DR. PORTIER: I'm going to different differ with my colleges on this issue. And then I have another point.

First of all, I'm going to reiterate the fact that the Agency has done exactly what we asked them to do. I especially liked the reparameterization to direct the estimate of BMD in the algorithm. I thought that was clever and very useful. But for my comment that's going to come in a minute.

The panel may forget that our discussion regarding the use of potency was the fact that in the previous model the assumption was not dose addativity; the assumption was being used was potency addativity. And under the model that was being used, potency addativity was equivalent to dose addativity.

However, now as Steve has pointed out, we have gone to

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models that potential a have different shapes. The Agency has, in fact, stuck with dose addativity by using BMD10. So they have kept to what we asked them to do in terms of clarifying how they're going to deal with the addativity issues... by dose addativity or something else.

So I want to make sure that we don't keep rethrashing through the same argument over and over again. That be clear this time what we want to do with that.

And would have appreciated some discussion of signal-to-noise ratio in the estimates. It's something we raised in our last discussion about how to chose the BMD. Do you choose 10; do you choose 5? And the argument was that you want to choose something that constrains the variance. Optimal variance is probably around 50 for most of these. And so some discussion about how variance relates to mean estimate would have been useful in looking at the BMDs.

I would have, also, have liked some objective demonstration of the choice of the BMD. Not just to use BMD10, but to chose 5, chose 1, chose 10 and then evaluate it and tell me 10 falls within the range 95 percent of the time; 5 falls in the range of the data 65 percent of the time. Just some observations that would allow me to feel more comfortable about the choice of 10 as compared to something else.

Per the question of whether the BMD10 or 5 or whatever that's

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chosen for relative potency should be the same one as point of departure, I do agree with that concept in the context of this model; that if we have a optimal choice for a V and R for a response and you chose the BMD for that and do relative potency on that, I'm really happy with that. But what I'm not going to be happy with is that the margin of exposure is always going to be the same if I'm using 10 percent, 5 percent, and 1 percent.

So I think the adjustment is not in terms of what we choose as our point of departure because to me it seems logical to use that as point of departure some optimized ought to be cross multiple data sets that deals with the concept of dose addativity. It's going to be in the margin of exposure that we have to make some adjustments because we're using in this analysis 10 percent and they use some other chemical a few years down the road where they use 1 percent because we have better data. And I think that's where the adjustment factor should be.

DR. BRIMIJOIN: I'm not sure if we can pull. I think we should try and see if we can reach some consensus on this point because EPA wants some specific advise from us. And as you say, they reacted to some specific advise. Before we're now fixating on some fairly obvious problems with that recommendation.

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So the question I would pose to my fellow panel members is: Do we go forward saying that BMD10 is a point of departure and elements of relative potency is fraught with problems but is, in fact, the best compromised solution we have at the moment? Do we do as you seem to be suggesting, and it has some attractive features, is ask EPA to reevaluate their data sets. And if they can determine that with without too great a loss in precision, one could go down the scale.

And so we're talking about 5 percent or 2 percent or even 1 percent effects that everyone would be more comfortable with that as a point of departure in lieu of the old days of the no adverse effect level.

So I think we should either, if we can reach any kind of consensus at all, recommend going forward as is with the possibility of reevaluation; or recommending that some sign of internal data or modeling review be conducted and a further decision be reached on the basis of the outcome of that.

We've heard one panel member expressing concern with 10-percent inhibition of brain activity as a possible issue. And, you know, I guess I share that concern even though I'm well aware that it's almost impossible to detect acute effects at a behavioral level or from any inhibition that's much less than about 30 percent, even take 50 percent. And yet I'm, also, uncomfortable with the idea that this

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would be kind of the starting point.

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I, Jane F. Hoffman, Stenotype Reporter, do hereby certify that the foregoing proceedings were reported by me in stenotypy, transcribed under my direction and are a verbatim record of the proceedings had.

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JANE F. HOFFMAN

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JANE F. HOFFMAN

849 S. Irving Street

Arlington, VA 22204

SS#305-52-5988

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DR. DURKIN: It seems to me that -- Chris has kind of put his finger on it here. You folks aren't approaching this from an RFD point of view, but you are looking at it as a margin of exposure. It seemed to me that where Chris might be going, and please correct me if I'm wrong here, is that if the stability, the confidence intervals narrowed at a higher effect level, that might not be a bad thing to do.

But then you would simply want to say, well, we're not going to accept an MOE of 100, but maybe an MOE of something higher.

And that seems to be a reasonable approach, which is not to say I think that there is going to be any consensus here that you want to do anything differently.

I mean, the ED10 is a little disquieting. It's not bringing down the house. You are not going to have folks lined up down on the floor. So it may be reasonable to have an ED10 with an MOE of 100. It could be reasonable to pick an ED50 perhaps and, depending on how the data are, and simply say as a judgmental approach that now we're not happy with an MOE of 100 anymore, but we're going to increase that by some factor.

And I don't know that there is a truly analytical way to get at that. I think that may just involve somebody probably down at that end of the table going out on a long limb.

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But the gist, I think, of our comments here is that what you have done appears to be reasonable. There are other things that you can think about, but there is nothing really wrong here.

DR. KENDALL: I can accept that.

DR. BRIMIJOIN: One more comment, then we should turn to some of the other questions.

DR. PORTIER: I'm just going to highlight one of the things in my comment, which I have written down. And that is, an objective criteria for choosing a benchmark dose.

All I'm asking for is some objective criteria for that. And then we can talk about the risk characterization later. But that's the thing to look for, is why choose 10 or 5 or 1.

DR. BRIMIJOIN: The next point that is raised here is a question about the expression of inhalation exposure in the same units as the oral doses.

That was something that EPA was told to do by the previous meeting. They have done it.

Does everyone agree on that point?

THE MEMBERS: Yes.

DR. BRIMIJOIN: So that brings us to consideration of the impact of individual animal data instead of summary information.

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And Dr. Durkin had a comment on that.

DR. DURKIN: Well, I would like to beat my dead horse, if I could, and just get some clarification for my own benefit and the benefit of others who are going to be looking at this method.

When we got together, I guess a couple of years ago, I made a relatively impassion plea for the use of individual animal data. You people would not accept this study if that data weren't there.

I made the point that it is not that hard to get. And it is not that hard to treat. You have been at this for a long time. I honestly think you are going to be at it for a lot longer.

And it seemed quite reasonable to me. I did work that in to the SAP recommendations in the report.

The last time we got together, I thought I heard somebody at EPA essentially say that it can be analytically demonstrated that if we use the mean and some measure of variability associated with that mean, it can be analytically demonstrated that it's just not going to make any difference at all.

And I think I heard a murmur of approval from those statistically knowledgeable around the table here. And again, I will point out that I am not now nor have I ever been a statistician, mathematician or anything else like that. I am uneasy when I read

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your response -- and overall, again, I think you have done a great job in responding to our criticisms, but this one you essentially quoted our last report which had a bit of a milk/toast thing about individual animal data are nice, but it probably wouldn't make that much difference. And I think we might have been echoing back what we heard.

I have tried to understand better, read a few things with all sorts of Greek characters that gave me the willies.

We do have a lot of really good stat people here. I just want someone to whack me on the head to tell me that I'm wrong. But this is my understanding. If the measurements from the individual animals are reasonably symmetrically distributed about the model measurement, it is probably not going to make a great deal of difference either in the central estimate of exposure or perhaps even in your assessment of the errors that might be associated with your dose response model.

If on the other hand that is not the case, and for something like acetyl cholinesterase inhibition, I'd rather suspect that especially in the lose dose region, if you have a group of 10 animals, you are probably going to see eight of them that are just honky dory and two that start heading south, that it still could be worth looking at the

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individual animal data, at very least to better explicate to people like myself why it is not generally necessary.

And at least do it for one or two chemicals to show us that it isn't necessary.

But I really think you have to document it better and in some way qualify it so that if this huge effort that you have undertaken is indeed used, as I suspect it will be used as a model or other similar assessments, there are some guidelines.

And it may well be the case that you can analytically demonstrate that we never have to look at this data. I doubt that's true.

There probably have to be some guidelines given. And I think you should do a fuller job discussing in the document why in this case you have elected not to take that additional step and, again, educate me and perhaps put in at least a single example of here is a case where we use the individual animal data as well as the group data and it just doesn't make a lot of difference.

So I remain very skeptical about the decision. It is about the only criticism I have of what you have done to respond to us, but about this decision to ignore the individual animal data.

I'll get off the soap box now.

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DR. KENDALL: I would welcome a response.

DR. SETZER: There are a number of issues surrounding the individual animal data.

One of them is the one you have alluded to. And it has to do with sort of the shapes of distributions and the nature of the response. I basically agree with your concerns about that.

The other issue, and that was one that people -- I think we talked about a lot in the last SAP review, had to do with the issue that for the blood measurements, plasma and red blood cell, we had repeated measures on those data sets.

And in fact in that case, we can't even do a legitimate analysis of the data without individual animals.

Imagine my joy to hear that we have decided to work on brain instead of plasma and red blood cell. We have eliminated that.

DR. DURKIN: It doesn't get you off the hook.

DR. SETZER: I understand that it doesn't get us off the hook. But it changes the relative priorities of various sorts of analyses.

Part of the problem has to do with the relative efforts involved in getting individual animal data for all these chemicals. The data are there, my understanding is, on paper stored away somewhere.

Turning those into something that we can analyze is doable, but

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labor intensive and can take time. And I think my understanding is we couldn't get it done before our deadlines.

However, we do have the sort of data sets you are talking about. We have an example data set. At the moment I can't give you the details. It is several chemicals and at least more than one study at least for some of the chemicals.

We do have easily -- already extracted the individual animal data. And it is our intention to analyze those data. We just didn't get to it yet.

DR. DURKIN: In terms of some of the problems that you have talked about in optimizing your model, the thing that I have found at least with kinetic studies is your optimization may head south if you use group measurements.

If you do pull in the individual animal studies, a lot of times your models will optimize better.

I'm not making a guaranty here of course. But I'm just trying to encourage the agency to at least think about it.

I know that it is clerical work. And I appreciate that. And you have to QC it. And there is all sorts of troubles.

But it would certainly make me feel better to at least see in the body of your report we don't use individual animal data because it just

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ain't necessary, or whatever you want to say and to see at least one example to get this guy off our back. It just didn't make a whole lot of difference.

But I do suspect that with cholinesterase it will give you perhaps an insight into what is going on with the animals that could be useful.

DR. KENDALL: Dr. Durkin, I think you have made your point. And it's well taken.

DR. LOWIT: Can I make one more response? We thought about this a lot.

And Woody is correct. The vast majority of the data we have right this second is in paper in shelves and everything else and have made efforts to make images of the pages and everything else.

We have roughly between 15 and 20 for which we have been able to take TIF images and convert them to electronic data sets. And honestly, I ran out of time.

DR. KENDALL: Thank you.

Dr. Portier?

DR. PORTIER: I'll briefly reiterate a point we made at the last meeting just so it is on the record again this time.

And that we would encourage the agency to prospectively think

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about beginning to collect all of this data electronically for any future studies so that you can do individual animal data analyses.

Not necessarily retrospectively for this one, but clearly there is some advantage to doing that in the future.

DR. KENDALL: Good point. Very good.

Dr. Brimijoin, I know you are going to make it through this first question.

DR. BRIMIJOIN: Yes. We're getting close here.

The last question is about the derivation of oral doses from the actual dietary intake rates.

Again, that's a cryptic summary of a recommendation from September. And I take it that the point was measure actual rates. Don't just guess what levels are being ingested.

Is the panel satisfied with the response in the present document?

THE MEMBERS: Yes.

DR. MCCONNELL: I would only add one thing. This is a small point, but it's one that bugs me all the time when I see it, is that exposure and dose are misused quite often in this document.

And I think it would for the purists in the crowd it would certainly help that when you talk about dose you are talking about what really is absorbed into the body versus exposure, what we get in

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our food and what we breathe and what we get on our skin.

And there are two different concepts. For toxicologists, it is one of those pet peeve things.

DR. BRIMIJOIN: Turn this over to the next group?

DR. KENDALL: Yes, Dr. Conolly?

DR. CONOLLY: I mentioned this earlier, but I got to read the draft cancer guidelines last month. And in the guidelines is a very explicit delineation of what they call exposure. I think it is applied dose and internal dose.

And it might be useful, I think, for the agency as a whole to harmonize their terminology perhaps in these terms. It is very clearly worked out in the cancer guidelines.

DR. KENDALL: Any further comments from the panel, Dr. Portier, for Question 1A?

DR. PORTIER: I'm going to assume that we have the ability to go beyond the list of items here to some of our other recommendations that were done and comment on your handling of those other recommendations.

Is that agreeable to you?

DR. KENDALL: Yes.

DR. PORTIER: There was one more point which I raised in my

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questions but which I will now formally comment on.

And that is the CELs and the use of the CELs in this analysis and the comparison of the CELs to the benchmark dose numbers.

I still believe that this is inappropriate. I still frown upon the agency using NOAELs and LOAELs in any context. I believe the regression based techniques indicate to you when in fact you don't have sufficient information to make a dose response analysis. And to use LOAELs and NOAELs in those situations are just going to be somewhat misleading.

There are a few pathological cases where you might make a good argument for a LOAEL or NOAEL. But I think as a general rule I would prefer regression analysis.

In addition, there are some, I'll call them, throwaway statements, for lack of a better term. In the risk assessment document, they talk about inability to fit some of these data to dose response models, which I find difficult to believe in looking at the data that I was looking at.

So again, I would encourage you to extend the regression techniques across all data sets.

And failure to do that should tell you something about the information you have in hand.

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DR. KENDALL: Dr. Reed?

DR. REED: I think I was the one who made that comment during the last meeting, that last request about deriving oral doses from actual dietary intake rates.

My comment was in the context of when we were looking at where is the beginning of this, 21 days or 28 days or any further. And at the time I understood that the dose was calculated based on an average body weight and consumption rate in a long term study, for example, a two-year study.

And it isn't quite sure right now to me if that had been looked at since then or -- I was under the impression that there was no further analysis since September's meeting about the data sets.

Am I correct on that?

I mean, did the agency go back and did reanalyze or reenter the dose response based on --

DR. LOWIT: I believe the document number is III B -- I'm pretty sure it is 4.

There is a section in that document where we did a pilot and -- somewhat of a pilot using subsets of the studies where each time point the dietary intake from a window close to the time of the cholinesterase was measured was used as opposed to the whole study

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average. And that is in that section as a pilot.

And I assume when they -- this side of the room nods their head that that was okay, that they saw that.

DR. REED: That's what I thought. But then it was confusing when there was a statement about half an hour ago saying there is no reanalysis of data. And then I was confused about that.

So there was. Okay.

The other thing is that I probably don't have as strong a feeling against using NOAEL as comparison point when you don't have enough data, but I was also under the impression that with the oral studies there is situations where, because we're using brain cholinesterase inhibition now, that you might not have as many data sets and there is situations where you only have one data set with the oral data.

So how does that differ from the inhalation and dermal studies having lack of data? I understand that in certain situations you just can't model it. But I also would like to echo Chris's comment about if it is possible to see how they model.

I understand that not every case you have the luxury of doing that even with one data set.

DR. KENDALL: Dr. Bull?

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DR. BULL: I saved this until last because it's not the most important thing.

One of the things that I missed as I read through this, and I had to read some parts of it very quickly, I would have liked -- I realize you don't have all the pharmacokinetic mechanistic information you need on all 29 compounds, but as you are going through these processes, as did you when you dealt with the shoulder on the response, it would be useful to kind of check your assumptions against the data that are there.

One of the things I saw no discussion of is -- 4 is more of an example.

The degree of cholinesterase inhibition at any given point in time reaches a steady state based on the rate at which react with the enzyme and the rate which is either regenerated or resynthesized.

And it would have been nice to just kind of touch base with that and say, well, in the rat we know that the enzyme is regenerated with a half line of X, Y or Z.

Some of the -- maybe your shoulder even might relate to the fact that somebody's phosphate esters are going to hydrolyze at different rates than others depending on the structure of the phosphate ester -- and so forth.

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If you could find -- if could kind of spend a little bit of time, not a lot, because you are still going to have to go back, as I think you did to the descriptive data in the end anyway, it would just make those of us that are a little bit more inclined towards mechanism if you bless that part of the effort.

It's just a general comment.

DR. KENDALL: Thank you. For the panel in terms of moving forward here, we will go onto Question 1 B, complete that and take a break.

Then I would like, because we are doing very well, Mr. Lewis here has recommended that we proceed to the next question, which would have been scheduled for tomorrow morning, and to achieve that question today, leaving us to begin in the morning with the assessment of food exposure. That's where I would like to be.

And there is some consideration as recommended to me by Mr. Dorsey as trying to finish all the panel's deliberation by Thursday evening instead of going into Friday.

I want you thinking about that, EPA.

So we will proceed as deliberately as needed, whatever time is needed, but this is a possibility. And it would, I think, be more efficient in time and resources if that was achieved.

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Nevertheless, let's go to Question 1 B. And that has been presented to us. And Dr. Heeringa, would you lead off, please, sir?

DR. HEERINGA: Let me for the record just read the question, Question 1 B.

DR. KENDALL: That will be fine.

DR. HEERINGA: Several of these issues were addressed by the application of the nonlinear mixed effect model for combining cholinesterase data.

In addition, EPA utilized the profile likelihood method for estimating horizontal asymptotes when they could not be estimated jointly with other parameters. Please comment on the use of these statistical procedures in the dose response assessment of the organophosphate pesticides.

I'm going to lead off with a few comments.

DR. KENDALL: Yes. Thank you, Dr. Heeringa.

DR. HEERINGA: The question of the nonlinear mixed effect model, and that's a long title for a statistical procedure, let's break it down for a moment, it is quite clear that the nonlinear component here, even if we assume normality of the error terms, essentially what we're saying is that the conditional means of these expected responses are nonlinearly functions of a series of parameters.

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So that piece is quite obvious. And I think that has been recognized for a long time.

But one thing about nonlinear modeling of any sort is that the data must be adapted to estimate the points of inflection in these nonlinear models.

Just my sort of naive exposure to this is that a lot of the dose response studies that we appear to be dealing with appear to be more optimized. In other words, their spacing of dosings in the underlined studies themselves appear to be more optimal for linear estimation such as probe it type dose response regression functions.

And looking through the actual graphs that were presented, which were very, very helpful for me because I'm pretty much a visual person on a lot of statistics, it is quite clear that for a lot of the things that we're dealing with, such as the shape and displacement parameters in the expended model, that a lot of those parameters in the current studies are being estimated in zones of observation where we have very little data.

If you look at it, a lot of times we get data points preceding the inflection points represented either by the parameters in the basic model or the S and D parameters in the expanded model.

And that's not something that the EPA can do anything about.

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However, I think in encouraging, if we move on to use these models in cumulative risk assessment for organophospates, I think it behooves all of us to begin looking at measurement strategies that are more optimal for estimating these particular models.

I'm going to leave comments about the expanded models for the next question.

The second is really the mixed effect in that here we're talking about mixtures affixed and random effects.

My only comment here is that mixed effect models are very, very useful. And I think that this is an appropriate adaptation of mixed effect models.

Now, we have to remember what we -- when we include random effects in models, you essentially -- random effects are included to reflect effects of things that pretty much are random in the observation process, like the animals themselves, their responsiveness, whether you get a particular batch of rats that has a particular disposition to cholinesterase inhibition.

We expect that to vary about some mean for the standard series of rats that are being used or other animals that are being used, the particular preparations, which might be errors at the local level, but they may vary about calibration standards or other forms of

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measurement error.

One of the things that we're including in these models as a random effect are essentially the data sets within the studies.

And I asked the question this morning about what distinguishes those. And the point comes up that duration may distinguish one data set from another.

And I had asked the question if we're treating data sets as random effects, we're really treating duration as a random effect. Is duration a random effect or a fixed effect in modeling cholinesterase inhibition.

These are sort of rhetorical questions which I ask myself. And they are not criticisms. But you need the minimum of two observations to estimate a variance.

And when we get into these random effects, one of the principles here, and without looking at power E calculations, but we need to have a significant number of observations on the random effect itself.

And if that is a study, we need to have I believe more than two studies to be pretending they are random effects. Otherwise, we could say we have effective a particular individual or a particular teacher. But if it is Mr. Smith and Ms. Jones and those are the only two

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observations we have, we really have fixed effect to Mr. Smith and Ms. Jones. And we're averaging that.

So we have to be a little bit careful in using the mixed effect model here when we have a very few observations on a particular random effect that we're trying to model.

One other question I had related to random effects too, and I should have asked it earlier, and that is is there any way that we can reflect the degrees of freedom. And that is the statistical information in these data set means and standard deviations.

In other words, the quantities going into these models are actually estimates of means which are based on varying numbers of individual observations on individual animal subjects.

And there is information there that in terms of degrees of freedom that is not being reflected unless it's somehow being built into as some sort of weighting for the actual variance of the mean that has been estimated.

Finally, on the use of the profile likelihood, the whole issue of data density arises here as well. We all know full likelihood is really a function of the distribution that we assume. Here it is normal with a conditional mean and defined by the exponential functions and the amount of the individual data.

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Look at the graphics that were presented in this report. And they are excellent. I understand some of it has been redone, but I wouldn't expect these conclusions to be completely overturned. When there is data, the profile likelihood is very well defined. Obviously, decisions to use a profile likelihood method to fix values of some of these parameters that can't be separately estimated I think it makes sense.

Other cases, though, and it generally happens when other parts of the modeling break down, the profile likelihoods often wind up being sort of ill-defined or somehow narrowed to a fairly wide plateau on the likelihood function.

For example, I noticed very rarely, though, if the model fits well to the data, and just by physical inspection, if the model fits well to the data, these profile likelihoods are fairly well-defined.

If they're needed to fix values of these asymptotes for lowest threshold or lower level of effect, I think that it is probably an appropriate use.

Some things -- I only noted one case. And that was dichlorovos where in the profile likelihood, and again, this may change with the analysis that has been done subsequently, you get a saddle likelihood. The model fits well, but the profile likelihood has this sort of saddle

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shape.

So you don't know whether to go to Hill A or Hill B. You are sort of stuck in the saddle in between.

Profile likelihoods for the expanded model when I looked at those, they are -- when -- are informative at all, really. I felt they are primarily limited to knowing that the displacement is a very small number. And with a fairly wide range, don't do much to narrow the region of the optimum on the shape function of the curve.

So essentially, it informs us a little bit about how large that displacement might be in the model, but, again, leaves us pretty much wide open with the data to choose an optimum S.

The benzylthide (ph) example which we saw in the screen here and which I noted in my own notes was probably the exception. That had the nicest sort of by more to likely or by very -- profile likelihood for the expanded model.

In general, I would say that I think that as a general model, the nonlinear mixed effect model is appropriate.

And in cases where we have a good number of studies and a rich base of data that spans a wide range of doses, it appears to work well and is clearly the preferred model.

I think like everything else in statistics when we begin to run

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out of data, all of this begins to become a little more questionable.

And I really don't have any alternatives for those situations where we're in the situation of sparse data, except to get more data, and that doesn't help you right now.

DR. KENDALL: Thank you, Dr. Heeringa.

Dr. Portier, Dr. MacDonald?

Dr. Portier will go first.

DR. PORTIER: I will read the points I put down up to this point.

I think the mixed effect model corrected for many of the problems we highlighted in the previous review. So I think a lot of things have been taken care of that we talked about.

In terms of the comment concerning the profile likelihood or the question concerning the profile likelihood, my intuition in looking at this is that if the optimization, if the algorithm used for optimization dealt with boundary value problems, you would probably skip that profile likelihood step.

It seems to me in the way you are doing the profile likelihood visually and saying, well, this one is going to converge, but that one doesn't, the failure to converge is at the boundary value situations.

And so it's the log transforms, the inability to go to actual zero

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is the thing that may be driving the lack of convergence more so than an actual failure to find an optimum.

And I think you should -- one suggestion is to look at that. I don't think it will have any impact. Because the choices you are making in the cases where you are getting stuck to the boundary is exactly the choice in algorithm that dealt with the boundary value problem we deal with.

I will reiterate that clarity of the model and methods would be greatly appreciated. Again, showing a model in mathematical form that talks about the variance construction and the fixed and random effects that go on would be useful.

One point that comes to mind in hearing Dr. Heeringa's comments just now is that in the decision tree where you were evaluating how to move through the various models, it is a good question to ask why go to a single B value with a random effect as compared to a fixed sex effect B value as the third voice.

And the fact that you never choose the third choice may be simply because the third choice and the second choice are effectively equally parameterized.

And you would pick up the sort of almost the same likelihood in the two separate cases.

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And finally, one concern for me is the actual expanded model itself. In essence, you have gone from the basic model to the expanded model, and you have jumped in two parameters in doing it.

One parameter deals with sort of a shape issue and the other parameter deals with sort of a point of discontinuity breakpoint off the zero Y axis response point.

It might be interesting in thinking about how to move forward with this to separate those two issues out and ask yourself do I really need a shape parameter or do I really need a point of discontinuity on the zero response point, and choose one or the other rather than having to choose both in the analysis.

Because I am concerned about them collapsing in degrees of freedom as they both get towards zero or infinity depending on the parameter you are looking at in the expanded model.

DR. KENDALL: Any questions from EPA? Dr. Setzer?

DR. SETZER: I would like to respond. If I can remember the points, I want to respond to a couple of those points.

As to the issue of basically -- the first part was sort of the issue what is going on. How come we can't always estimate this horizontal asymptote.

And Dr. Portier has said that it has something to do with -- has

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to do with not being able to get to zero for the parameter on the right scale.

One of the things I have done, since December, and it's not anything you have seen or I didn't talk about it today because it is complicated to describe, and I'm not sure how -- if it was worth spending a lot of time on, but I'll bring it up.

There is an approach to analyzing parameter redundancy in nonlinear models, which essentially looks at the degree to which over the -- either for an experimental design or sort of over a range of the independent variables, the degree to which parameters and the model sort of -- multiple sets of values for the sets of parameters can give you essentially the same model shape.

And I applied that to the specific designs we have in this study.

What happens is that the models where we have to fix a piece of B or we have to affix B are exactly those chemicals where the degree of association between the benchmark dose estimate and the piece of B are highest.

So basically what happens is we could -- is that if you adjust piece of B a little bit, you can also adjust the benchmark dose estimate a little bit to give you essentially the model shape.

I don't think that is a function of the transformation used. I

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think that's actually a function of the designs that we have to work with.

I have forgotten my second point. So I'll let it go.

DR. KENDALL: Dr. Portier?

DR. PORTIER: I do agree that there are going to be cases where the estimate of P of B is going to be so unstable that anything in a broad range is going to work and you are going to get extremely flat likelihoods. That should be reflected in the variance, not necessarily in the convergence of the algorithm plus or minus error.

So the only problems I have ever seen in convergence of algorithms for optimization are: One, I set my criteria for convergence to be too tight.

Two, I have got multiple modes, I've got multiple humps. And one time I get this one, another time I get that one.

And the third time is I have got nonidentifiability, and I just don't know it. I have parameters that are so correlated with each other that finding one value adjust the other value, and there is just an infinite number of solutions, which is sort of what you are talking about in the case of P B.

But the worst one I have ever found, the one that always hits me is when I don't deal with the boundary value problem the way I should

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deal with the boundary value problem. And I try to log transfer my values and it keeps trying to go to negative infinity, and it just can't.

It can't ever converge because it just keeps chopping away little pieces and parts.

And algorithms that specifically project you on to the boundary and then send you along that boundary can converge quicker in those situations than things that try to log transform you along that way.

I think it is worthwhile in future derivations of your code to look for an optimization algorithm like a David and Fletcher Powell or a gradient -- B F G S modified David and Fletcher Powell to deal with the boundary conditions.

DR. KENDALL: Dr. Rhomberg?

DR. RHOMBERG: I hesitate to say this because we have been already raising the question about how biologically interpretable the shoulder equation is.

But if you send that all the way to zero by allowing yourself to do that, by dealing with the boundary value like Dr. Portier is suggesting, that is also, I think, equivalent to making K M equal to zero.

And if that kind of a biological explanation is the cause for the statistical problem which you have here, that causes all sorts of other

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issues.

If there really is a detoxification step that gets saturated at such low values that K M is not detectably different from zero, that's going to affect the pharmacokinetics of other O Ps that are co-occurring.

And when they are not tested one by one, that's already an issue that will come up later, I think.

And so I guess I would hesitate to say this is just an estimation problem and we should let it go to zero if it wants to.

We should worry something about the biological basis of this, even if we're not trying to turn it into a pharmacokinetic model to make sure that we're not doing something statistically that would cause it violence to the biological hypothesis of the reason for the phenomenon in the first place.

DR. KENDALL: Thank you.

Dr. Conolly, Dr. MacDonald?

DR. CONOLLY: I think Lorenz just made a good point for why you want to call it an empirical model. I think as long as you call it an empirical model, then you don't have to worry about the interpretation of K M too much.

Otherwise, I agree with Lorenz.

DR. KENDALL: Dr. MacDonald?

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DR. MACDONALD: I agree pretty much with everything that has been said so far. So I'm not going to repeat that.

But I think in talking with Dr. Setzer and listening to his presentations, it is really a work in progress. You have made a lot of changes since the material we got as a handout was prepared.

So I would assume that this isn't really the final version and that you are going to continue to refine it. I think you will probably have more success in fitting when you have tried a few more things.

Certainly, one advantage of working in R is that not only do you have access to the source code, but you know who wrote it, and you have access to the developers.

And generally speaking, they are very helpful if you want to modify or improve it. So that's another very useful route to go.

This issue of whether to iterate on logs or on the original parameters is something I have been dealing with in the last few months. And what Dr. Portier and Dr. Setzer have said I agree with.

I don't have an answer yet, but it is just the sort of situation where with experience you eventually do better.

I think, though, that we shouldn't get too hung up on the inability to estimate all the parameters or even on the biological reasonableness of the model.

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I think much of this is a red herring. Because really, all we're trying to get out of this is a BMD 10. In most cases, you don't need to have accurate estimates of all the parameters to get a good BMD 10 out of it. The stability of that estimate is really what we need to be looking at.

But it is a very elaborate mechanism that has been set up to get one number when you have to get so many other numbers in the process.

Though, certainly, the idea of using the mix model and combining studies, that introduces the extra variances. But I think they are of interest in their own right for the sorts of people that like thinking about variability.

DR. KENDALL: Thank you. Any further comments to this question?

Dr. Portier?

DR. PORTIER: I want to make sure a comment I made is not lost. I think all of my comments will have minor impact on what is actually done here.

I think the basic point for comment 1 B is that much of what we wanted, much of what we asked for, has been done. And I think now we're tweaking.

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DR. KENDALL: Well said.

I guess the long story made short is you have done really well since the last review and congratulations. I'm going to close this session. We'll take a break. 15 minutes.

Dr. Perfetti, I would like to begin the assessment, the next question, the hazard and dose response analysis.

Okay?

If you have any comments you want to make as we begin that.

DR. PERFETTI: Question 2?

DR. KENDALL: Yes.

Think about that after the break. That's what we will begin with. So a 15 minute break. Thank you.

(Thereupon, a brief recess was taken.)

DR. KENDALL: We'll reconvene the SAP meeting to now the session to deal with hazard and dose response analysis.

Dr. Perfetti has relayed to us he has no opening comments he needs to make in order to encourage the panel to move forward.

I would like to ask EPA to put the Question 2 on the screen, which they have done.

If they could read the question for us and then we will begin our deliberation.

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DR. LOWIT: An exponential model was utilized by the agency in the July 2001 Preliminary Hazard and Dose Response Assessment of the Organophosphate Pesticides. Based on the equation used in the July document, cholinesterase activity decreases linearly in the low dose region of the dose response curve.

Stakeholders present at the technical briefing in August of last year and also a few members of the Science Advisory Panel from the September meeting suggested that a flat low dose region may be a more appropriate modeling approach. In response to this issue, EPA has further investigated the shape of the low dose region of the dose response curve.

Two versions of the exponential model were used in the December hazard and dose response assessment. One version called the basic model describes a linear low dose region and is similar to the approach used in the July document. All 29 OPs were fit to the basic model. A second version called the expanded model incorporates two additional variables, shape and displacement, which describe a low dose flat region.

The female brain cholinesterase data supported a flat low dose region for eight OPs, which has now been revised to, I think it is, 17 -- 17 once the errors in the code were fixed.

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We would like you to comment on the mathematical derivation of the expanded model in addition to the use of the profile likelihood method for estimating the shape and displacement parameters when they could not be estimated jointly with the other parameters.

DR. KENDALL: Thank you. Dr. MacDonald, you are to lead off.

DR. MACDONALD: I feel that this has already been quite fairly discussed in previous questions. I don't have a lot to add. In fact, I used up my best ideas already.

So I'll just comment that I think that this model is very elegant in the fact that it has a very simple biological basis. We don't have the data to support anything more elaborate.

And I think with a little bit more experience we might have more luck in fitting it over a wide year class of data sets.

DR. KENDALL: Thank you, Dr. MacDonald.

Dr. Harry?

DR. HARRY: As we were already trying to poll whether we thought this had been covered or not, I think a number of us thought that it had.

The only questions -- I like the biology that was behind trying to come up with this. It seemed well thought out. And that was a very

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impressive process -- and very difficult, I know.

The question that I had raised was based upon that, and I tried to raise that earlier in the quality of the assays for comparison. And I talked with Dr. Brimijoin over the break, and we were sort of talking two different things when we were talking. And I feel very comfortable with the assays that you guys are using for the enzyme assays, that they are pretty comparable for potency chemical A to chemical B on the assays.

My only hesitancy would be to cross that over to a lot of other types of assays that may not be as equivalent between them.

But as far as the approach, like was mentioned, I think most of your statisticians around the table have made their comments. I can only come at it in a biology. And I was impressed with the thought process that went behind trying to pull that out and getting that low dose expression of what may be happening with that shoulder effect.

DR. KENDALL: Thank you. Dr. Rhomberg?

DR. RHOMBERG: I think also that most of my comments have actually come up somewhere along the line already.

I guess I would like to just spend a second, though, reiterating this notion that even though we're being empirical here, and I think you made a very clear point of the fact that this is an empirical factor

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that is not intended to be a physiologically based pharmacokinetic model, it is only being inspired by some possible biological explanation, that it is worthwhile thinking what biological phenomenon could account for it in principle.

And do we know enough about them from other sources of data, not from the shape of the dose response curve, to say whether that's plausible or not.

And beyond whether it is plausible or not, if you invoke those phenomena, what would those phenomena, then, say about other situations. And I touched on this briefly before.

What this is basically saying is that the main pharmacokinetic thing of concern here is other kinds of esterases in the liver that are able to metabolize these things away before they really get a chance to do their dirty work on acetyl cholinesterase inhibition.

How many of them are there? This is something I don't know very well. How specific they may be.

But the possibility arises that if that is really the case that that is going on, then low doses to some of these ones that have shoulders big enough to sort of be in the shoulder region there, or getting to the end of their shoulder region are saturating some of these enzymes.

And it will affect the way other compounds go in their relative

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potencies.

What affect will that have on the compared potencies that compounds have at the low doses where they are actually being experienced compared to the BMD 10. And I think it is just worthwhile thinking through those issues.

Not that you can do anything about them with dose response data. I agree, you can't. But trying to bring some of these other things in just sort of as a reality check I think is important.

It occurs to me that if this really is a pharmacokinetic phenomenon, to a large degree it should probably also apply to the same compounds for the RBC data. And not quite in the same way, since, I suppose, there is not really a first past exactly in the same way for the RBC, since it gets to the blood first no matter where once it gets into the blood.

But nonetheless, this isn't really strictly a first past phenomenon anyway. I think it really is just a matter of saturation of metabolic clearance. That should apply to the same compounds for the RBCs.

And the question then is in looking at the RBC dose response data, do you get the same kinds of things for the same compounds.

It would be interesting if you did. And if it was completely different, it would make you wonder a little bit about the biological

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interpretation of that phenomenon.

I think that the issue of actually estimating the two parameters for this, we have gone on about a lot, and I think I have made my point there as well, which is that for the purpose of just using this as an empirical factor for the dose response curves, the difficulty in the S and D issue doesn't really make an awful lot of difference.

The reason that it is difficult is because it doesn't make a lot of difference. So it is not really something to be worried about too much.

On the other hand, when the biological consequences of that, if any, come into play, if they do, then those issues do become important, the relative importance of S and D, because that influences the shape at the low dose part of the curve, which is where small doses of the OPs would be and where their relative potencies would actually be coming into play. And that would be important to work through.

But I would encourage working those things through not with the S and D that you fit by this empirical thing, but actually trying to go to real pharmacokinetics to do it at that point.

That's all.

DR. KENDALL: Anything to add, Dr. Conolly?

DR. CONOLLY: No.

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DR. KENDALL: Dr. Durkin?

DR. DURKIN: Again, a lot of what has been said covers this topic.

I simply wanted to say that when I first looked at what you had done, the term that crept to mind, not to get too technical, is I thought it was cute as a button.

I did not have the chance to pop this into mathematic. I'm assuming that the arithmetic is more or less correct.

And I thought you did a very nice job of making that transition from we have an empirical model here but we tried to at least base it conceptually on something biological.

I too agree that the best thing to do is a formal PB PK PD analysis. I'm not really convinced we have the data yet to do that.

If you were to go away and work on this for another decade and get the experimentalists involved in giving you the kind of information that you need, you probably can do it at some point.

I don't know that you can do it now. I have poked around a bit in the literature. I think there is stuff out there. I saw on a break -- Vicki was kind enough to at least give me a peak at some work that you guys are doing that I think is worth pursuing on the PB PK PD end.

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But I think you did just a really nice job of admitting, frankly, that we can't do a biologically based model. But you have come up with an approach that I think is just fascinating to at least give us a taste of a biological basis for the dose response model.

So I'm extremely happy with what I saw.

DR. KENDALL: Dr. Bull?

Thank you, Dr. Durkin.

DR. BULL: This is just to add. One of the things I noted is we selected female brain cholinesterase activity inhibition because it was empirically more sensitive.

Just to add a little bit I think to what Lorenz was saying, it would be real nice to know how that played out in the male brain cholinesterase. Because often, metabolic differences are accounting for that and you might get some consistency or explanations for the difference between the sensitivity in the male and female and be very intellectually satisfying to say, yes, we picked the right one.

Otherwise, you are sitting there without really knowing a basis of the difference in sensitivity. Up to this point in time, I looked at your graph. I was pretty well convinced that the females are more sensitive. But that doesn't mean that number 30 is.

So you kind of need to know what the basis of those things are

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as you take it down to the next group of registered pesticides.

So it would be nice to know what the basis of that is.

DR. KENDALL: Any further comments? Dr. Portier?

DR. PORTIER: I was going over my notes from all the public commenters to make sure that your promise that additional questions that they wanted to ask the panel would be addressed by the panel, but I don't see any other than the BMD 10 to BMD 01 question that pertains to dose response.

The rest pertain mostly to exposure. So we'll deal with them tomorrow.

I did have one comment, something for you to look at and think about. I do not have an answer for. In looking at the expanded model versus the basic model, you have eight cases where the expanded model is significantly improved over the basic model, as I understand what is presented to me in the tables.

And there may be a number of reasons why that occurs. But let's talk about what it means. And I don't think you talked about what it means. I think you talked -- you enumerated it for me, you pointed out that there were these cases. But what does this mean in terms of what is a general shape of a dose response curve for this type of effect and this type of population.

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Is there something that can be drawn out from that? For example, you did 29 analyses. And so had you seen only one in 29 analyses that was statistically significant, one might conclude that this is not major nonlinearity in the dose response for this type of pattern.

The fact that you see eight significant out of 29, and it's actually less than that because some of them don't fit, does that tell us something about the presence or absence of flat regions in the dose response curve as a general rule in this data?

Had we addressed the data in the opposite way instead of testing the hypothesis in the sense that we reject the higher order nonlinear model in favor of the linear model, but going the other way would we be looking at a different picture.

So I think as an agency you need to look at this and decide would it be more appropriate even though overparameterized to use the nonlinear or the more flexible model as a general rule in evaluating these data simply because you see it eight times significantly better across these data sets.

I don't have an answer, but I would love to see some discussion of that in looking at what you are doing in here.

DR. KENDALL: Any further comments? Then that will conclude our Session 1, hazard and dose response analysis.

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Margaret, we are prepared to move forward to Session 2, assessment of food exposure, should you want to.

DR. STASIKOWSKI: We would prefer to wait until tomorrow morning to start the discussion.

DR. KENDALL: Could you be prepared tomorrow to be ready to proceed through Section 2, assessment of food exposure and the assessment of drinking water exposure?

DR. STASIKOWSKI: Yes.

DR. KENDALL: I think we will probably be able to get at least through those two sessions, at least, if that would be possible.

DR. STASIKOWSKI: Yes. And if we're ready to start residential, we'll be ready for that as well.

DR. KENDALL: Outstanding.

I ask the panel to get a good night's sleep. We may go further than we think tomorrow.

Nevertheless, this has been an excellent day. Really incredible.

The word's incredible, the progress you have made. And quite seriously, there have been no real serious criticisms outside of the fine tuning and looking at procedure that can be best clarified and justified.

This will conclude our session today. And we will reconvene at 8:30 in the morning.

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And I would like to ask if our designated federal official for the meeting, who I have enjoyed working with, would like to have any comments for the panel or other administrative issues.

MR. LEWIS: Thank you, Dr. Kendall, for moving us along today and keeping us, if you will, ahead of schedule in allowing for a good deliberation by the panel and for comments from a couple commenters and allowing the presenters to move along at a good pace.

If I could ask all the panel members to reconvene in our breakroom at 4:15, I just want to discuss with you about any assistance you may need for compiling your comments and in terms of drafting your responses as part of the discussion today. I would appreciate it.

DR. KENDALL: This will close our session. Thank you.

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[Whereupon, at 4 p.m., the meeting concluded.]

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I, Frances M. Freeman, Stenotype Reporter, do hereby certify that the foregoing proceedings were reported by me in stenotypy, transcribed under my direction and are a verbatim record of the proceedings had.

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FRANCES M. FREEMAN

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FRANCES M. FREEMAN
21168 Wildflower Square
Ashburn, VA 20147
703/723-3550

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DR. KENDALL: We have two individuals scheduled for public comments. So we will reconvene the SAP.

The first individual would be Mark Russell from Dupont.

Dr. Russell, welcome. Please state your name and affiliation for the record.

DR. RUSSELL: Mark Russell. And I work with the Dupont Crop Protection. But today I'm here on behalf of the F Q P A Implementation Working Group.

And I have several brief comments on the EPA methodology used to estimate drinking water exposure.

The first comment before we get into any details here is really to commend the EPA for the enormous amount of work that they have done in figuring out a creative way to address cumulative assessments.

Something that may not be apparent to the SAP here if you don't do modeling yourself is there is 1,001 details. And it only takes one or two going wrong for the whole thing to create a real nightmare. They have done a lot of work here. There has been a big challenge of combining data from different scales, adapting existing models to do things they weren't originally designed to do and finding creative ways of addressing the problem of doing a cumulative assessment.

The first thing I would like to point out here about the index

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reservoir model -- and all these things were essentially covered rather thoroughly by Kevin and Nelson, is that this is -- the index reservoir model is a conservative lower tier screening model. And that is how it has been described.

It is based on a single vulnerable watershed. So it does mean that when the model generates all these numbers and we use them for regulatory assessment purposes, there are other areas within those watersheds with much lower exposures, much lower drinking water concentrations.

So there is a worst case element built-in right there.

They did follow SAP recommendations and regionalize it where they have adapted the environmental and climatic data on the 12 different regions or actually condensed them a bit.

But this model does assume edge of field run-off and erosion directly entering the reservoir. That is just part of the limitation of the PRZM/EXAM model.

So it is not properly a watershed model, but it's an adaptation of it to try to estimate that. And we need to keep that in mind.

Finally, the numbers out of this model are being treated as the exposure indicators for a large multi-state region with growing multiple crops.

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So you have adapted this worst case scenario for that purpose.

In '98 and '99, the EPA presented a number of comparisons between the results obtained from this model with monitoring studies.

One of the frustrations that occurs is you only have a handful of monitoring data, and the model predicts daily data.

They tried to do some comparisons to get a feel for were they overpredicting, underpredicting. What they generally found was that for high use rate chemicals used over a significant fraction of the watershed, they did a pretty reasonable job. The model was reasonably conservative.

But for many other chemicals, it provides higher estimates than the existing monitoring data.

I think people tend to focus on a few numbers where maybe the model will underpredict a single event or two.

But systematically, the model is more likely to overpredict because of how it has been put together and how it is being used. That's no fault of the EPA. It is just the limitations of this technology.

In the interim, the EPA has also added a spray drift component, or revised it, actually. And there is the potential that could contribute to some additional overprediction or bias.

This last point, the previous speakers have agreed they

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recognize that they need to do this, the EPA should perform a comparison of the model to monitoring data. Essentially, pull it together and publish the results for peer review to more clearly define the capabilities and the limitations of this drinking water assessment method.

There are a number of very significant accomplishments, though, that the EPA has made through offering of this tool. And the first and foremost is the use of distributions of daily concentration. They are now compatible with Calendex.

The one slide that we showed earlier that had the nice little, bright red line, the one in ten year concentration, you can just imagine what contribution that makes to an assessment as opposed to using more realistic distributions of data that vary in time. So that's a significant upgrade.

And then the practical fact is that use rate determines concentration. And using the typical use rates and typical numbers of applications, adjusting those with cumulative adjustment factors are all EPA's attempt to come up with a cumulative assessment that realistically reflects the concentrations likely to be out there. And we applaud those kind of efforts to add realism in refining these assessments.

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And I have already mentioned before, there was regional variation of data as opposed to using one big national scheme.

Our bottom line assessment when we look at what has been offered up, we agree with what is being done for the OPs in that if water is a minor contributor to the overall MOE, it makes sense to say that this methodology is sufficient.

It is generally conservative. It provides a high end estimate in general. It seems to be a sufficient way to cap the potential exposure from the drinking water.

However, if water proves to be a major contributor, it is probably appropriate to consider refining this methodology and ensuring that the predicted values are as consistent as possible with monitoring data.

So that the whole weight of evidence of both modeling and monitoring tend to agree rather than acknowledging some kind of systematic bias.

And my final slide is the need for a more refined assessment has been recognized by a number of groups, including the EPA, USGS and USDA. A working group has been established to develop improved modeling methods based on national monitoring data.

The IWG and Crop Life America strongly support this effort to

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produce more realistic evaluations of pesticide concentrations in drinking water.

Thank you.

DR. KENDALL: Thank you.

Any questions from the panel for Dr. Russell? Dr. Roberts?

DR. ROBERTS: Let me ask you this question, and maybe the EPA wants to respond as well.

At the end of their presentation, we were talking about how far off the model predictions were from the monitoring data. And it was mentioned that in some cases the monitoring data were up to an order of magnitude higher, but that those tended to be in things like streams, which is -- in high intensive agricultural use areas.

And I can see there is sort of perhaps a locational mismatch in terms of trying to take monitoring data from streams and comparing it for a predicted concentration for a reservoir that would be presumably downstream.

Can you give me your assessment having taken a look at this data, the data that are available of comparing them on the same basis, in other words, monitoring data from reservoirs versus predicted concentrations for reservoirs, how far are they off and what directions and sort of in what frequencies.

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Can you kind of give us a feel for that?

DR. RUSSELL: There are two recent reservoir based studies. One is a study of OPs done by OP registrants. And the second is a 12 reservoir study conducted by the US EPA.

I haven't systematically -- there is no way that you just off the cuff directly compare those to the results that they have generated in this OP case study.

But in general, if you look at the concentrations, the model seems to have the general capability of overpredicting what has been observed.

When people talk about the model underpredicting basis monitoring data, very frequently it is just one or two data points.

And then it raises some concern because monitoring data is only collected periodically. You don't know for sure what went on in between those sampling events.

There could be the presumption that it was uniform. But in a stream, that's not true. It is usually very flashy. So in a stream, if there is -- if the model underpredicts, it may not be as much of an issue as if it were a reservoir.

DR. KENDALL: EPA, would you care to comment?

MR. COSTELLO: There were a lot of things he was talking

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about running through my mind. Would you mind just repeating that again so I can make sure I focus on your --

DR. ROBERTS: I'm sort of interested in model versus monitoring data comparisons on what I think, suspect, is probably the most valid point, which it would be reservoir data, since that's what the model is trying to predict.

Stream data is arguably something different. So if we sort of throw those out and just concentrate on monitoring data that most closely represent what the model is trying to predict, how far are they off --

MR. COSTELLO: If we did that, in a lot of those areas we would not even have anything to compare with.

We are just now in recent years starting to see more systematic monitoring of reservoirs. One of the reasons for the USGS EPA's pilot reservoir monitoring data was to start asking a few questions about what do we know about the nature of pesticide occurrence in drinking water reservoirs so that we can do that.

And that study has just recently been published. And we're looking through that. We are looking at some other areas, but I think a lot of that was designed to start answering some questions how frequently do you sample, how often, when do you focus it.

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The working group that Mark Russell mentioned is another step along those lines in terms of getting national monitoring data focusing on reservoirs and some of the areas where we need to fill in the holes.

Part of that is -- the reason I gave you the comparison I did is because that is what we had to work with. As Kevin pointed out, we don't have any single definitive study to focus on. So we're pulling together from as many different sources as we can.

MR. THURMAN: And remember, just because our current modeling tool is reservoir tool, it doesn't mean that monitoring data we get from streams is not important.

They are a very important source of drinking water around the country. And if we were to see large potential exposure from drinking water derived from streams, then rather than not consider that, we might have to reconsider how we're doing our drinking water assessments.

DR. ROBERTS: Thank you.

DR. KENDALL: Any further questions for Dr. Russell?

Dr. Portier?

DR. PORTIER: I'm going to beat a dead horse because you pointedly asked the question about relative myriad of the water data. I'm going to re-ask Steve's question again.

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For the reservoir monitoring data that you have in comparison to what you predicted, how often, what is the largest magnitude error you are seeing, and how many data points is that error occurring in.

That's the real question in terms of whether you are conservative or not. If there are a million data points and you are off one time, you are conservative.

If there are five data points and you are off one time, I would argue you aren't conservative.

That's the question I need answered.

MR. COSTELLO: One of the challenges -- let's take a look at USGS, the pilot monitoring, because that was the one we had available at the time we were doing comparisons, that we had available for any length of time to look at.

Of the 12 reservoirs they looked at, only one was located in a high use area, in one of the regions that we did our assessment. So there was only one where we could do that direct comparison.

DR. PORTIER: High use for the OPs?

MR. COSTELLO: High use to the OPs. That original study was designed to target a number, variety of pesticides.

It wasn't specifically focused on OPs, so we weren't necessarily expecting it to be that way everywhere. We are just now looking at --

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an initial eyeball's looks is that we're in the same ballpark. We're not way off on that. We're still doing an analysis of that part of it.

The other thing to keep in mind is that when we were doing that comparison, that was basically run in two years. Particularly, when you look at the area, the reservoir where we were taking a look, which to do direct comparisons in North Carolina, the first year in the east we had basically a draught. The second year or part, toward the end of that year, there was a hurricane that went through and pretty much overwhelmed things. So we had two extremes.

And we really had trouble trying to interpret what that data meant directly. So that's part of our trouble that we have on that.

When we have looked at the water, the stream monitoring, we know that's a different -- whenever I basically seen there is one or two with few known detects, we basically started looking not just one or two higher. We were taking a look at a number of things.

How many are higher. And if -- if there was one that just stuck out as an outlier, we basically said, okay, that could be just one spike that we hit. But we were looking at several that would come up on that.

MR. THURMAN: But if you think back to the slides where we gave the history of coming to the SAP and getting guidance, this is a

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direct result of the SAP guidance to focus on monitoring to allow us to develop and evaluate -- monitoring so we can develop and evaluate our models.

So here is where we are in the process. We have a pilot reservoir monitoring study. And the OPs came up soon after.

So this program, which is exciting to us, is early on. And that kind of data will be used to develop and evaluate for future modeling.

DR. KENDALL: Further comments for Dr. Russell?

Thank you.

We have one more registered public presenter, Dr. Judith Schreiber from the New York State Office of the Attorney General.

DR. SCHREIBER: Good afternoon. Dr. Schreiber from the New York State Attorney General's office.

I had a couple of points. First, a point of clarification for myself. I might have missed something, but I just want to make sure that it is true that if the OP has been canceled, then the water route of exposure is not considered in the assessment. Correct?

MR. THURMAN: That's true.

DR. SCHREIBER: For groundwater I know, at least in my experience in New York state, there certainly are occasions where when groundwater is contaminated it remains contaminated for a

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substantial period of time afterwards because it doesn't really lend itself to cleansing out as it does in surface water situations.

So I was wondering whether the EPA has assessed the impact of residues in groundwater that remain even after the cancellation of the organophosphate in question whether you have conducted any modeling or assessment to look at how long these residues might be expected to remain in groundwater.

Also, one big item that I didn't recall, hear being discussed, maybe it was discussed and I missed it, is sole source aquifers.

In New York state there is a number of sole source aquifer areas. In particular, Long Island, which is a heavy populated area outside of New York City where many, many people rely on groundwater as the only source of drinking water.

Has the EPA looked at sole source aquifers in the nation to determine whether in fact your assessment has adequately taken into account people who rely on groundwater, and that groundwater supply, if contaminated, is really, highly unlikely to cleanse itself in any short period of time.

And then, finally, not to beat this dead horse with the infant formula, but let me just give it one more stab, and that is for infants zero to six months of age, either they are ingesting breast milk or they

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are ingesting formula, period.

Children that young do not eat solid foods, baby foods or anything else. So even though the level of OPs in drinking water may be very low, at that stage of an infant's life, especially given the sensitive neurological development, in fact, the reason why we're doing this OP assessment in the first place, I would think that the EPA should really take a hard look at that very small period of time when the infant is being exposed theoretically to organophosphates in drinking water directly used for formula or more indirectly through the mother's breast milk which may have contaminant levels.

I would also point out that I do take issue with the statement made this morning about the similarity of human breast milk to cow's milk in terms of its contaminant levels.

I would feel pretty strongly based on the work that I have done, I have done a lot of work on maternal and children's health issues, including breast milk exposures, that, in fact, women are exposed to a much wider variety of OPs than are cows. And therefore, being higher on the food chain than cows, also would be most likely to have more organophosphates in milk than a cow would.

And I can provide you with some of that data if you are interested.

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So those are points that I had as questions. I don't know if anybody wants to answer those or have a discussion.

DR. KENDALL: Thank you.

Would EPA care to address some of those issues?

MR. THURMAN: To the extent that in our presentation we discussed the possibility that groundwater exposure is not fully addressed by our surface water assessment, I guess I would have to stand by that.

There are certain -- there are a few of the OPs that in our original assessments were seen to be great contaminators, if you will, of groundwater.

And as far as a cumulative assessment go, we have no data, actually, that indicates that OPs are found -- that they co-occur in groundwater.

Our biggest constraints were first, again, the lack of a model to allow us to get daily distributions for use in Calendex and then the lack of monitoring data. Especially, monitoring data that actually shows OPs getting to groundwater.

As a class, they are not a groundwater concern compared to many herbicides, especially. But we have to look at some of the individual OPs.

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As far as looking at sole source aquifers, I guess that was part of what I was trying to address when I said in our regional assessments.

For those areas that groundwater was the main source of drinking water, we did try to look at what the hydrology and the local geology are.

I know that in Florida, for instance, we considered that -- in southern Florida a sole source aquifer there, and had to basically just characterize the risk because we could not quantify the potential for risk through drinking water -- groundwater sources of drinking water.

MR. COSTELLO: We have already done individual screening assessments for all those chemicals.

And so part of what guided us to saying surface water -- if we focus on surface water, it is going to be protective of groundwater is based on those individual assessments.

You can get some pesticides that do persist in groundwater, but it depends on the chemical properties of pesticides.

We don't have a whole lot of monitoring -- we have a few monitoring, continual monitoring on a couple of OP pesticides. They are not suggesting years and years later they are still there.

And I think that's partly because of the properties of the

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pesticide in terms of their persistence.

There is a lot of uncertainties we have. And we're just basically going by what we have in terms of --

MS. SCHREIBER: What I heard before, what I thought you were saying is that the groundwater wasn't considered because there wasn't enough monitoring data and there was no good models available. So it was kind of wrapped in to the surface water assessment assuming that if it is conservative enough for the surface water, it should also work for groundwater.

Is that basically what happened?

In other words, if it is protective for surface water in your view, it would also be protective for --

MR. COSTELLO: That's based on a number of things, including individual assessments as well. There's a wide variety of things. We're trying to say in a number of minutes what we have wrestled with for years and months to come up to --

MS. SCHREIBER: I realize a lot has gone into the assessment.

MS. MULKEY: One thing that may be helpful with regard to all the public comments is that we will work to be sure that as part of our public comment process we have a response to comments document.

So that we have a forum and a mechanism to assure that we

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want to be as forthcoming as we can in this forum and every other.

But we also want to make sure that we don't treat this as the only way that we can effectively communicate our approach.

It is clear that there is a lot of public interest in some of these issues. Breast milk we knew was an issue of considerable public interest, formula.

And obviously, we're trying here to seek science peer review. But we will also make every effort to be sure that we clarify the kinds of things we're saying.

And we welcome public, both factual inquiries, which we will try to answer informally as well, and then comments that we can focus on and address along these series.

DR. SCHREIBER: Thank you.

DR. KENDALL: I think that's well put. You have to understand they are hearing some of these questions for the first time. They need a chance to think through and get a good response to you.

And I think they have tried to at least address some of the issues. I'll ask the panel later on when we get into the question and answer period, I'm going to ask some of these questions, maybe some of their perspectives on it too.

DR. SCHREIBER: I was just going to mention that I will try

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when we send in our comments to attach data that we have that might be helpful to look at some of these issues.

DR. KENDALL: I was going to ask you to do that. That would be very valuable. Will you do that?

DR. SCHREIBER: I certainly will. Thank you.

DR. KENDALL: Thank you very much. We have one additional public presenter that has just requested to speak, Dr. Jennifer Sass from the National Resources Defense Council.

DR. SASS: Hello. Jennifer Sass, NRDC.

With regards to the water risk assessment, also the cumulative risk assessment and a little bit of the food risk assessment, it occurs to me that public health uses are not included anywhere in the risk assessment.

Section 18 are emergency exemptions. Those tolerants that are issued are not included anywhere in the risk assessment.

As an example, which is in my written comments that I submitted, coumaphos, which is very potent as a toxic OP currently has tolerances that number over 150 right now for bees.

It's a very important public health concern if you are a bumblebee. There is over 150 tolerances out. It is detected in the honey, and it is not considered anywhere in this cumulative risk

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assessment as very potent.

In the water, we have assumed typical uses. Not even the uses that are the maximum allowable uses on the label. Forget illegal uses. We're not even going to the maximum label.

And it occurs to me that there is a lot of regulatory decisions that are being inserted in this cumulative risk assessment that aren't being allowed to be discussed as regulatory decisions.

And I would challenge the EPA to take some of those regulatory decisions out so that we can argue them later in the proper forum and challenge you in the water assessment to give us an assessment that includes typical but also includes maximum use rates the full gamut of label and application use rates and patterns and anything that you have data on in terms of illegal or over-uses or those possibilities.

And in addition, public health uses where in states like Florida these are very routine. These are not unusual.

Thank you.

DR. KENDALL: Any questions for Dr. Sass?

MS. MULKEY: Maybe it would be helpful. We are going to try to address some of these. Public health is discussed in the residential analysis, for example.

But there was one comment that I simply didn't understand.

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Maybe everybody else did. But I didn't understand the statement about regulatory decisions, that people are not being allowed --

DR. KENDALL: I did not understand that.

MS. MULKEY: Maybe it would be helpful just to have that comment clarified.

DR. KENDALL: I agree. Can you clarify it for us?

DR. SASS: Yes. It feels to me that we are already making a decision to bias to the mean in a lot of ways.

We're making a decision to choose the average to assess on as in average or typical use rates and patterns which are going to result in average or typical exposure so that in this risk assessment I'm comforted to know that on an average or typical day for an average or typical person they are going to be average or typically safe.

But that is not what this cumulative risk assessment is supposed to be addressing.

MS. MULKEY: I understand the point now.

DR. SASS: Is that clear?

DR. KENDALL: I think so.

Any questions from the panel on clarity of that issue?

Thank you very much.

Does anyone else choose to approach the panel for public

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comment?

If not, we will close the public comment period.

Now, gentlemen, read the first question.

MR. THURMAN: After evaluation of available monitoring data and consideration of the available tools for estimating pesticide exposure in drinking water, the agency adapted available tools to provide watershed level estimates of residues in drinking water sources.

These tools have been presented to the SAP in the past in relation to individual chemical assessments and have been improved as a result of panel feedback.

Because of differences between individual and cumulative assessments, this assessment reflects novel uses for some of these tools.

The approach used in the preliminary OP cumulative risk assessment, first, used PRZM/EXAMS with the index reservoir along with local site characteristics to estimate concentrations in drinking water reservoir.

It simulated multiple OP uses on multiple fields within that watershed.

It adjusted for area within the watershed that potentially

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contributed OP loads to the reservoir using a cumulative adjustment factor.

It provided a qualitative rather than quantitative assessment of treatment effects on residues.

So the question, are there significant flaws in this approach and its assumptions that would be likely to lead to consistent significant underestimation of daily levels of residues in surface water across the calendar year, for instance, an order of magnitude.

If such flaws exist, what can be done to correct them. What additional information and/or tools might be available that will meet the goals/needs of the cumulative OP assessment.

DR. KENDALL: Dr. Capel, could you lead off, please?

DR. CAPEL: Sure. Thanks. First of all, I would like to compliment the OPP staff in the use of the modelings and the choice.

I think at this point in time it's the appropriate choice to do.

I think that you have advanced the use of these tools by going to multiple compound, multiple application time and making it geographically specific and realistic. There is some real progress that has been made.

But I think as you said to start with and the public comment, that this is still a first tier, adequate for organophosphate phosphates,

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but as we look forward to the future, there are going to be needs of future generations of more sophisticated or more different types of models that are needed.

I'll make a number of comments here that are somewhat unrelated but they kind of fall in this category of significant flaws. I think it's a unique choice of question.

The first is the water treatment processes. And this is kind of outside the PRZM/EXAMS modeling, but it is part of this question here.

There was done some qualitative work on chlorination and softening hydrolysis reactions. What hasn't been thought of or included are other oxidation reactions like ozoanation (ph), which is becoming a very important disinfection step in many water treatment plants and also the effect of absorption of activated carbon and anthracites and others.

In the reservoir study that we talked about, the 12 reservoirs, I think nine of those include some sort of activated carbon anthracite removal step.

So it is not a nontrivial part that I think needs to be considered in the water treatment side of things.

I still have the question that I asked before about the

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incorporation of the transformation products in the model. It is not explicit of how those were incorporated. And I think it would help to expand the text and help the reader to understand exactly how you incorporated the transformation process in the modeling scenarios.

And if I read the literature right, the auxins are not trivial in terms of their environmental production. So I think categorically leaving them out may lead to a significant underestimation of perhaps the exposure.

The modeling scenario that you presented is kind of a mixed bag. It's a vulnerable area, but it is typical rates. Other people have made this sort of comment. It is kind of an ill-defined scenario. Kind of worst case, but not really worst case.

And in a couple places in the document, you make the comment that OPP is confident that this is a conservative estimate.

I think you need to quantify that comment. And one way of doing it is by some sort of sensitivity analysis that is over the range of crop application rates, over the range of application times, over the range of KOC values or field half lives.

There is all sorts of different ways to test the robustness of the numbers that are coming out of the model.

And in some ways you have done that through using 36 years of

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weather. You have looked at sensitivity analysis from weather things.

I think as you move forward, that sort of sensitivity analysis would be very valuable.

One of the things that is not accounted for is the contribution of organophosphates from nonagricultural sources, particularly urban home and garden sources to surface waters.

And we know that many streams have urban or small residential areas that will contribute and then go down and enter an agricultural area.

We showed a few years back that probably the predominant source of diazinon to the Mississippi and to the New Orleans drinking water intake is urban use and in the mid west rather than agricultural use.

And so I think there is some nontrivial urban sources that should be considered in the overall picture.

Kind of looking forward, groundwater is an important for the organophosphate phosphates. I think that is correct in general. But again, I think in one way you kind of lucked out with starting with the organophosphates here, because many other compounds we're going to need a significant groundwater exposure component.

So thinking ahead, that's going to be a nontrivial component to

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put forward.

The model and monitoring comparison data that is in the appendices and what some of the panel have asked about before I think is rather simplistic and can be expanded. Maybe something like simply comparing the distribution profiles of the model versus measured data might help, rather than just discussing the maximums. Because I think we lose a lot in that.

The one public commenter from the IWG commented on addition of the spray drift model to the EXAMS and the overestimation that could contribute, I think it is another good addition to add and to evaluate what is that and, again, to do a sensitivity test.

It will probably turn out as not significant to the drinking water. But it does raise an important part that I think is missing from the overall assessment. And that is, exposure through ambient air.

We have exposure through residential use air. But there is also a background that we're all exposed to year round. And we know this from observations of the organophosphates in air, organophosphates in rain.

So this is something that might be added to the overall picture, not necessarily linked to drinking water itself.

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Finally, the point that more monitoring data is critical, I can't agree with more. Both EPA and the public commenters have made this. And I think we need to think down that pathway to help validate these modeling tools.

DR. KENDALL: Thank you.

Dr. Engel, would you like to carry on?

DR. ENGEL: Thank you.

Let me first again commend EPA for their efforts in this task. I guess I have seen that you have really taken to task a number of the SAP comments in the past, and those have certainly shown up in this work. I think you are to be commended for that as well.

I guess in general, my thought is that the approach that has been taken should provide fairly conservative kinds of estimates. Certainly, we have heard some discussion of things that would maybe not make it as conservative as one would like.

But I think at the same time as you dig in and look at your approach, there are a number of things that tend to be overly conservative.

So on whole, I think you end up in a fairly conservative place.

A sensitivity analysis, I guess, would help in following up on some of that and making sure that you are as conservative as one

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would hope to be.

Beyond that, let me go through a number of somewhat random comments here. The order may not make a lot of sense. But those are the order on my screen.

So let me tick through those so I don't miss any of these. Some of these will be duplicates of issues that have been raised already.

First, I think additional validation of the model in modeling approach would be extremely helpful to you and would be useful to the scientific community as a whole.

So I think that builds on a number of things you have heard already suggesting that. So I would encourage you some validation would be very helpful and please publish that.

You have already stated as well that in the cases where observed data were higher than your predicted results you are following up and digging into that a bit more.

I would encourage also you to continue to dig into that so that you can better understand what has caused that. Is that due to extreme weather that you didn't see with your model. Is that due to pesticide spills. Is that due to urban influences.

So if you can help quantify why that is occurring, I think, again, that will help you in understanding just how conservative you are

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being with the model and whether you are on the right track.

Sensitivity analysis. Let me follow up on that as well. In particular -- you had indicated that the pesticide application timing should provide a conservative estimate. I'm not sure that's the case.

Based on some work that we have done, it may turn out that a distribution of timing just because of the weather you get from a limited number of years will in fact give you higher estimates.

So I would hope that you would really dig in on the sensitivity analysis with pesticide timing to make sure that in fact what you think is conservative is conservative there.

A couple ways you might approach that, one, moving that timing around, assuming some distribution or longer weather periods.

I think with longer weather periods with a single date of application you are more likely to catch weather that would result in kind of worst case kinds of run-off events.

I noted that in some cases the weather that you used is not all that local. And I guess in particular, in your heartland region your watershed was in Illinois, the weather that you used was in Ohio.

Probably, that is not too bad of an assumption for that part of the country. I didn't look as closely at some of the other regions as to how well watershed location matched the weather location. But that

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may be an issue in some cases. It is worth investigating as well.

So more local weather data would seem to make a lot more sense in those instances.

Again, the urban impacts within the water, that seems to be overlooked. It may not be significant in this particular case, but I think something that does need to be discussed. And you will have to find some way, I think, to deal with that and treat that.

Subsurface drainage and irrigation. We can probably kind of lump those together. I think the assumptions that you use there you probably need to very explicitly state those and really, again, make sure that those give you some worst case or something toward the conservative end of things.

I'm not sure that you are dealing with subsurface irrigation for this particular set of model runs in the future with other products that may be more significant.

And I would offer some ways that you might think about dealing with that. We'll make sure those get in the report. But in general, one approach we have taken is to use the subsurface estimates of pesticide movement to the bottom of the root zone, use census of agriculture data about subsurface drainage and make the assumption that those multiplied together represent the portion of material moving to

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groundwater that shows up in surface water.

I'll provide additional details about that in the document. But in the future, that may be a way to account for subsurface drainage.

I guess the remainder of the comments are repeating what you have heard earlier, so I would stop there.

DR. KENDALL: Thank you, sir.

Dr. Richards?

DR. RICHARDS: Thank you.

Coming third in a list of three respondents, you sometimes find that your points disappear right out from under you. I still have a few left amazingly enough.

Like the other two, I want to commend you on really pushing this process forward. And I think the level of detail and subdivision that you have been able to accomplish is a big step forward and an important one. And, obviously, makes for a very complicated pile of stuff to analyze too.

To respond specifically to the thrust of the first question, it seems to me, at least, based on my experience, that this approach is unlikely to lead to substantial underestimation of the exposures, particularly, to sort of throw together some of your chosen words, particularly ones that would be, say, consistent significant

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underestimation by an order of magnitude across a whole year. I think that's highly unlikely.

However, there are some ways in which I think I can see the possibility of underestimation occurring. The one I would comment on is that the model in effect or the approach in effect only models nonpoint source run-off processes.

And in our work, looking at run-off in northwest Ohio and other parts of the midwest, a few of the highest concentrations that we have observed over the years for pesticides in general really don't appear to be due to nonpoint source run-off processes.

They don't happen during storm run-off. They happen at a time of year when typically we don't particularly expect to see high concentrations.

And they quite possibly represent either spills or intentional dumps of left-over pesticide material.

These, I think, are not something that the whole approach is basically able at this point to take into account.

Now, to try to put them in perspective, I would say that based on our experience to see one of these on a watershed once every 10 years might be -- I would expect to be no more frequent than that and hopefully less frequently than that.

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On the other hand, I did a very simple kind of a calculation. If I were to get an episode of this sort on one day out of the year and assuming kind of typical concentrations for the river system as otherwise, that one day might increase the exposure by something on the order of 30 percent for the annual average.

So it's a significant bump. It is not an order of magnitude. And it's a low probability event. But it is one which I think we don't have any current way of taking account for.

So one of the things you may want to think about is what other processes may be lurking in the background that really are potentially mirrored by monitoring data, and a part of the reality that we're dealing with, that this approach to this point is not dealing with.

A second point that I will make, if I can get my cursor to move, is that I think there are really important differences in the temporal patterns of concentrations in rivers and streams as opposed to reservoirs.

And there has been some mention made of this particularly sensitive to this because that's what we primarily look at.

The reservoir model doesn't really do a good job of mimicking the temporal signature of concentration patterns in rivers as it unfolds day to day.

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I think that average concentrations may be somewhat higher in drinking water drawn from rivers than they are in drinking water drawn from reservoirs given this kind of difference in pattern simply because the residence time in the river is likely to be less than the residence time in the reservoir.

And therefore, there is less time for natural degradation processes to cut down the concentrations.

Certainly, the day-to-day variability would be higher in the rivers. If the health effects are determined really only by medium to long term average concentrations, then they this may come out in the wash. It may not be an important point at all.

But if fluctuations in exposure from day to day or something semi acute in the response system is important, then the current approach really doesn't do an adequate job of reflecting the reality of rivers and streams.

And while no one probably would claim that it did, it reflects a need to develop further modeling approaches to deal with that end of things.

I guess the final comment that I would raise is, again, it has been somewhat touched on by some of the other respondents, I'm just curious how OPP believes the PRZM/EXAMS index reservoir approach

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compares to what would really be present if you could actually go out to that same hypothetical reservoir and that same soil type and do the monitoring there.

We recognize that we're dealing with an unrealistic situation.

But most of the discussion seemed to focus on, well, we feel pretty comfortable because the high concentrations that we see in monitoring are about the same as the high concentrations we see in modeling.

But I'm curious about what about the whole range of concentrations. There are several aspects to the structure of the PRZM/EXAM assumptions that I would expect would lead to conservative estimation, to a higher average concentrations, for example, than would occur in that system if it was really monitored.

Particularly, I'm thinking about the fact that you have 100 percent delivery of everything that comes off the field right into the reservoir with no opportunity for capture along the way in the stream system or degradation, whatever.

So I think it is important not only to be concerned about whether we are unpredicting, but also -- underpredicting, but also to be concerned about ways in which we may be overpredicting the concentrations that would exist in that very system that we're tempting

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to model.

I don't pretend to know how you evaluate that, particularly when you are not modeling a specific system that you can go to. But I think it is important thing to look at from both sides of the coin.

And with that, I'll pass.

DR. KENDALL: Thank you. Dr. Bull, do you have any further comments?

DR. BULL: I'm not sure how much I need to add. In fact, I'm not that familiar with the modeling. So I could excuse myself from that.

But I do on the bottom line kind of agree with the assessment that drinking water would be a minor source of organophosphorus pesticides, that I don't think carries over to other pesticide classes necessarily.

There are some other issues, and it just happens, I think as you said, it's fortunate you started with the OPs.

And I was also going to -- I'll just indicate, bring up this issue that Dr. Richards brought up to some extent, and that is, I see any impact of organophosphorus pesticides in drinking waters to be very rare events.

What I would like to know is if I could get a handle on it is how

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frequently I could expect that event to occur. And I don't think -- you may be able to find in some cases at least some idea what the concentrations actually are in those situations, but I would be actually more interested in how often those spills or whatever they are, the genesis of that.

Because if there is a hazard in drinking water, it is going to relate to that kind of activity, I think. The rest of it, I think, is just going to kind of go away.

There are imbedded in that also some questions I think that you purposely avoided in this particular, and admittedly so, in this particular analysis.

And you live in an agricultural area, you see some practices that go in a particular demographic group, such as farm workers, and you think, well, it is probably easier to get a drink of water out of the irrigation ditch than it is to go down to -- you know.

So there are some other exposure scenarios that play out on an individual basis. Very small part of the population and so on and so forth we should have some concerns over, but I don't know that it is even possible to capture that with the data, the information you have to date.

I have to admit it was a little hard for me to figure out how you

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ruled out certain things looking at the write-up. I don't know if some clarity can be added.

It just kind of like made the conclusion. I couldn't tell why you came to that conclusion. I have to say in most all the cases your presentations clarified that pretty nicely. I was a little left up in the air in some of those situations.

The one thing that I touched on in my earlier questions, and I think you were alluding to as well, is the heterogeneities in those regions are just huge. I mean, I think there is more variation in your fruitful rim in terms of weather pattern and agricultural practices than there may be across the United States. Or as large as. I guess it can't be larger.

But those regions are not very comforting to me because of lot different -- very different geography, very different distribution of crops within those regions.

Some of them are quite concentrated. The apple are not grown throughout Washington. They are grown right on the river or on some of the streams, whereas wheat is all over the place.

So you get a little uncomfortable when you come back and then play that against this -- the one problem I have with the reservoir, we'll come to that in a minute, is that trying to play that out all in one

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reservoir to capture that whole region bothers me for that reason.

Because I think if you had a reservoir, it is more likely to be in an apple growing area, getting stuff from treatment of apple orchards in one case. I think you get real variation, which I don't think you capture terrifically here at least.

The other thing I got acquainted with, the naqua (ph) study that was done in the Saint Anna (ph) river, was very impressed with the kind of work there. There was nothing in that naqua study that would indicate that there were dangerous levels of organophosphorus pesticides or any other pesticides.

But it did make real clear some of the points that you raised in terms of, well, some of that comes from agriculture. Some it comes from residential run-off.

Residential run-off in that area depends on which way the rain is coming from.

So you get even in a small area like the Saint Anna watershed. You have heterogeneities that have huge influences on what you're seeing in the river.

So you have a lot of work to do. I don't know how much effort is -- I'm talking about a huge amount of effort. I don't know how much effort is really warranted considering the fact that it is probably

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a minor input.

Probably the -- I'm not unhappy with the reservoir work because I think the small reservoir (inaudible). But to be more realistic, you need to really get to the question.

I think the getting at the question the way you did when I asked the question earlier about the stream, why did you have values higher than expected was a very good way to approach it on a case-by-case, I can explain this because that's not a water supply.

But if you are really going to do this on a real cumulative risk kind of area, you really need to find a way of getting a lot more realistic relationships to the water intakes.

There is no surface -- particular surface water sources in the Columbia river until you get to where I live. And we have a population there that's fairly substantial in the tri cities. There are 150,000 folks. And we're mostly on surface water. We drain the Acomaw (ph) River too.

So if you had a surface water impact, it may not be in the Acomaw River. It may not be further upstream or in the apple growing region. It might be in fact down where we are on the Columbia.

And so there is some unreality or discontinuities, I guess, here that bother me a little bit.

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But anyway, I think you have done a wonderful job with what you have at hand. It may be because it reinforced my prejudices.

DR. KENDALL: Thank you.

Any further comments from the panel?

Dr. McConnell?

DR. MCCONNELL: Yes. Thank you very much, Ron.

I have -- possibly it's from my naivety, but first, you've to herculean efforts in pursuing this. And you did essentially, I think, what the SAP asked you to do.

I followed the logic. And I thought it was reasonable logic in the steps you took.

But my question goes to some of the comments I think Chris made, Steve, Dr. Richards.

This seems like an awfully complicated way of getting to the truth, the truth being how much, how many OPs and what level are there in the water that we consume.

So I guess I would go back to this statement that while you have gone through this and you will have to go through it because of the limited amount of data that you have, I would like to see the agency pursue finding out what really is in drinking water.

Why can't you go to distribution centers and do the same

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analyses you are doing on the streams? Is this such a horrendous task that it is not possible?

Certainly, you would focus first on those areas where you have the most OPs. Second, you could take one of those, and if you see in your largest contaminated areas that this is not a problem in the water that we drink, then I think you can assume in areas that don't use OPs that, similar type of logic that you have used, that you won't have any in that water or not a significant amount.

So it is not clear to me why we can't go right to the source of the drinking water and analyze it for OPs rather than going through this complicated exercise of modeling.

And while I was -- if I were doing that, I would take a look at some groundwater, particularly, in single aquifer areas, and see if there are indeed OPs in that water or not.

And if there are, what levels and what kinds and so forth. And then if there aren't there, you can at least be assured that this is not a problem for those sorts of areas.

Now, with that, how would you go about that? Evidently, this is a big time project, what I'm talking about. I don't know.

But it sounds like from what you have said that that is a problem. I'm wondering as a biologist if there isn't some way of

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finding a generic assay for OPs. I don't know if there is or not. That's why you have ORD, as I understand it, is to pursue some of these problems.

There might be some simple biological system that you could put water into and see if OPs are in there or not, generically.

If they are not there, you don't go any further. If they are there in significant amounts, then you would want to find out which ones they are and whether the more potent ones are not.

I don't know if this is possible or not. But I would think the agency might want to spend some of its resources in this area because it certainly would be -- it wouldn't be a guess. And it would be right on the money.

Feel free to respond.

MR. THURMAN: One quick thing. I know that a number of OPs in OP transformation products are on the unregulated contaminated monitoring list, the new lists that have been coming out last year, this year.

I think that in the future that at least for some of them there will be more drinking water data for these.

DR. MCCONNELL: What is the problem that they are not being analyzed? Again, help me here. It is not clear to me why this wouldn't

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be one of the things that people that analyze water would be analyzing for.

MR. THURMAN: I think the fact that in -- historically, OPs have not been identified as the most likely to contaminate surface water or groundwater.

It means that resources haven't been directed that way as much recently. I believe that in studies further back when the OPs were new, '50s and '60s, to the extent that anybody looked for anything back then, they were much more included, but in talking to the states, I know that what monitoring money they had was most often directed toward looking for herbicides because they are much more likely to get into drinking water and because they had mandates to look for some of them.

DR. MCCONNELL: And I accept that. But since OPs are on the table today and since they are apparently an important consideration in the cumulative risk of OPs, then I would think you could take 10 reservoirs in the most contaminated, OP contaminated areas of this country and you could look at the water that is coming out of a distribution center, for just those 10, and you would find out very quickly whether you have a problem or don't have a problem.

Am I missing something here?

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MR. COSTELLO: You start running into -- even if you focus on 10 reservoirs, how frequently do you sample.

I think part of what we're finding is, it hasn't been done because there is a cost basis there that is a lot higher than a lot -- because I think there was -- when we first started doing these assessments, we said, let's just monitor for this.

And as we started looking into the feasibility of setting up a monitoring system to pull together the data that would give us the answer to the question we did, we started realizing the expenses started getting --

DR. MCCONNELL: Well, that's an answer.

MR. COSTELLO: -- astronomical.

DR. MCCONNELL: That's an answer. But I'm wondering if -- again, while that's -- I'll take your word for it that that would be an expense for 10 reservoirs.

Reservoirs don't turn over that often. Particularly major reservoirs. Not like a stream --

MR. COSTELLO: The other thing I would add is the idea of the pilot monitoring study that USGS did was to start getting at some of those questions.

This working group that Mark Russell mentioned looking at

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national monitoring is trying to get at some of those things. And we were looking at pesticides in the future.

It was not lost on us that -- there was a good reason from our point of view on water that OPs came first, because that's gives us a chance to work, refine our methods and ask some questions and poke around so that the next generation --

DR. MCCONNELL: Plus, they are important pesticides. And there is a lot of them out there. I can understand why you would focus on those.

Again, I make a plea that you talk to somebody at ORD and see if they might want to look at finding an assay that is inexpensive and quick.

If you put a little brain power on it, you might be surprised what you come up with.

Thank you.

DR. KENDALL: I think they heard you, Dr. McConnell.

DR. MCCONNELL: I hope so.

DR. KENDALL: Any other questions or points?

Dr. Portier?

DR. PORTIER: I have two points.

First, I want to agree that you have done exactly what we asked

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you to do when we looked at this model.

I'm not sure we'd ask you to expand it beyond a screening level model for cumulative risk assessment. But I think your attempt to do that has been valid and an exceptional effort on your part.

When I looked at this question, I actually had a real problem with the question. That's why I kept pestering you, asking you about the issue of maximum values.

The real issue here is underestimation of what. Underestimation of the mean? I doubt it.

I think when people talk about you being conservative and they are fairly happy that you have done this and that it is a fairly safe estimate of water exposure, I agree that -- I would love to see the monitoring data.

I'm not convinced. But let's say that my intuition says that you are in fact fairly conservative with this model for the mean.

Now, what about a 21-day drinking water exposure in a rural population from a small reservoir in a local drinking source? Are you going to be conservative to that? Is that what you want to be protective of?

And that was my problem in why I was asking you all these questions. I don't know where your underestimation, overestimation

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will be. At some point you will obviously be below a percentile in the distribution of water exposures in the United States for 21-day phases. I couldn't make that judgment.

So that's, I think, something you have to ask yourself as you look at this, is what degree of conservativeness are you actually trying to achieve, and can you demonstrate that to me scientifically.

The other question, and regretfully since I won't be here tomorrow, I'm going to take it here, but it pertains to all the sources of exposure and to the overall cumulative risk assessment as it is done.

Centers for Disease Control has obviously looked at human urine levels from exposure to organophosphates in a random population exposure.

To what degree do those numbers from those urinary outputs and back predictions of what the exposures might have been from those urinary outputs compare against the distributions you are predicting for exposure in the population in the United States?

Are they agreeable? Are they not agreeable? So that's a question on the exposure side that I would have liked to have seen addressed in this overall risk assessment. That's a very critical piece of data if you can pull it away from CDC.

The second part of that, though, is we've got a lot of animal

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data where we could potentially predict tissue level or urinary output from the animal.

How does -- so regardless of the exposure as you estimated in the U.S. population, how does urinary output distribution as seen in the U.S. population from the CDC data compare to urinary outputs in the rodents at the levels at which they were producing 10 percent or 5 percent reduction in cholinesterase activity.

I think you could ask those two questions and assure yourself from the CDC data that potentially you are doing a good job of protecting the population if neither of those two things raise a big flag for you.

But I would like to see that in the overall evaluation of the exposure data and the risk data.

DR. KENDALL: Any further comments for Question 1 from the panel?

Let's move to Question 2.

MR. THURMAN: Question 2. It is not feasible to conduct drinking water assessments for every watershed in which OP pesticides are used.

Therefore, regional water exposure assessments were used to represent exposures from typical OP usage conditions at one or more

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vulnerable surface watersheds in the region.

Each regional assessment focuses on areas where combined OP exposure is likely to be among the highest within the region as a result of total OP usage and vulnerability of the drinking water sources.

In this manner, OPP is confident that if the regional cumulative risk assessment finds that exposure in water is not a significant contributor to the overall OP exposure in that area, it will not be a significant contributor in other areas in the region.

Does the SAP see anything that would call this assumption into question? If the regional approach with its assumptions is inadequate, what can be done to improve the approach?

DR. KENDALL: Thank you.

Dr. Richards, can you lead off, please?

DR. RICHARDS: Thank you.

I guess -- I think the assumption that the regional assessment is protective of the region as a whole is going to be largely valid. And I would expect that, if there are exceptions, they will be relatively minor.

I can think of a couple situations which may suggest a greater likelihood of such exceptions. And these would typically involve small surface water systems perhaps involving a component of the

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heterogeneous application that people have alluded to, quite possibly small rivers or streams, perhaps private sources that are serving less than 25 people so they don't qualify as a public water supply, or the other possibility would be something unmodeled like the spills that I was referring to previously.

I think in the overall picture, these represent a level of reality that may be essentially impossible or impractical to model. And maybe even impractical to try to manage. But I think they do have to at least be acknowledged.

I think by and large for the kinds of systems that service most of the people, the assumption that the regional assessment is protective would be valid.

I only have one other point. And it goes back a little bit to my comments previously. I certainly understand and sympathize with the need to be conservative in estimating exposures through any of the pathways considered in the assessment. And I think you have done a good job with that.

But I also would ask particularly when you take this index reservoir and you consider it as a surrogate for all the drinking water sources in the region how strongly conservative do you think it is.

Let's say it provides a fairly reasonable estimate of the situation

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for the worst water supply in the region. Is there going to be a percentage of water supplies which have a concentration distribution that's an order of magnitude lower than that or two orders of magnitude lower than that?

I would expect there would be a number of systems that have lower concentrations. But by how much, I haven't a clue. And I think some attempt to estimate the degree of conservatism is useful both from the standpoint of seeing how protective you are being and also just for increasing the reality of the assessment.

I suspect that, and most people have already alluded to, for the question of the OPs in particular, the drinking water issue seems to be a relatively minor one. So if you are two orders of magnitude high, no one really cares.

But for other future uses of this kind of an approach, this may be a much more important kind of thing to get a handle on.

So it's really a question in this case of the distribution of concentrations from site to site within the region and how that compares to the distribution you predict from the worst case model.

DR. KENDALL: Thank you very much.

Dr. Bull?

DR. BULL: I don't have too much to add to that. I actually

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made most of my points in the last question. But I will kind of go back over the issue of heterogeneity.

I'm a little bit worried about how representative the one or two locations are within each area. And I don't know or didn't gather how, what you did to try to confirm that was representative, I guess, because I -- you mentioned weather and a few things like that.

And I'm aware of the heterogeneity of crops at least in certain parts of the country that I don't feel are well captured.

So I'm a little bit worried about the representative nature of it, even of the worst case.

But all in all, I think what you did was kind of the pragmatic thing to do, so to speak.

DR. KENDALL: Thank you.

Dr. Engel?

DR. ENGEL: I too would agree that in general your assessments should be fairly conservative for the region as you have performed those.

A couple of items that I would point out related to this.

One, you lead this question off with a statement, It is not feasible to conduct drinking water assessments for every watershed in which OP pesticides are used.

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That may have been true a number of years ago, but I think that assumption or that statement is not as true as it once was.

With some of the spatial databases and other databases that are now available, one can automate and step through again with assumptions modeling of most all of the watersheds, if not all of the watersheds, within the country.

I know our group has been using a model similar to PRZM. We have stepped through every 100 meter grid cell in the state of Indiana again with assumptions and pulling data from databases to build up runs that would be comparable to what you are doing.

So with a little compute time and with the right databases sitting behind this, I think that assumption begins to potentially go away.

So I think longer term you may want to think about how you potentially could run for more watersheds.

The one other comment I have related to this, in the documentation, I think you have done a commendable job in highlighting assumptions that you have made and how those come to play in some of this.

I guess I would ask if you would look at those again and make sure that you have explicitly documented the significant assumptions

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that you are making with respect to some of this and make sure that those get documented.

So what was there was very helpful. But please review those and make sure that there are not other significant assumptions that should be documented.

DR. KENDALL: Thank you.

Dr. Capel? Anything to add?

DR. CAPEL: Thanks.

A number of the places in the document you make the statement that drinking water is local and that modeling should be done or assessment should be done at the local level. And for practical reasons you went up to a regional level.

And that disconnect is still there. The approach you have taken where you have picked the most vulnerable area and called that protective is again probably okay for the organophosphates, but as we move on into the future, this disconnect between local water use and kind of regional modeling or, well, the heterogeneous areas probably is not going to be adequate.

Is it protective? Yes. I would make one, raise one question. And that is going back to the transformation products.

We know that some of the auxins are perhaps more toxic than

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the parent compounds. And so one can play simple mathematical games by asking themselves if the degradation products are there at a tenth of the parent concentration or equal to the parent concentration, when do we start losing our margin of protectiveness and how important are these transformation products.

And so I think doing those sort of scenarios might help firm up or erase questions about how protective the modeling efforts are. Because I think, again, it is an important piece of the puzzle that isn't adequately captured.

DR. KENDALL: Thank you very much.

Any further comments from the panel on this question?

Dr. Bull?

DR. BULL: Just to reinforce his last point, I think in the case of -- there is the concern on the OPs, but I think you really need to pay attention to this transformation of pesticide residues in water treatment.

That's going to become an issue. You have nitrosamine forming pesticides and so on and so forth that have been documented.

And then you are talking about something that is -- that kind of drives a risk in a whole different direction. So I think that particular area should not be thought of only in that context of the OPs.

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DR. KENDALL: Thank you. Any further points?

Would EPA care to respond to any of the recommendation or issues?

MR. COSTELLO: Actually, we want to thank the panel for your recommendations to help us in terms of improving what we're doing both for this and for future ones.

DR. KENDALL: Thank you.

MR. THURMAN: The one thing we do want to add, because the issue did come back up in terms of residential use, is that with particularly chlorpyrifos and diazinon cantholtis (ph), you've knocked out your major residential use OPs.

MR. COSTELLO: And the other one that was a major one that we saw was malathion, which by relative potency factor had such a low relative potency factor that it knocked it out too.

Not taking those, chlorpyrifos and diazinon, from residential sources into account, this is why they didn't drive where -- those uses did not drive where we placed our watersheds.

MR. THURMAN: At the same time, you did point out -- by raising those questions, you pointed out areas where we need to be more clear and transparent what we have done in that.

MR. COSTELLO: But also, as you say, maybe that was just

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another bit of luck for us with the OPs that those very important uses happened to be canceled.

Well, they didn't happen to be. We were voluntarily canceled.

DR. KENDALL: Okay.

Then this will close our responses to this question.

I think it has been a good day. We have been through both the food and drinking water. I personally compliment the agency in, I think, doing a remarkable job at responding to the recommendations of the SAP from our previous meetings. And particularly from the last meeting.

I appreciate the panel's work today. You were very well prepared. It was obvious. And I thank you for that.

The audience has been extremely patient with us. We have had challenging, other activities in the building. And we got through it together.

We are approximately a half a day ahead of schedule now. And Mr. Dorsey and I have talked. Mr. Lewis and I have talked.

I will close the session in just a few minutes, don't leave yet, this afternoon.

Margaret Stasikowski, do you want us to proceed with residential? You guys look a little tired over there too.

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What would you like us to do?

MS. STASIKOWSKI: I think we would like to do the residential assessment starting tomorrow morning.

DR. KENDALL: Okay.

As I mentioned, because of our progress yesterday and in due process and good deliberation, we made good progress, there was the potential to finish the meeting tomorrow evening.

I think that potential is quite excellent. So at this point, we have the residential section as well as the risk characterization section to do.

And with a cooperative panel in good spirit, that perhaps could be achievable. Mr. Dorsey asked if we could at least attempt to do that.

But we will not cut short the discussion at all. Okay?

As has been our customary procedures, we rotate and help each other. Dr. Roberts will move to session chair in the morning to take over with residential.

We agreed that I would get us through drinking water and then he would take over with residential and finish with risk characterization.

So anyway, he will move to session chair. I'm not abandoning

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the ship, but moving more to the rear. So anyway, Dr. Roberts will move to session chair.

Other than that -- Dr. Portier, did you have a comment you wanted to make?

DR. PORTIER: Yes. Again, I will be leaving after today's session. So I will not be here tomorrow. Don't everybody smile. That is why he is saying we'll be finished early tomorrow.

But I do want to reiterate the point that I commend the agency for an excellent series of presentations.

As a quantitative scientist sitting on the EPA science advisory board, for years I have been fussing at you about the quality. And this particular time I have seen exceptional quality in the work that is done. I have a clear understanding of how you did it and the assumptions made in making your choices. And for 99 out of 100 of the choices I agreed with them.

I really do want to thank you for the excellent presentation and some excellent work on behalf of the public of the United States.

Thank you.

DR. KENDALL: Thank you very much, Dr. Portier.

I particularly wanted to acknowledge Ms. Mulkey for staying with us almost all day. This is unbelievable that she could give so

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much time to help this panel and contribute to it.

So I personally believe your presence and engagement was an asset. And thank you.

MS. MULKEY: Thank you. I appreciate the preparedness of the entire EPA group today. That's one of the reasons we're ahead of schedule, I think, good preparation. The panel was prepared. It is amazing what people working together can achieve.

DR. KENDALL: This will close our session today. Thank you very much. We will reconvene at 8:30 in the morning.

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[Whereupon, at 4:45 p.m., the meeting concluded.]

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CERTIFICATE OF STENOTYPE REPORTER

I, Frances M. Freeman, Stenotype Reporter, do hereby certify that the foregoing proceedings were reported by me in stenotypy, transcribed under my direction and are a verbatim record of the proceedings had.

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FRANCES M. FREEMAN

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FRANCES M. FREEMAN
21168 Wildflower Square
Ashburn, VA 20147
703/723-3550

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METHODS USED TO CONDUCT A PRELIMINARY CUMULATIVE RISK ASSESSMENT FOR ORGANOPHOSPHATE PESTICIDES

February 6, 2002

[8:30 a.m.]

SHERATON CRYSTAL CITY HOTEL
1800 Jefferson Davis Highway
Arlington, Virginia 22202

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PARTICIPANTS

FIFRA SAP Session Chair

Ronald J. Kendall, Ph.D.

Designated Federal Official

Mr. Paul Lewis

FIFRA Scientific Advisory Panel Members

Herb Needleman, M.D.
Christopher J. Portier, Ph.D.
Stephen M. Roberts, Ph.D.
Mary Anna Thrall, D.V.M

FQPA Science Review Board Members

John Adgate, Ph.D.
William Brimijoin, Ph.D.
Richard Bull, Ph.D.
Rory Conolly, Sc.D.
Patrick Durkin, Ph.D.
Natalie Freeman, Ph.D.
Jean Harry, Ph.D.

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Steven Herringa, Ph.D.

Ernest McConnell, D.V.M.

Peter MacDonald, D. Phil.

Nu-May Ruby Reed, Ph.D.

Lorenz Rhomberg, Ph.D.

Lauren Zeise, Ph.D.

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DR. KENDALL: Good morning, this will convene the meeting of the FIFRA Scientific Advisory Panel to continue our discussions on methods used to conduct a preliminary cumulative risk assessment for organophosphate pesticides. My name is Ron Kendall. I'm the chair of the Science Advisory Panel and will be chairing this session.

I'd like to again thank EPA for being ready, and I thought we had an excellent and productive day yesterday. And I'm looking forward for the continuation of our discussion today.

We have several new panel members that are seated; therefore, I will, as a matter of protocol, ask the Panel to reintroduce itself in total. I'd like to begin on the far right and then move around. And, please, for the record, state your name, affiliation, and expertise if you would briefly.

DR. CAPEL: My name is Paul Capel. I'm with the US Geological Survey Water Resources Division. My expertise and water chemistry for the drinking water exposure part.

DR. ENGEL: Purdue University. My expertise would be in the hydrologic water quality modeling area.

DR. BULL: I'm Dick Bull with Washington State University. I'm a toxicologist.

DR. DURKIN: Pat Durkin with Syracuse Enviornmental

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Research Associates. I am a risk assessor and I've worked with the Agency in development of methods for mixtures risk assessment.

DR. HARRY: Jean Harry, National Institute of Environmental Health Sciences in North Carolina. My research area is in neurotoxicology.

DR. CONOLLY: Rory Conolly, CIIT Centers for Health Research in Research Triangle Park, North Carolina. I'm interested in mechanisms of toxicity and risk assessment.

DR. RHOMBERG: Lorenz Rhomberg, Gradient Corporation, and also the Harvard School of Public Health. I'm interested in quantitative risk assessment methodology.

DR. MCCONNELL: Gene McConnell. I'm a veterinary pathologist-toxicologist. My area of expertise is in the design, conduct, and interpretation of animal bioassays.

DR. ROBERTS: Steve Roberts; toxicologist; University of Florida.

DR. PORTIER: Chris Portier, National Institute of Environment Health Sciences in Research Triangle Park, North Carolina. I direct the environmental toxicology program and manage the national toxicology program. My area of expertise biostatistics and risk assessment.

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DR. ZEISE: Lauren Zeise, Kelly P. Office of Environmental Health Hazard Assessment. My expertise is in risk assessment.

DR. RICHARDS: Pete Richards, director Of the Water Quality Lab at Heidelberg College in Ohio with expertise in exposure patterns in agriculture systems in the upper Midwest and the statistics applied to those.

DR. ADGATE: John Adgate, University of Minnesota School of Public Health, exposure analysis and risk assessment.

DR. REED: Nu-May Ruby Reed, California Environmental Protection Agency, Department of Pesticide Regulation. I do pesticide risk assessment.

DR. FREEMAN: Natalie Freeman, Robert Wood Johnson Medical School and the Environmental and Occupational Health Sciences Institute in Piscataway, New Jersey. Residential and children's exposure.

DR. MACDONALD: Peter MacDonald from the Department of Math and Statistics at McMaster University in Canada. General expertise in applied statistics and model fitting.

DR. HEERINGA: Steve Heeringa, the Institute for Social Research at the University of Michigan. I am a biostatistican. My specialty is in population-based research.

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DR. KENDALL: I'm Ron Kendall from Texas Tech University. I direct the university's Institute of Environmental and Human Health. My area of expertise is in environmental toxicology and risk assessment.

I'd like to now introduce our designated federal official from EPA, Mr. Paul Lewis, for any administrative procedures that he needs to inform us on to get going today. Paul.

MR. LEWIS: Thank you, Dr. Kendall. And again thank you again for agreeing to serve as our chair for this challenging and interesting meeting over the next four days with our Scientific Advisory Panel. I want to thank the members of the panel to agreeing to serve and we're looking forward to your upcoming deliberation and challenging discussions beginning with what we had yesterday and carrying on today and beyond and for new members that have joined us this morning for discussion on vary exposure considerations.

I want to remind everyone again that this meeting follows of the guidelines of the Federal Advisory Committee Act. This is an open meeting. There's an opportunity for public comment. All the materials for the meeting will be available in a public docket. In addition, the primary background materials and our subsequent report that serves as meeting minutes for discussion during this week will be available in

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the docket edition on our SAP web site.

Thank you again. I'm looking forward to both a challenging and interesting over the next few days. Dr. Kendall.

DR. KENDALL: Thank you, Paul. Yesterday was a very aggressive and forward-looking day. We actually got much further than we thought we would. Therefore, today, we are at the point of assessment of food exposure in terms of Session 2 as we continue our review.

Dr. Perfetti, would you like to introduce your group or Margaret, either one of you?

DR. PERFETTI: Thank you, Dr. Kendall. First of all, I'd like to welcome the panel to today's session on food and drinking water. And again I would like to thank the panel for all your valuable past advice on the total assessment as well as yesterday's very interesting discussion on hazard and dose response.

For the food presentation, Dr. William Smith, sitting to my left; and Dave Miller will provide that presentation on food. Presentation on water will be performed by Kevin Costello and Nelson Thurman.

I have a few points that I'd like to make, Dr. Kendall, before we continue.

DR. KENDALL: Very well.

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DR. PERFETTI: As mentioned yesterday, we intend to address all of the points brought up yesterday during the public comment period. We intended to address many of those points anyhow in our presentation; but we have modified them such that we think we will be able to speak to all of them.

To that end, we heard yesterday that OPP would be receiving an OP cumulative assessment using the CARES software. OPP has also contracted the Lifeline Group to perform a cumulative risk assessment for the organophosphate pesticides.

This project has three components. The first is to modify the Lifeline version 1.1 software as required to allow estimation of cumulative exposure and risk for the organophosphate pesticides. In addition to modifying the software, Lifeline Group will perform a cumulative risk assessment for the OP and revise the user and technical documentation to the Lifeline model so that it can be used by all of the risk assessment community. We have done this in order to -- basically, we thought ahead. We did this in order to have yet another software package for cumulative risk assessment.

And, finally, I cannot stress strong enough that OPP has no intention of exclusively endorsing a particular model for estimating pesticide exposure and risk. We'll accept any and all risk assessments

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conducted in accordance with EPA and OPP guidelines and performed with an appropriately peer-reviewed model. That can never be stressed more strongly or often enough.

Thank you, Dr. Kendall.

DR. KENDALL: Thank you. Well, at this point, we can begin. Let's go ahead and begin the presentation. Dr. Smith.

DR. SMITH: Good morning. This is an outline of what I plan to discuss today. I want to cover three general areas in this discussion. First, I would like to summarize the exposure inputs to the cumulative food assessment. This includes the residue data, primarily from the PDP monitoring program for food consumption data from the USDA continuing survey of food intakes by individuals.

Secondly, I'll briefly review the residue adjustments involved in the cumulative assessment. These are fairly simple calculations compared to what we dealt with yesterday. This involves a conversion to index equivalent residues, that is, methamidophos equivalence, the relative potency factor method.

And then last, we'd like to review the preliminary assessment as published in December which is a probabilistic exposure risk assessment using the DEEM software.

Also, I will include some analysis of the important assumptions

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that were incorporated in the exposure calculations and the beginnings of the analysis of important contributors to the exposure distribution.

Essentially, all the residue data that we used in this assessment are from the PDP Program. We, also, considered FDA monitoring data, but this was primarily as background. There were only very limited uses of it on a quantitative basis. All of these data are available on the internet at these Agency's internet sites.

The OP active ingredients that are included in this assessment are all included in the PDP monitoring program. What you see here are essentially the parent active ingredients. PDP also analyzes for important metabolites of these chemicals and degradates. And they are also included in the assessment. I think between the span of 1994 to 2000, PDP has done significant analysis on maybe 70, or approximately 70, OPs, either parent active ingredients or metabolites. The extent of how we use these data are the extent of the availability as well as how we use is available in our preliminary document in the appendices.

We do not include cancelled uses in the assessment nor do we include violative residues. Now these are tolerance-exceeding residues or residues from nonregistered uses. Violative residues are generally infrequent and for the most part at low concentrations. And

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both PDP, our primary source, and for that matter, an FDA data, which is designed to enforce tolerances.

I do not have an exact accounting of our the effect of our omission of these violative residues. But it will be available with the final assessment. But I can offer some general statistics.

In the most recent PDP data, tolerance-exceeding residues are on the order of .2 percent of the analyses. And residues from nonregistered uses account for a little bit over 1 percent. The FDA monitoring, which one would expect to have more violative residues since it is designed to analyze raw commodities close to their source, has a little bit more. It has with domestic, approximately 1 to percent violative residues; and import, closer to 4 press.

So for just as a general background response to public comment about this, that is what we generally see in all the monitoring data. Also, the data bases that are available on the internet from these agencies as well as our data -- let me retract that. Our data do not flag the violative residues, but the data bases as available from USDA and FDA do. So one can easily pick out of the residues. There is a field in the data base that identifies these.

There has been approximately 50 different foods that have been analyzed in the PDP Program since 1994. And this is, of course,

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counting some processed forms such as canned, frozen, this sort of thing. All of these foods are included in the assessment. But some specific chemical commodity combinations have been excluded to account for cancellations or tolerance revocations and phase outs of uses.

The residue data for these foods as supplied by PDP have been adjusted by processing factors where suitable to include all the related food forms found in the CSFII survey. Again, for example, using a raw commodity with a processing factor to estimate residues on a cooked, canned, frozen form, possibly a juice or dried form.

These data were extended to the extent possible by translation. And in this case, it was done to food crops that had similar use patterns. I will come back to these crops a little later in the discussion of the preliminary assessment.

These are based on SOPs that we have developed for single chemical assessments, and they are limited to crops for which use patterns are similar. So we done translate a chemical that would not be appropriate to the other commodity.

Although, we primarily use FDA's background, there are some exceptions. Eggs and seafood were included in the assessment. And in both cases based on a long history of analysis by FDA with

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negligible appearance of OPs. It was our judgment that we could include these in our assessment as negligible residues.

Also, we included, based on the FDA total diet study, which is a study -- the available data now on the internet goes through 1991 to 1997. These are market basket analysis -- actually, at-the-plate analyses of prepared foods. Based on these assessments, it was our professional judgement that we could include an estimate in our assessment for the meats: Beef, pork, sheep, and goats. This is an conservative estimate of residues based on the maximum values determined from the total diet study. It's the only exception in the assessment in which we use what one may consider a default assessment. As it turns out, we have seen no real impact of this on the total assessment. These values are still very low.

There are some other foods that were assumed negligible, although we did not have extensive monitoring data. These are sugars and syrups that are highly processed and refined. Based on that fact alone with information we have on related commodities, led us to conclude that we would not expect OPs to be present in these. So they were included as negligible in the assessment, also.

Now, as a means of getting one perspective of assessing what portion of the diet we're covering by these data that I've just

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summarized, we ranked the foods as consumed by children from the CSFII survey on a per capita basis in a descending order. And then for each food we assigned it a percent value based on the total consumption.

And what I have here in the table is an indication of what proportion of the per capita consumption is covered by the things I just summarized.

In this case, the PDP data, both of the raw commodities and any processed commodities that we translated these data to, account for approximately 86 percent of the diet. The translation that indicated, I showed you, about 20 different crop names up there, account for only 1.3 of the per capita consumption. The data, the FDA-supported data on eggs and fish and meat, account for approximately 6 percent of per capita consumption.

Our assumption of negligible for sugars and syrups is another 3 percent. And this leaves approximately 4 percent of the food per capita consumption that we have not included in the assessment.

Again, with this ranking of foods for children three to five in this case, the top 30 foods in this ranking are included in the assessment. And the top cumulative 95 percent of this diet that is comprised of 556 foods, of 52 those are included. The ones I excluded

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are dried beans, some corn-processed commodities and onions.

Other foods. Those and the other foods that are not included, we do not expect to impact significantly on the assessment; although we do have means to still test this and it is ongoing. Many of these are highly processed or blended foods; therefore, you wouldn't expect to have very high levels of these chemicals. And based on FDA data and chemical registration data, we believe that all these would have infrequently detected residues or low levels.

Moving on now to the residue adjustments. We're all familiar with our way of dealing with exposure and risk here. We talk in terms of margins of exposure, which would be a point of depart divided by an exposure. The point of departure is in this case is a benchmark dose 10. The exposure, of course, is composed of residue and consumption.

The residues for this assessment are the cumulative residues. We can converted chemical-specific residues on food samples to a common residue. And this is an index-equivalent residue. This was done on a sample-by-sample basis.

So an index-equivalent residue on a given PDP sample would be estimated by multiplying that residue value by any applicable processing factor and by its relative potency factor -- its potency

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relative to methamidophos. And these residues would be summed for each sample to become the cumulative residue in terms of methamidophos.

Then these cumulative residues become inputs for the assessment. Either as distributions of cumulative residues with each number in the distribution representing a PDP sample or average cumulative residues for some highly blend foods.

For our consumption modeling we used the CSFII, years '94 through '96 as supplemented in 1998. There are over 20 thousands participants in this version of the CSFII. The surveys were conducted. It was 2 days that were approximately 3 to 10 days apart. And this does contain a 1999 supplemental children's survey where an additional 5,500 children from birth to nine years old were included.

This survey is a significant increase for the number of children as compared to the '89-'91 survey which we have been using at OPP for you all of our single chemical assessments to date. This is illustrated in this table which compares the number of children of various age groups between the '89 to '91 data and the more recent. You can see, for example, for children one to two, the number of individuals is increased from 574 to 2,179.

The assessment, as currently published, includes four population

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groups. Other age groups can be assessed easily, but none has exposure estimates that exceed these groups we have. And the children one to two are the highest exposed.

The exposure assessment models that we're using in this assessment are DEEM and Calendex. My comments are going to be restricted to the assessments as conducted with DEEM. David Miller will be discussing some issue after I'm finished that incorporating the Calendex. And he will highlight differences at that time.

DEEM combines residue and consumption distributions in a Monte Carlo-like procedure to produce a distribution of one-day exposure and associated margins of exposure.

We're using the FCID version of DEEM, which has recently been released. This uses EPA's food commodity and intake data base and commodity definitions. This may lead to some confusion on the part of one who is reading through our assessment as published because this came at a fairly late date in our assessment. And you will find that we are referring to food forms as defined in the earlier CSFII. But when we get to the actual assessment, we translate these to the FCID form.

And, of course, among the differences in these, that is, one difference in this FCID version of DEEM is that foods do have

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different codes and many of them have different names. There are some separate breakouts, for example, commercial baby foods are broken out for each appropriate commodity.

Another significant difference is that this version of DEEM uses publicly available recipes for relating the foods consumed to the raw commodities or the values that would be plugged into the for estimating exposure.

So this is the preliminary assessment as published in December the 3rd. And this plot is a representation of the entire distribution from zero to 100 percent of the exposure distribution. The top line of the graph represents the BMD10 of .08 milligrams per kilogram per day. The bottom line represents a value that is one million times lower than that.

And there are four populations on this graph. If we can move to the next one. This focuses in on the top 10 percentile of the exposure range. And from this, I think you can begin to see that children one to two are the most highly exposed population group. And then with the specific numbers broken out for these four populations between the 90th and 99.9th percentile.

By June of this year we expect to have completed all the refinements of the preliminary assessment and this includes, of course,

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consideration of all the public comments as well as some QA on our own part, changes we know need to be made. So this is very -- we're very actively pursuing this.

We, also, have been conducting sensitivity analysis to gauge the relative importance of the assumptions that have gone into the inputs. We first revealed some of these in the case study that we presented to the panel in December of 2000. And in principle, our results have not changed from that in terms of the validity of those assumptions as we tested them. And we're, also, beginning the process of the interpretation of the results.

So next. Could you go back one. So, first, I would like to show you a few results looking at the potential effects of input assumptions and refinements on the assessment. Look at the effects of translation of PDP data to other foods using processing factors to estimate residue.

These data on this slide if you recall I showed you about 20 foods for which PDP data were translated because we feel they have similar use patterns. And, of course, this is subject to question always. This is a test of just what effect -- if we were making wrong assumptions, what effect this would have on our assessment. And this somewhat confirms our rankings that we had from the per capita

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consumption, too, the foods to which we translated make up a relative small proportion of the consumption and the total exposure. At the higher percentiles, there is very little difference in the assessment if one removes the assumption of OPs from all the translated foods. And that's what this represents.

We have a particular case here of a translation of data to a process commodity. In this case, we do not have processing factors or other information input into the model for conversion of OPs from the raw commodity to the baby foods. And, of course, we wanted to test and see how this assumption could effect our end result.

And with the new version of DEEM, one can selectively remove the contribution from all the baby foods. We did this for children one to two. And it confirms that there is essentially no effect on the assessment. This is probably not totally unexpected.

We, also, have done the same thing for children less than one. And there is no effect because they eat more baby food. However, children less than one as a group have a lower exposure than children one to two.

This is somewhat of a boundary on all of our processing and other extrapolations that we made. In this case, the top line, the top row, is the full assessment. And the other row of information

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indicates that a similar assessment in which we removed all translated commodities and all extrapolated data so the only information, the only OPs incorporated into the assessment, are directly related to PDP analyses.

So there are no assumptions of processing factors; there are no processed commodities unless PDP analyzed that processed commodity. And there were no translated crops. And we felt this was interesting to just sort of set a boundary on what we could expect to accomplish with a number of refinements that we want to make to these assumptions.

This is the previous slides in a graphical form the top 15 percentile of exposure. The top line represents the full assessment and, also, coinciding on it in this scale is using only not translating to other crops. And the lower lines represents removing all extrapolations.

Now, we gave you a revised question, one for food. This is partially the result of the limitations in time we have in doing some of these analyses. And we were working on this part of the assessment at the time we submitted the question. Based on the complexity of what we were getting and the fact we did not have time to finish some of the analyses, we choose to focus on some later things we're going to show

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you. But I wanted to show you this anyway because it has come up and it has been put on the internet.

In this case, we have questioned all along what the impact might be of the fact that our PDP data ranges in the time frame of 1994 to the year 2000 now. That's approximately seven years of data. Some of the information comes from only the earlier portion of that time; some from the later; some is spread across the seven years. We have as little at one year of data for a food and as much as five years. We wanted to evaluate the later data to see if they better represent the current use practices.

This is incomplete; but at least in terms of an assessment, I can show you how removal of older data, to the extent that only the most recent two years maximum was included for any given food, has some effect on the upper portion of the distribution. Maybe not a dramatic effect, but it is shown in this slide.

So this analysis is not complete. We need to carefully look at use pattern changes that have accompanied this. And we can, also, look at specific chemicals that were removed by removing the older data. So these are complex factors. We know, we did know, we were working with multiple distributions representing different segments of time.

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Now for the final portion of this, I'd like to briefly summarize our progress so far. I want to first qualify this by saying that we are beginning to analyze critical exposure contributors; however, we're doing this on the preliminary data. So for this reason, although the process is of interest to us and we want as much input that we can get on this process and how we can interpret it, the actual results that we're getting at this point we're sure may be subject to some change; therefore, we're going to speak in terms of pseudonyms again. I apologize for that.

This case we were looking at -- could you back up one? I should point out that the DEEM software has a critical exposure commodity analysis incorporated in it. This is a means of looking at the top much as 5 percentile of exposure to get an idea of which food commodities are food are contributing, which food consumptions are actually contributing to that part of the distribution. And we're looking at this to get some idea of which foods and, also, which chemicals are important. And we also, by keeping track of our sample analysis on a sample-by-sample basis, we also have a history on all these numbers. So we can go back and actually get sample details, such as the origin, whether it's domestic or import data and whether sample was taken in 1994 or the year 2000.

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So working with the preliminary results and looking at, in this case, we're looking at the area of the distribution between the 99.8th percentile and the 100th percentile of exposure. And the critical commodity exposure element does give you a listing of sort of a descending ranking of foods that are contributing to that portion.

And over in this range, under the conditions of our run, which, again, are preliminary, we had over 60 percent of the contribution to this area was coming from three foods in all their forms. This could include the raw commodity; it could include juices, dried forms, sauces. It's three food crops that are contribution to this. And we examined the impact of removing these residues from the assessments to see how this may impact the upper part of this distribution.

Again working with children one to two, we looked, we compared the full assessment. Two runs in which we removed singly each one of the foods. Food A was the most abundant in this part of the distribution. And if you remove only Food A, that second row illustrates what effect that has on the distribution at the higher end. Removing only Food B, there's less of Food B; the effect is less. And same sort of thing with Food C.

Taking both A and B out, again, depending on one's perspective, probably not a lot of change. It required removing all three foods in

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all their forms to affect the change at the very top end of the distribution of a two-fold change.

And this is just illustrating graphically what we have here that as you go toward the lower parts of the distribution, effects can be observed. But at the very top end of the distribution, it's difficult at times to tell the significance of the differences.

And, again, just another way of looking at this. Also, I've included the 50th percentile here which may not be in your background materials. Just comparing the ratio of the MOEs at these different points in the upper part of the distribution, you can see that the upper portion of the exposure distribution is not affected very dramatically by removing of these major contributors singly. And, again, to get a two-fold change, required all three.

So our interpretations of the risk results are a little premature to do that. But we do conclude at this point, that the PDP residue data do cover the major food consumption items. We, also, based on what we have so far, further refinements of the PDP data are not likely to drastically alter the results at the higher end of exposure distribution. And a rather nebulous conclusion here: Complex factors are contributing to the exposure distribution.

There was, also -- if you back up, there's also a calendar-based

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exposure which we used for food as well as the other pathways of exposure. And David Miller will discuss that next.

So now I think probably that ends my part of the presentation.

DR. KENDALL: Any points of clarification? Thank you, Dr. Smith. Very good. Any points of clarification from the Panel before we move to the next section? Dr. Bull.

DR. BULL: This last piece is a little counter-intuitive to me; maybe not to others. I think you were saying is the higher the exposure, the less able you're able to account for causing that exposure. That's my interpretation of what you're saying. I would have thought -- and just to give you a minute to think -- that something would be driving that very high exposure and that's not what you seem to be ferreting out of that data.

DR. SMITH: In a sense, that's what we're asking you is how do we interpret these results to help us however you can. As you go to lower parts of the distribution, of course, the total exposure is decreasing to very low values. So for that reasons, there's not much difference.

DR. KENDALL: Go ahead. Dr. Portier.

DR. PORTIER: Following up on that same question, it seemed to me that there's two possibilities for what could drive these margins

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of exposures and reducing them for single commodities. One is the commodity which very seldom has an OP level in it, but that OP level is rather high when it's in there. That would contribute to the high end of the tail of the distribution.

The other possibility is a commodity that has a fairly common OP contamination in it but at a lower level. And it seems to me the analyses you focused on for the commodity here is to find the rare events. Did you know that when you went into that, or have you thought about looking at reducing the entire distribution by finding potential commodities that have low levels by consistently there?

DR. SMITH: Yes, we have thought about that. And there is a companion part of this output from the DEEM in that you actually see those highest exposure events. What I was talking to you about was a summary of these highest events. And but we can also pick out the actual food consumptions that contain the highest residue or the highest consumption value. And we are trying to compare those. And it is a little less straight forward.

At this point, we can't say much beyond what we've done -- it is easy to pick out the top foods, you know, the ones that are coming to the top of the assessment. And they of course, you're right. There is a combination of having and some of them have a high percentage of

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residues and/or high residues. Both factors are there. In addition, of course, to whether it's a high consumption or not.

DR. KENDALL: Dr. McConnell,

DR. MCCONNELL: Two questions. First, are we are allowed to ask what A, B, and C are? Oh, we have to go to the top.

MS. MULKEY: We made a judgment that we could obtain the science thinking about this without identifying at this stage.

DR. MCCONNELL: Well, sure.

MS. MULKEY: Because there is a real market place, we thought it was prudent we get the benefit of an enhance understanding of the science before we did that.

DR. MCCONNELL: I guess the PC cops are out today.

What has been your experience over the past seven years? Have the percentages of exceedence been going up or down, or finding that in the particular commodity has it been increasing or decreasing with time for the, if you will, for the problematic commodities?

DR. SMITH: Exceedence, well, there's exceedence of tolerance.

DR. MCCONNELL: Maybe I didn't use the right term. I think you know what I mean.

DR. SMITH: Yeah, you mean just the occurrence of these.

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DR. MCCONNELL: Yes.

DR. SMITH: In general, the terms are hand to pick out based on the information we have, but there is a decrease. So from 1994 through the year 2000, one can see the appearance of a decrease of occurrence. This is -- I hesitate to say that that's a fact because this is being observed without extensive statistical analysis. And of course, we are interested in that and part of our goals are to decrease the levels on foods.

DR. DURKIN: You have identified the top three foods. You have, but we can't know it. What about the top three chemicals? Is there a parallel analysis where you look at it by chemical over the total diet so you can identify the chemicals that are there?

DR. SMITH: We are also looking at the chemicals in these top foods, and we can track that because of the way we did the distributions. We kept it tied to a PDP sample ID. And we do know the processing factors and the origins of the samples. And in these three chemicals -- I can say there are more than three chemicals involved in those three foods; yes.

DR. DURKIN: I just want to be rear clear here. There could be a parallel analysis where essentially you could spit out a vector of the chemicals combined over the total diet. So if we wanted to identify, as

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I'm sure you do at some point, what are the specific chemicals that contribute most to risk and how is that laid out? Is that possible with the software you have now?

DR. SMITH: Yes, it is. That is also underway. I choose not to discuss it. We can selectively remove a given chemical's contribution from the cumulative assessment. We can do it for a given food chemical combination or just across the board. And that's also actively in progress. But I just don't have -- I don't have any anything really to relate to you on that at this point.

DR. KENDALL: Dr. Rhomberg. Dr. Durkin, any further clarification? Dr. Rhomberg.

DR. RHOMBERG: I'm stepping a little bit out of my realm of expertise here. It seems to me that one could say that it could be that all sort of common diets are the same and every eccentric diet is eccentric in its own way. So that might say that it would be a mistake to focus on the single chemical or single food that causes the biggest contribution to risk if that's something that's ubiquitous and unavoidable.

It's sort of raising the baseline for everybody. And then the people that have various odd combinations of things, which would be very different for each of the different people, are the things that are

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causing peaks and throwing a certain individual into the tail of distribution one way or the other. That would be very important to know for risk assessment purposes.

Is there a single thing that you can do? Is the way to avoid problems that are caused by single unusual events in people because of an exceedence or very eccentric diet is the way to handle that, lowering the level of everybody, sort of lowering the average level so that the peaks don't go higher or to attack the peaks particularly?

As I say, this is out of my realm both from the point of view of assessing diets and from risk assessment. But I think it would be important to pull out those kinds of observations from these things. So that in a way, when you're looking at the peaks, maybe the thing isn't the biggest contributors; it's the ones that are most different from the main stream of people farther down in the distribution and are there consistencies there that can be got at.

DR. PERFETTI: Dr. Rhomberg, if I understand correctly, I think what you're asking is do the peaks represent unusual consumptions.

DR. RHOMBERG: Unusual consumptions or unusual residues, whatever. Just things that are -- it's got to be unusual something because there has to be some reason why they go up into the peak.

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DR. BULL: Otherwise you wouldn't get that distribution that we just talked about. I was right.

MR. MILLER: The CEC does print out essentially those individuals in the upper tails of the distribution. It lists out the consumption and lists out the residues associated with that. And what we do is look through that and get an idea of what's doing it. Is it unusual consumptions entirely by one commodity or unusual residues or such. So that is something we do look into in evaluating these things and judging their reasonableness.

DR. SMITH: You know, to not be totally precise in describing this, it is a very complex and even some of our single chemical assessments maybe were not that different in their complexity. But in this case, we are -- we do have the overlapping situation of distribution of consumption, a distribution of a variety of possible chemical uses. So more than one chemical is involved. And there's not necessarily a direct correlation between the frequency of occurrence and the relative potency of that chemical because these are all adjusted relative to methamidophos and we have a wide range of potencies in the chemicals over a few orders of magnitude.

We have, to our way of thinking, a fairly complex overlay and the possible time frame consideration, a possible, fairly complex

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overlaying of potential distributions. And we are look thing for what are the single things we can do to interpret what this means. And to this point, it's not necessarily a single thing; it's a combination.

DR. KENDALL: Dr. Portier.

DR. PORTIER: I was going to try to clarify Lorenz's comment. But I think it's more appropriate for a discussion later on.

DR. KENDALL: I agree. Dr. Heeringa.

DR. HEERINGA: I have a very quick question about the mechanism of the simulation where you remove foods A, B, and C. When you do that in the simulation, do you literally strike those foods out of the sample child's diet; or do you sample children who consume those foods on that day? In other words, is there a replacement of other diets that's taking place in the simulation?

DR. SMITH: We're removing the OP contribution to that diet.

DR. HEERINGA: You actually sample the child. And if it happens to be a contribution A, B, and C, so you're essentially lowering an expectation the overall residue consumption.

DR. SMITH: Correct.

DR. KENDALL: Dr. Freeman.

DR. FREEMAN: Two things. When you did this, are you only looking at commercially used pesticides as opposed to residential

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fruits and vegetables that are treated? And the second thing is, a number of these commodities, based on the data that we were provided with, are produced in very specific regions. You know, they're either warm weather crops or they're cold weather crops. And so you may have three areas of the country that are generators of, say, one of these crop items.

Have you looked at the differences in pesticides according to the regions from which the samples were obtained? And have you tried to do some sort of weighting based on some sort of distribution across the regions as to how it's going to impact on the pesticides in these foods?

MR. MILLER: The assumptions in this assessment is that PDP does sample proportionate to a national basis proportionate to production. So if 20 percent of crop A is grown in California, or consumed in California, 20 percent of the samples would be from there. So overall, on a national basis, yes, it is proportionate to that.

In terms of looking at regional residues, for example, we assume essentially it's a national distribution of the commodity. So we don't look at specific regions and don't look at specific residues in specific regions.

DR. FREEMAN: Yeah. I'm a little concerned about that

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because you see a constellation of pesticides in one region for say apples that you may not find in another region that grows apples. They have one or two that are the same, but there may be differences. And that might impact your results.

DR. KENDALL: Dr. Adgate.

DR. ADGATE: I'm curious. What's the rationale for removing the violative residues?

DR. SMITH: Should I pass that to the end of line or try it myself?

MS. MULKEY: In pesticide regulation, there's always the challenge of whether you regulate to violations or regulate on the basis of the assumption that people comply with the law. It's not unique to this situation. We face that issue a lot. And if we believe that violations are endemic, that there's sort of an inherent aspect of the lawful use, we will consider violative scenarios. I'm talking now generally, not in this one. I think we do not have a basis in these examples in believing that the violations predictable, sustainable, sort of unavoidable by product of lawful use.

But if we did or had some basis to, then that would be the situation in which would typically take into account violations. This is not a policy we developed just for this approach. That's been our

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longstanding approach to the way we thought about pesticide regulations. And it involves not just foods but other exposure situations, too.

DR. KENDALL: Dr. Portier. This is the last question.

DR. PORTIER: No, this is four or five. I was waiting to see if anyone else would ask them. Again, hopefully, these are just clarification questions. In what you just presented, those are single day resamples for single-day diet; is that correct?

DR. SMITH: Yes. But it's using both days of the diet.

DR. PORTIER: Okay. I don't understand that. Run that by me again.

DR. SMITH: They are single-day exposures, but they are obtained by using a survey that is composed of two separate days.

DR. PORTIER: And in the two-day survey that you're using, you're just using the one of the days as the resampling for food consumption.

DR. SMITH: No, in DEEM, both days are used.

MR. MILLER: The count is separate. I'll get into it a little bit in my presentation. The account is essentially separate people. In the diet food Person No. 1, Diet No. 1, counts as essentially a separate person than Diet No. 2 for that same individual.

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DR. PORTIER: But you're sampling the day's diet.

MR. MILLER: Yes.

DR. PORTIER: For one of the two days by random draw.

MR. MILLER: Yes, yes.

DR. PORTIER: So that was the second part of my question. There is a random draw for diet as well as a random draw for pesticide residue.

MR. MILLER: Random draw. But the random draw for diet is connected to that individual. Well, actually, I'll talk about it a little bit more in my presentation.

DR. PORTIER: We talked about the violations issue. I wanted to raise that again. I think you want to look that the policy, at least try to collect some data on what percentage of violations are actually caught.

The PDP data is market basket from food stores. Does it include market places? Road-side buys? Anything like that?

DR. SMITH: PDP is primarily from food distribution centers. It's not at the grocery store in general. In some commodities, for example, some of the grains and I think maybe grains were taken from a earlier point in the distribution, the idea was to get it as close to the distribution as practical to be able to reproducibly over time go back

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and resample.

DR. PORTIER: To follow up on that question we had a minute ago, I didn't understand the resampling scheme. If I resample a diet and the child gets two apples in one day, assuming apples may or may not be exposed to OPs. But I'm going to choose apple for the fun of it. Do the apples get two separate random draw residues independent of each other, or do the two apples get the same residue?

MR. MILLER: In the DEEM, what it does is it totals it over the day. So if your child has, the person you're drawing, has two apples in one day, they will, essentially, be combined in consumption of grams per kilogram. And then it will draw one random residue value for that.

DR. PORTIER: That basically assumes, I guess, the two apples have the same residue which is fine for me.

And there was a another statement you made, and this is my last question. When you looked at the population groups assesses and noted that the children one to two years old have the highest exposures of all these groups, I gather, because you did not show us, you did not do less than one year and you did not do the other groups. You are assuming that those other groups are not as high of an exposure; is that correct? Or did you actually do the less than one year olds?

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DR. SMITH: We have done less than one and the exposure is less. Some -- I mean the possibilities are, you know, you can go in and adjust the years that you want to take. So there are a number of possibilities. And at different stages in the assessment, we've looked at other combinations. At this point, I cannot give you an assessment, say, for children one to six all inclusive. We have three to five broken out from one to two, and we have looked at less than on. We just haven't included it.

DR. PORTIER: And do you intend to include that in the final? We got several questions about that yesterday. And I'm trying to understand why it's not in here then.

DR. PERFETTI: I mean, basically, not just this analysis, but with a lot of them. One to two are the most highly exposed right down across the line. We could put zero to one in or all the other age groups, but it would always, be to our knowledge, and, Dave, I think you can agree with me, it's always the one to two because they have the largest consumption with respect to body weight. So they always are going to get quote the "highest exposure". So if you know that one to two are going to be the worse case, everything else, the exposure is going to be less.

DR. PORTIER: I guess you can assume I'm from Missouri. I

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like to be shown. "Show me" is the basic tenet here.

DR. KENDALL: Thank you. Any further points of clarification? Dr. Zeise. Remember, Dr. Miller, we'll go forward and probably clear up a lot of these questions. The presentation is quite long so I didn't want to break in the middle, at least let people to have a chance. So points of clarification.

DR. ZEISE: Yes. I was, also, wondering what the teenager, the upper end might look like for teens. Just curious, looking through, they're conspicuously missing. And I also wondered in terms of thinking through what might be happening with the tail if you looked at the issue of using composite sampling. What that would do is you're smearing out and probably have more zeros, more cases of zero and then higher values and that the composite sampling is actually also doing some smoothing at that upper end.

DR. SMITH: Actually, we do have limited -- we do have information from single serving versus composite samples. PDP has looked at three different commodities: peach, pear and apples. And there is also an industry market basket study that was done on single-serving basis; although, they do not have a composite direct comparison to a composite.

At this point we do not see a lot -- maybe surprisingly -- a lot of

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difference between the distribution in the PDP between the single serving and the composite.

DR. ZEISE: At that upper tail.

DR. KENDALL: Dr. Bull.

DR. BULL: Just a real quick clarification of Chris's. When you looked at the less than one year old, is that distribution more or less the same; or is the high end exposure still even more exaggerated? When you say "across the board," I was trying to figure out what across the board meant. Am I making myself clear?

DR. SMITH: I'm not sure I can give you correct answer on that.

DR. BULL: Well, you have a curve that describes the distribution of exposures in terms of MOEs, the fraction of the MOE. Is that slope of that curve similar in the less than ones as it is to the one and twos. I could see the extremes being more marked in that group.

DR. SMITH: That's a good point. And I haven't carefully looked at that. We do know that they are less exposed in terms of comparing the curve shapes, we haven't gotten to that. But that is a good point.

DR. KENDALL: Dr. Reed.

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DR. REED: This is a quick clarification question. Because you didn't see a great difference in residue distribution between single-serving-size surveys and the composite samples, and that's the reason you didn't use single-serving-size data; is that correct?

DR. SMITH: Yes. Possibly another reason. That's part of it. And just the feeling that if we have this huge data base of composite samples, and to use the single serving, we're limiting ourself to one small segment of data. If it did not make a difference, the composite samples, it would be consistent kind of analysis. We feel that composite samples may be better suited for catch catching co-occurrence. Can't prove that; but that's our general sense of it. That would be another reason.

DR. REED: Thank you. The other short question is: There's mention about choice years of PDP data. The analysis seemed to indicate that maybe you don't need that many years of data. There's a mention in the document about correlating that or the concern for pest pressure. Have you gotten any chance to go back and sort of looking backwards to see if there's any past pressure situation in that the PDP data actually picked that up in terms of residue?

DR. SMITH: That's part of the analysis that led us to change the question somewhat because we have not completed that. We are

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interested in whether we can pull that out. We don't know.

DR. KENDALL: Any further comments related to this stage of the presentation? Before we move to Mr. Miller, I'd like to welcome Ms. Marsh Mulkey, the Director of Office of Pesticide Programs. We appreciate you joining us again. Would you like to address the Panel?

DR. ADGATE: No thank you.

DR. KENDALL: Mr. Miller, are you ready to proceed?

MR. MILLER: Just to kind of go through quickly the outline of the presentation. I'll provide an introduction, background information. It will be a brief overview and recap of probabilistic techniques used in preliminary cumulative risk assessment, or PCRA. I'll then talk a little DEEM(FCID) versus DEEM(FCID)/Calendex. As Bill had mentioned, his talk was on DEEM(FCID). And all the FCID means is the new recipes, the new publicly available recipes and the new '94, '96, '98 data. Do a little talk about the difference between those two and how the one includes a time component.

I'll talk a little bit then about the time frame considerations. Why it's important. There will be more details relating to this tomorrow. Specifically, how to compare these with a tox endpoint.

Then talk about modes in which Calendex can be used for a cumulative risk assessment which goes directly to the time frame

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consideration issue. Consecutive daily estimates is one potential mode. That was the mode that was used in the preliminary cumulative risk assessment, PCRA, that provides separate estimates for January 1, January 2, January 3, et cetera. And alternative, methodology, which is available in DEEM which was not used for the December 3 document was rowing or sliding assume time frame approach. Again, there will be a little bit of discussion of this in terms of interpretation on this on Thursday.

And then going to strengths and limitation of these modes and the associated issues. This will include a comparison of some runs we've done comparing the 1-day assessment with the 7-, 14- and 21-day rolling averages. And you'll see those numbers here.

And then, finally, the questions for the SAP.

Just some points to remember, the presentation will not extensively review the step-by-step mechanics of DEEM(FDIC) Calendex algorithms. DEEM Calendex was reviewed in previous SAPs. However, I will try to give you a flavor of what's happening. And where it's important, I'll go into the details and differences between the modes.

The main presentation, here, concentrates on exposures through food. However, the principles apply to all routes. And, finally, I'll

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remind you that no decision has been made on an appropriate MOE or threshold percentile for regulation.

When I talk about X-percentile graphs, they are meant to be illustrative only, intended to illustrate the concept. It's not that we've made a decision or are leaning toward any specific percentile or MOE.

Just some background, DEEM(FCID)/Calendex provides probabilistic assessment of exposures through food, water, and residential pathways. DEEM(FCID)/Calendex incorporates the concept of a calendar to aggregate or accumulate exposures -- it's a time-based approach -- which allows us to look at individual days of the year. Importantly, the approach allows appropriate temporal matching of exposures through food, drinking water, and residential pathways.

These temporal aspects are important for OPs to the expected seasonal use patterns. For example, it would be important to match springtime exposures from one applications through exposures through drinking water associated with spring runoff. Likewise, it would also be important to preclude or appropriately discount nonsensical or low probability events, perhaps treatment of house for fleas during the wintertime in the northeast.

So this is what Calendex allows us to do. Thus Calendex uses

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probabalistic techniques to appropriately combine exposures from the food, water, and residential pathways in a manner which incorporates probabilities of exposure, use and application practices, human activities patterns, et cetera. Importantly, it considers their associated seasonality and timing.

So we expect, for example, probabilities of exposure, one can input as a data for Calendex at maybe perhaps 6 percent of the individuals users of a pesticide, or the 15 percent of apricots contain residues. So the probabilities of exposures can be counted in that way.

Use and application practices can also be accounted for. If the label directions say apply in spring, then it will be applied in the spring as per Calendex. If the label directions say, for example, or if we know that 80 percent of the users apply it one time and 20 percent apply a second application 2 to 4 weeks after the first, that information can be incorporated as well.

It also incorporates human activity patters, time spent on lawn, for example, time spent inside, et cetera.

The result of the result of the Calendex analysis is a collection or distribution of aggregate exposures, that's food, residential and drinking water combined, for each day of the year for the relevant

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region. These exposures can be plotted as a time lime or profile of population daily exposures for any given percentile in this distribution. This is illustrated on the next slide.

This is just a quick 3D graphic which kind of summarizes DEEM Calendex output in a compact form. You can see the vertical access is the exposure. That's plotted against a time line in the bottom of horizontal axis from zero or 1 to 365 days. And the depth is the percentile for any given percentile. In other words, what we can do is plot exposures as a time line against any given percentile.

The graph emphasizes an important point that a time line, time-based profile exists for any selected percentile. We've shown some specific ones here, 10, 30, 50, et cetera. For example, there's one at 99 here which goes on. It goes along there from January 1 to December 31. And what that does is it shows or plots out the 99th percentile exposures for each of the 365 days of the year. 99th percentile for January 1, 99th for January 2, et cetera.

The three 3D graph essentially summarizes output that's specifics to DEEM(FCID)/Calendex as opposed to DEEM(FCID) which Bill talked about. Again, you get the three-dimensional part because of the time component is added here.

DEEM(FCID) analysis assess exposure from food alone, as Bill

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said, without respect to timing or seasonality issues. What it does is it randomly matches report food consumption by individual with residue data. There's no time component to this. The result, as Bill described, is a single distribution of exposures and a single value estimate of risk at any percentile of exposure.

How does DEEM(FCID)/Calendex, which incorporates the time component differ DEEM(FCID) when we do an aggregate or cumulative assessment in which pathways are combined, time and considerations become important? DEEM Calendex performs this analysis in a manner in which time considerations are incorporated. It does this by performing separate analyses for each day of the year. The result is 365 separate distributions of exposures for each day of the year. And exposures can be at any given percentile, 99th, 95th, et cetera, can be plotted as a time-based exposure profile.

These differences are summarized on the next slide. DEEM(FCID) considers food alone; whereas the DEEM(FCID)/Calendex considers all pathways, food, water, residential. Timing is not considered in DEEM(FCID). There's no day-to-day variation, whereas timing is considered in DEEM(FCID)/Calendex. There's some day-to-day variations in the diet. That will be explained a bit later in this presentation.

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And another difference is single-exposure estimate is provided DEEM(FCID) at any given percentile; whereas, DEEM(FCID)/Calendex provides 365 sequential daily exposure estimates for any given percentile.

With that as background and the knowledge that DEEM(FCID)/Calendex can consider time, there are several issues to the SAP regarding time-frame considerations. Remember that exposure's only half the risk equation. It's important to consider how the estimated exposure is compared with the toxicity endpoint.

In the preliminary cumulative risk assessment, PCRA, toxicity endpoint is based on the BMD10 which reflects a multi-day dosing study or a series of multi-day dosing studies. And you heard about this yesterday from Anna and Woody. You, also, heard about it last September at the 2001 Scientific Advisory Panel meeting.

In the report you provided, there were two statements that cumulative risk assessment should ideally compare toxicity endpoint and exposure durations of the same time frame. And, also, to the extent possible, comparison should take into account the pattern of human exposure.

Again, you're scheduled to hear more about this comparison tomorrow under the risk characterization session. But in my talk here,

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what we'll focus on is the time-frame issue and how it's handled by DEEM and Calendex.

DEEM Calendex program can perform analyses using a variety of time frames. You heard from Bill the single day. This presentation considers two specific modes of analysis which are available in Calendex. One is the single consecutive daily estimates, January 1, January 2, et cetera. That was the analysis that was used in the PCRA.

The second is a rolling or time-frame approach where it takes a rolling average, considering, for example, January 1 through 7, then January 2 through 8, then 3 through 9, et cetera. It provides an average exposure over that time period.

I'll emphasize that the examples I'll give you here are illustrative only, intended to illustrate the concept. The numbers are not real. And PCRA used, again, the first option; the single-consecutive day rolling estimate not the rolling time frame. Although at the end of this presentation, you'll see those results for the rolling time frame and be able to compare the two.

Just first option, the single-consecutive-day analysis, the analysis we used in the December 3 assessment, provides separate independent exposure and risk estimates made for each day of the year. And I'll show this in the next few slides, summarize how that is

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done.

The estimates, then, are arrayed chronologically into an exposure time line for any selected percentile and graphed. These represent independent daily estimates of risk on each day of the year. Importantly, they're not necessarily -- as you'll see in the following slides, they're not necessarily the same individual on consecutive days. What I mean by that is the next several slides show how this is done by DEEM Calendex.

So for a single-consecutive-day analysis, the analysis that was done in the assessment, and, again, the numbers here are not necessarily -- they're not necessarily the numbers. It's illustrative only. What DEEM would do would begin with January 1. DEEM(FCID)/Calendex begin with January 1, CSFII, Individual No. 1.

What DEEM Calendex would do would then estimate the exposure and plot that exposure to the individual on the histogram. So that could come across as -- essentially think of it as a first block of a histogram would be located someplace along there.

How is that exposures estimated? It's done for that Individual No. 1 on January 1. It's done by randomly choosing one of Individual No. 1's self-reported diets and then randomly selecting a residue for

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each component of that diet. And that is essentially summing them up and estimating an exposure based on that.

And the same thing would be done with Individual No. 2. And that would work out -- actually, if you could back up for a second. That would be the same thing would be done for Individual No. 2. And the result is a slowly build up essentially a distribution which might look something this, a histogram with a shape that looks something like that.

In this case then what we do is, if we were choosing to plot out the 99.9th percentile, what we would do is estimate what that is. In this case, it might be individual No. 10,456 that would plot out at the 99.9th percentile and essentially estimate the exposure from that individual at that percentile. That might, for example, translate to a MOE of 84.

We than move on to January 2 and do the same thing. Starting with Individual No. 1, estimating the exposure and plotting. And, again, we do it for all the individuals. Individual No. 1, 2, 3, et cetera.

In this case, these would be plotted out for all the individuals. In this case, the 99.9th percentile individual exposure might be Individual No. 1,492. We estimate exposure. And that might work

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out to be, for example, an MOE, margin of exposure, of 92.

We would proceed through each day of the year in this through December 31, which is here. In which case of the 99.9th percentile individual or exposure, might be Individual No. 18,912. again, we'd estimate an MOE with that exposure.

The net result of this is we end up with 356 different 99.9th percentile values. Again, what we've done is for each day of the year we've run through each individual and we can pick out the 365th -- the 99.9th percentile values.

What we do is take each of these 365 99.9th percentile values and then plot them out for each day of the year, January 1 through December 31, that population percentile. The resulting time-based exposure profile represents, in this case 99.9th percentile exposure for each day of the year.

It's important to remember that each day of the year is considered independently. It is not the same individual. If you remember on January 1, it was Individual No. 10,456 that was at the 99.9th percentile. On January 2, it was a different individual.

One can see this plot on the next slide here. The vertical axis. These plots are central to the understanding and interpreting the cumulative risk assessment. I'll go through it in some detail.

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Remember, this is the single day assessment as we used in the preliminary assessment.

This is the vertical axis here. It's the exposure. Here is the time line. The horizontal axis is the day of year from January 1 through December 31.

Continuing with the example, if you remember, January 1, the 99.9th percentile exposure value was associated with Individual No. 10,456. He had an MOE of 84. So that would be plotted here for January 1.

For January 2, the 99.9th percentile individual, the value associated with the 99.9th percentile exposure would also be plotted. In this case it might be an MOE of 92. It continues through the year through December 31.

Just some key points. These are all, again, each different individuals. These are also one-day exposures.

How is this interpreted, for example? Day, for example, if you wanted to interpret the MOE associated with Day 31, this would essentially look up here, and this would be perhaps an MOE of 58.

How is that interpreted? On Day 31, the day we were looking at, on the next slide, the MOE for food, the interpretation would be the MOE for food at the 99.9th percentile would be 58. The

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translation of that would be the exposure to the 99.9th percentile individual on Day 31 is 58 times lower than the BMD10.

Day 32, it may be that the MOE was estimated as 66. The translation of that would be that the exposure to the 99.9th percentile individual on that day is 66 times lower than the POD. Remember, it's very likely that that is a different individual than the 99.9th percentile individual on January 31. Just as on January, the 99.9th percentile individual was different from the individual on January 2.

The next slide shows some pros and cons of this method. This was the method that was used in the PCRA. It's easier to identify risk contributors and sort them out using the CEC function of DEEM. That's the function that Bill had talked about some.

It's also health protective from a multi-day standpoint. When one looks at a sustained or extended period of time of elevated exposures, it's unlikely to be the same individual that's being exposed.

However, there are a number of disadvantages to this. One is that the point of departure, the BMD10, is based on multi-day exposures. The animals, if you remember from yesterday, are dosed daily for an extended period of time to estimate the BMD10. It might of be of concern would be the relevance of comparing a series of elevated single-day exposures to a multi-day endpoint.

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Another disadvantage is the second consecutive daily estimates are likely to over estimate multi-day exposures to an individual at the higher percentiles. For example, it's not possible to interpret an extended serious of elevated exposures on consecutive days as representing extended period of exposure to the same individual. In other words, we haven't strung together consecutive days for the same individual. So the individuals are different.

If we were to string together consecutive days for the same individual, what we'd get from DEEM we'll be able to have essentially a rolling time frame approach. And this is what this next series of slides considers. And I'll talk about stringing the days together and go through a detailed example of how this is done.

It can, also, be looked at as essentially a multiple sequential day option. In this rolling-time-frame option, a rolling average exposure is calculated over multiple days for each individual. For example, January 1 through 7, then January 2 through 8, and January 3 through 9, et cetera.

It's this series of multi-day average exposures that then serves at a basis of comparison with the BMD10 -- with the POD. More, specifically, this distribution of individual-based multi-day average exposures is compared with a multi-day BMD10.

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The next slide show an example of this. And, again, the numbers are not real but are meant to be illustrative only.

Specifically, this specific example will deal with a 7-day rolling average. It begins with individual No. 1 on January 1. And you can see this is going to be this January 1 through 7 rolling average. This exposure to this individual on January 1 is estimated from this DEEM Calendex software as .012 milligrams per kilogram per day. That's estimated, as always, by randomly choosing CSFII Individual No. 1, Day No. 1 or Day No. 2 diet; randomly choosing residues associated with each component of that diet; combining those; and summing them over all foods reported consumed by that individual on that day. So that point .012 is estimated in that way.

The same thing is done for that individual for January 2, again, choosing one of his two randomly reported diets. And January 3, et cetera, all the way through through January 7. You can see on January 2, the estimated exposure using that is about a little bit over .006.

The next step after that, after we've calculated exposure from each of those days is to calculate an average exposure over the entire full 7 days. Here the average exposure, you can see, is about .006 milligrams per kilogram.

We've done this then for Individual No. 1 for January 1 through

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7. We now move on to Individual No. 2 for this same time frame. Again, starting with January 1, estimating the exposure as before for each day, January 1 through January 7. After that's done, we calculate a 7-day average over this time period. Here you can see it works out to be about .007 milligrams per kilogram.

We continue this through all individuals in the survey, calculating it for January 1 through 7. If there were 15,243 individuals in the survey, for example for the last individual, the 7-day average exposure works outs to be .005 milligrams per kilogram.

If there were 15,243 individuals in the survey, we'd end up with 15,243 7-day average exposures for January 1 through 7. Then what we would do is sort them from high to low and pick out this 99.9th percentile exposure and plot this value for January 7.

So what we've done is for January 1 through 7, calculated for each individual a rolling average and picked out the 99.9th percentile values in this case just as an example.

For the next rolling time frame is January 2 through 8, we go back to Individual No. 1 and calculate exposures for each of the days, January 2 through 8, again randomly choosing each day one of his two reported diets and combining it with a randomly selected residue. We do the same with Individual No. 2, Individual No. 3, et cetera, for

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January 2 through 8. Continue all the way through and then slide along and do 3 through 9, January 4 through 10, et cetera, until we get to this last individual which would be January 1 through 6. It rolls around. We'd end up with 365 different 99.9th percentile 7-day rolling average exposures and plot them over time as we did before.

There are a number of advantages and disadvantages to this approach. One advantage is that it incorporates the variability in exposure for an individual across multiple days. This multi-day average exposure may be the actual exposure of interest to compare with a multi-day endpoint.

It's also likely to provide a more realistic estimate of exposures across multiple days. And, again, if it's not a series of single-day exposures we're interested in, this allows us to calculate high end multi-day average.

It's also flexible with respect to matching time frames associated with the POD. One can chose, for example, this example was 7 days. But one could chose 7-, 14-, 21-, or 28-day rolling averages.

There are a number of disadvantages, too, to this approach. Break down into two basic areas, one associated with food consumption and the other associated with residue. UDSA, CSFII

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does not provide consumption data across the multiple consecutive days which would be of interest. It's limited to two days of records of reported intake. Also, those two days are not consecutive. They are 3 to 10 days apart.

As a result, the multi-day average exposure for any individual uses only two days of reported consumption data for that individual. With the rolling average approach, what we're using is those two days of reported intakes to simulate 7 or more days of eating. It repeats these randomly throughout the time frame of interest.

The other aspect concerns food residues. There are no longitude and residue data available. For example, if I ate a star fruit yesterday and star fruit today, if they came from the same Safeway, they're likely to have the same residues than if the one I ate yesterday was from Safeway and the one I ate today was in the company cafeteria. So there's no longitudinal basis on residues for that.

Just more specifically on those two points regarding, first, on food consumption aspect. Any consecutive day period of interest for an individual will contain a series of repeated diets which would tend to underestimate the variability. This will tend to over state potential exposure at the upper tails of this distribution to the extent that reported food choices or diets are associated with higher exposure.

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On the aspect of the residues, the second aspect I talked about more specifically. Since residue values are anew at random, for each day during the time frame of two occurring on subsequent days, may not be accurately reflected understate potential at the upper times. If an individual exposure is associated with pesticide residue, two examples, one might be juice you drink from this morning, may very well be the very same one you drink from tomorrow morning. And it will have the exact same residue concentration. In DEEM(FCID)/Calendex, a brand new residue was selected for that second day.

Similar situation is bags of produce. The produce I eat today may very well be from the same bag I eat tomorrow. They likely share the same treatment history.

If the rolling time frame average in DEEM is selected, it allows -- the example I gave was 7 days. But it allows the user to choose various time frames. We've redone the analysis using a 7-, a 14-, and 21-day time frames. And you'll see these in the next graphs.

Increases, two things you'll note as you go through these. And, again, you'll note when the next graphs are shown. But increases in time frame, going from 1 to 7 to 14 to 21 over which the averaging is performed, results in two main things. One is the attenuation of

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variability; and this other is an increase in the MOE, essentially, a decrease in the exposure.

You'll see that in the next two slides. Keep in mind that it's a reverse log scale. And, also, the degree to which these changes occur are dependent upon the selected percentile. The effect seems to be greater at higher and more pronounced at higher percentiles than at lower percentile.

These are shown in this slide here. The very top one, the sky blue one, is the one day. What we did in the assessment using the one day time period. The next three underneath that are 7-, 14-, and 21-day time periods.

So, again. These are averaging exposures. You note the attenuation goes down as you go from the one day here, the sky blue down here, less variability. And the there's a decrease in the MOE. You're averaging additional days into it, so there's an increase in the MOE, a decrease in the exposures.

This is actually -- this is an example of this higher percentile example where the effects were more pronounced. At the lower percentile example, you can see the same thing except the effects are less pronounced. Again, the sky blue is the one day; and it looks like the 7, 14, and 21 are almost coinciding, but they're very close.

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I guess a series of questions would be the next set.

DR. KENDALL: Think I'd like you to have you stop there because we'd like to have some clarification from the Panel. Then we will take a break and come back with the public comment period. After that, I'll have you read the questions. And then we'll begin the deliberations.

At this point, any clarification questions from the panel? Dr. Durkin.

DR. DURKIN: I have three quick things and it may be a lack of understanding here. You indicated that Calendex makes assumptions about when the chemical is applied. So if the label said it's applied in the spring, that enters into it in some way.

MR. MILLER: That is entered into it in the residential side of the assessment.

DR. DURKIN: Only the residential. Okay. That's fine. We'll move on.

You showed some 3D graphs. If we asked for a 3D graph of the day of the year, the percentile, and then on Z axis the chemical, would that be possible? Can you spit those out?

MR. MILLER: If you were looking at a specific chemical.

DR. DURKIN: No. An array of different chemicals. It gets

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back to my previous question about can we track these by chemical. I guess that's what I'm trying to nail down real clearly here. It seems like you could do it from the food, the Calendex.

DR. SMITH: We think we can do that. It would be a lot manual.

DR. DURKIN: So it's not easily done.

DR. SMITH: It would require kind of a multi-step process.

DR. DURKIN: It wouldn't just spit it out. Okay.

And then the last item is really just a follow-up on a question that Natalie had. In any of these residues is home grown vegetation considered?

DR. SMITH: No.

DR. DURKIN: Okay. Thank you.

DR. KENDALL: Any further questions?

DR. RHOMBERG: On the residential exposure component, I assume, does that take into account some kind of attenuation of exposures over time in ways that are modeled according to residential?

MR. MILLER: Yes. Jeff Evans will be talking about that later today. But it does. If you applied that three days ago, it would attenuate that over the three day up to today.

DR. RHOMBERG: You made a big point of saying they were

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not real numbers for the rolling average. Was any of this real at any place? In that when these last graphs that you showed with the rolling averages, were those based actually on doing the exercise that you had described earlier?

MR. MILLER: Yes, yes. The point I wanted to make on the real numbers is that, when I was showing the average, the rolling time average, the Excel graphs from 0 to .014. Those real numbers there. We didn't go back and look at Individual -- that's good. We didn't go back. We didn't go back and look at Individual No. 1,492 plot out his exposures for example. There was some confusion about that at the technical briefing.

DR. RHOMBERG: Okay.

DR. MILLER: So I wanted to make it clear.

DR. RHOMBERG: And since you only have two days of diet for each person, you are sort of flipping back --

MR. MILLER: Flipping back and forth, yes, over those seven days.

DR. RHOMBERG: Randomly, you could pick the same diet twice in row if it happened.

MR. MILLER: Yes.

DR. RHOMBERG: And when you come up with different

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values, that's because --

MR. MILLER: Different residues.

DR. RHOMBERG: -- of different residues.

MR. MILLER: Yes.

DR. RHOMBERG: Okay. Thank you.

DR. KENDALL: Further questions? Dr. Portier.

DR. PORTIER: In essence on the flipping diet issue, you actually flipped the diets for 365 days for an individual, don't you, because the 1 to 7 is the same individual for 2 to 6.

MR. MILLER: Yes.

DR. PORTIER: And then you and 2 to 7 and then you add the 8. So the diet is flipped completely.

MR. MILLER: Yeah. But it's always connected to the same individual.

DR. PORTIER: Just so I'm really comfortable, I want you to reassure me again that the graphs that you show with the rolling time frames approach, the examples are clearly not OPs since those numbers are only 10 away from the BMD. Not the later graphs, but the early single rolling time frame graphs.

MR. MILLER: Yes, yes.

DR. PORTIER: I want to be certain.

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MR. MILLER: Yes. Those are not.

DR. PORTIER: The couple of questions I had about some of the statements you made in -- 1, 2, 3 further graphs down from that one -- you have pros and cons for rolling-average-based estimates. There.

The second point. Why? I'm not sure I understand this. Clearly, the assumptions that go into the analysis are violated; there's absolutely no doubt about that. The double diet back and forth is clearly not a realistic diet. The residues selected independently from day-to-day without any correlation structure is clearly going to be violated especially into details of the distribution. Why do you believe this is more likely?

MR. MILLER: Which specific slide and which specific point?

DR. PORTIER: It's this slide, Point No. 2.

MR. MILLER: Okay. Why do we believe it's likely to provide a more realistic estimate of exposures across multiple days?

DR. PORTIER: Yes.

MR. MILLER: If you're interested in a multiple-day time frame, we believe that it provides -- the alternative, the one-day time frame -- let me take a look.

DR. PERFETTI: Dr. Portier, in my own simple way. The way I

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look at it is, if you do this day by day, you're picking an individual, say, at the 99.9th percentile one day and you're picking that individual at that percentile is unlikely to be at that percentile on a following day. Whereas for this day by day, you got a different individual each time.

I mean if you get exceptionally bad day on one day, the chances that you're going to have an exceptionally bad day for the next seven days are rather low.

DR. PORTIER: But the question here, I guess, I'm interpreting maybe differently than what you're saying. I'm thinking about distributions. So I got a distribution for single-day exposures. And then there's a distribution for multiple-day exposure. And the way I read this is that you're arguing that the distribution seen here for this procedure is more likely to be correct if you're interested in truly multiple days --

MR. MILLER: It's multiple days, yes.

DR. PORTIER: -- than is the distribution for single exposures. And I'm not convinced of that. I was trying to give you an opportunity to convince me that the two assumptions that are violated don't simply drive us regression to the mean, which is why we might see reduced variability, why we'd see lower tail behavior, and to get some question

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-- have you done alternatives? There are some obvious alternatives. Don't use the two days back and forth. Choose random days and bring them together, find some correlation structure from day-to-day sampling, and use that.

Have you done any of that, some of the things we discussed when Calendex came up?

MR. MILLER: Yeah. We've talked about that one. One possibility is to hold the day constant -- hold the diet constant throughout the seven days, don't randomly bounce back and forth. Another possibility would be to choose different residues -- keep the same residues, for example, and find out how much of an effect that has.

We haven't gone ahead and done any of those analyses at this point. We're looking for recommendations and thoughts from you on how that might be applied.

DR. PORTIER: And let's see if I had any other questions. Yeah. Two more slides down I'm trying to understand this conclusion as well. Could you repeat the explanation for me.

MR. MILLER: Any I'll just read the slide first and then go through it. Any consecutive day period of interest for an individual will contain a series of repeated diets which tend to underestimate

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variability. So, for example, if we're repeating, if an individual has reported --

DR. PORTIER: That I got. It's the next one.

MR. MILLER: Okay. This will tend to overstate potential exposure at the upper tails of the distribution to the extent that reported diets are associated with higher exposure. So for example, if I consumed, for example, two ginkgo fruits over these two days -- and that's an unusual event -- I'm going to repeat consuming those ginkgo fruits through all seven days.

So it's kind of -- in reality over seven days, I wouldn't be eating those on all seven days. But it's artificially repeating that consumption pattern over the seven days.

So if to the extent that the diet is responsible for high residues, the choice of the diet, the food choices, that would have a tendency to overstate the potential exposures.

DR. PORTIER: Okay. I guess I understand that point now. And by overstate, you mean overstate to some true distribution that we really don't know.

MR. MILLER: Yes, yes. And that's just at the higher percentiles. It would be kind of a regression to the means. As you add more variety to the diets -- instead of repeating the two diets over

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and over again, if you're high, you would tend to move lower.

DR. PORTIER: And in the food consumption survey, were all diets two days?

MR. MILLER: All the diets -- okay. There were -- they asked everybody for two days and the data that we use in DEEM is only those individuals that reported the full two-days worth of consumption.

DR. PORTIER: So the individual-day diets are derived from the two-day diets absolutely guaranteed.

MR. MILLER: Yes.

DR. PORTIER: Thanks.

DR. KENDALL: Any further points of clarification? Mr. Miller, I thank you for an excellent presentation. We'll break at this point for 15 minutes. We will reconvene for the public comments. And then we will move into the panel discussion. Thank you.

[Break.]

DR. KENDALL: If everyone with take their seats, we'll reconvene. Okay, this are reconvene. We're in the public comment period now. We have had two individuals registered to speak. The first I would like invite to the table Ms. Ingrid Kelly of Bayer Corporation. If you would approach the public commentor position

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over there. The microphone is available. Please state your name and affiliation for the record.

DR. KELLEY: I'm Ingrid Kelley, Bayer Corporation.

I'm here today on behalf of the Implementation Working Group to talk a little bit about their comments on the OP cumulative risk assessment, especially the food exposure part of it.

First of all, IWG commends the Agency for doing such a wonderful job in their move forward toward producing a cumulative risk assessment, which is, as you all know, a tremendous job. The IWG recognizes the difficulties involved and we want to be sure to acknowledge that we believe that the Agency is on the right track. There are many, many improvements that can be made that we can see, and we would like to advance some of them here.

We feel that, as I said, we are on the right track. But the OP-CRA process and methodology is precedent-setting technology and methodology all of the other chemicals will be evaluated with a similar technology. That's why we feel, as Marsha Mulkey put it, it we need to put in the best and sound science. Science must be the basis for this risk assessment.

Transparency and understanding are equally important. Because if we don't have that, we don't really understand the science.

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Stakeholder input is equally important because each of us have our own little niche and we must be sure to listen to all the opinions and stakeholders, including the growers who have a particular interest in this risk assessment.

So we hope and, therefore, that the Agency will continue to improve this assessment; and, finally, will give us another opportunity to comment. In other words, we are hoping the Agency will produce an interim cumulative risk assessment where we will have the opportunity to see what the improvements might have done and how further we can improve this assessment.

I have to put my glasses on. IWG believes that the accuracy and realistic assumptions for the dietary data inputs are extremely important in the cumulative risk assessment, as well as single risk assessments. The assessment is, if it is peppered with overly conservative assumptions, often is taken as protective would then would mask the real risk drivers. Therefore, we have to be sure and not be overly conservative in our assessments then we want to find real risk drivers.

I have, myself, found this to be the case with individual assessments. I have some proof of this that conservatism can, in fact, lead you to the wrong direction.

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And with this in mind, we hope that the Agency, as they have indicated, will further refine the risk assessment. We hope that they will consider the following considerations. Perhaps they might reevaluate the blended and nonblended issues.

Part of the reason for that is because the new DEEM(FCID) does include new recipes, new food groups, that have never been there before. They should be evaluated whether or not an item is blended or nonblended. This makes a big difference in the risk assessment.

Processing information is plentiful. The Agency has at its disposal the processing information from industry; it has, also, at least 40 years literature around the world that has been produced by scientists in universities that show that OPs, especially, degrade when they are processed in homes by cooking and baking and other processing.

We are applauding the Agency for using registered and supported users only in the risk assessment. These are, after all, the only thing that the Agency or industry can do anything about. All of rest of it that might be illegal use should fall into a separate category.

We believe that the Agency should adjust the PDP data to reflect only current use patterns. In the lease 10 years, many companies, including my own, have come up with different and

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competitive chemicals to OPs. These have already replaced many OPs. And the 1994-1995 PDP data does not reflect this. I, again, have from my own company several instances where this is the case. I will forward those to the Agency, and they may share them with you as they wish.

Also, there is the OP market basket survey which was conducted on I believe 10 or 13 -- I'm not entirely sure -- commodities on single servings. This data is in the hands of the Agency. They have evaluated it, and we believe that it could be used appropriately.

We believe that the incremental changes taken collectively will improve the overall credibility of the OP-CRA. We also believe that in refining the assessment, the Agency will have a better tool for more reliable decision-making.

The stakeholders need to have opportunity and access to the EPA's CRA tools and data. As I have mentioned, the Agency has used the new DEEM-Calendex. None of our colleagues in our industry have access to this data base or this model. We have not had a chance to evaluate it. The versions that are out now have not been peer reviewed, even though older versions have been.

The new translations of recipes incorporate new food forms that include baby food. We are not familiar with those food forms. We

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have not really had a chance to get an input on that.

Also, these new translations -- and I don't understand how -- and this is where, perhaps, transparency gets lots. The new translations in some way incorporate into the new recipes processing factors, I was informed; and this is something where we need some clarification. Because whatever processing factors we might give the agency, they may not able to use but we won't know why. So we need to have some review state to find out what went on there.

Also, new PDP data have been used. We congratulate the Agency for working with USDA so closely to obtain this newest data. We are very glad for that. But the registrants and the stakeholders have not had a chance to see the data as yet. It just came out, I believe, last week publicly.

We, also, believe that it is useful, and the Agency did indicate, which we're glad for, that they will do analyses using the CARES and other software. We believe that is essential. Sometimes the different model will point out different problems in data sets or things that are important that have not shown up in one particular model because they have not been anticipated.

Finally, the IWG supports the rolling time frame average for the dietary CRA and the whole risk assessment. Partially, if the Agency is

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going to use the BMD10 based on a 21-day toxicology value, it kind of would match the hazard, the acetacholinesterase inhibition at steady state with the duration of exposure. We believe that this makes sense.

Also, Jeff Driver will later on, for the nondietary portion, inform you why there is also good reason why this makes sense for nondietary considerations.

UDSA Food Survey Research Group should be consulted on related food consumption issues as you have discussed when David gave his talk. There is, for the food consumption, only one- and two-day period for each individual that information was gathered. And it was not in consecutive days.

However, the UDSA, have older data bases that do is consecutive information. And this could be used to correlate consumption patterns. And in addition to that, ENHANES (ph) might be able to relate some of these food consumption patterns and see what is the best way to handle this particular data.

Our final recommendations from the IWG is that EPA should reissue or issue a revised or interim OP-CRA that has inaccuracies and improvements included in it. Hopefully, by then, there might be a comparison also and an analysis of the outcomes of alternative models, the Calendex and CARES and the Lifeline. I think we can learn from

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all of them.

We have to, also, evaluate the alternatives in methodologies as David has pointed out. I think the Agency is doing a good job in doing that. And I think they're going to go further on that. We appreciate it.

And, finally, we do hope and we do encourage the Agency to allow sufficient time for additional peer review and public comment before finalizing the OP-CRA. It is an important tool for now and for the future. Thank you.

DR. KENDALL: Thank you. Any questions from the Panel for Ms. Kelly. Thank you very much. The next public presenter that's registered is Dr. Judith Schreiber, New York State Office of the Attorney General.

DR. SCHREIBER: Good morning. My name is Judith Schreiber. I'm a research toxicologist in the Office of the Attorney General of New York State and a Senior Public Health Official there.

I have a number of comments, mostly clarifications, of what was discussed this morning. I didn't bring any prepared comments with me today. These are all really just questions of clarification. But my office will be submitted comments, written comments, to the docket.

We certainly thank the EPA and SAP for undertaking such a

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broad and comprehensive and very needed assessment on OPs.

That said, the hotel actually provided me with this apple as prop which was very nice. Just one comment regarding the ginkgo fruits and how many times you might eat them in a row. I would just point out it's much more likely that a family is going to buy a bag of apples and eat those apples over the course of a week, perhaps one time a day.

That's not an unreasonable assumption. I just wanted to point that out. My family eats a lot of apples. And I think children in general eat a lot of apples and apple products.

I was very concerned about the decision by the EPA of not including violative and nonregistered use residues in the exposure assessment. Of course, what goes into that model is very key about what kind of numbers you generate coming out.

I was interested in whether the EPA has conducted or whether the SAP had requested the EPA to conduct a sensitivity analysis of, for example, using those violative residue data and looking at how the assessment would differ. I think that's really very critical.

I don't know. Maybe someone on the SAP can inform me whether that was something that was requested or has EPA ever looked at that? Anybody?

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MS. MULKEY: Why don't we hear all the questions, and we'll try to address them just as we have tried with other public commentors.

DR. KENDALL: Very well. We'll try to summarize a response at the conclusion of your presentation.

DR. SCHREIBER: All right. I'd just like to emphasize that it seems to me would be just like having a high school student grade point average that we decide not to include his flunking grades, his failing scores, because he wasn't supposed to fail and so we're only going to include the passing scores to figure out these averages.

It just doesn't seem to make sense to me to exclude what we know as, we do have a lot of data, that indicate that there are residues on foods for which there is no tolerance for various OPs. Why not include those if in fact they turn up time and time again.

I had asked this question once before at one of the KARAT meetings, and I was told that the data is so robust, that it wouldn't make any difference. Well, if that's true, I'd like to see that analysis. I think it would be very important for both U.S. and imported products for those.

One thing that I'm not sure this is the appropriate time for it. But the MOEs have come up quite a bit through this morning's

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discussion. Has the EPA or the SAP considered what is the appropriate margin of exposure for the cumulative risk assessment? And I understand, at least in part from this morning's discussion, that that is something that EPA is not ready to is decide at this point.

If that's true, I think the risk assessment is missing the punch line, is missing the risk management part. And I think it would be very hard for public commentors to make any final determination on this risk assessment without that component. So I think that really is very necessary and perhaps either the EPA or the SAP can elaborate on what is the margin of exposure that is going to be considered to be sufficient under the FQPA for cumulative risks for OPs.

In following the previous commentor, I, also, do agree that if there is going to be substantial changes or elaborations of these kinds of points in the final risk assessment, that you public be allowed to comment once move before the document is finalized.

And one other point. I believe it was mentioned that the children age one to two are the most highly exposed population. And I was wondering, also, whether for the younger children from zero to one year olds is exposure through breast milk and contaminated formula included in the assessment in the OPs? Perhaps somebody could address that.

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That concludes my informal comments. And as I mentioned, we will be providing written comments to the EPA on this document. Thank you very much.

DR. KENDALL: Thank you. Ms. Mulkey.

MS. MULKEY: This might be as good a time as any to say a little bit more about the violative and also talk about the canceled and phased-out products. And then I'll ask our scientists. We have had this question about breast milk and the water in formula and so forth. So I'll ask them to go ahead and do that, and that will wrap this piece up if that makes sense to you guys.

DR. KENDALL: Yes.

MS. MULKEY: Since it is the same topic that we're in the middle of anyway.

DR. KENDALL: Absolutely.

MS. MULKEY: I explained a little bit of the policy thinking behind the way we have addressed violations in other context. But with regard to this particular data set where you have in the PDP data residue levels that are above the tolerance, I understand that Dr. Miller did give some data this morning about the frequency and the extent of those data in the data set.

And I think that is a situation which we've been very mindful of

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trying to understand the science implications of that policy choice. And I don't want to leave the impression that we are uninterested in that. That is why we developed the information about the extent to which we're seeing it and so forth. So I don't think I have anything more to say about that other than that's what led to our having the information we offered earlier about the extent of that situation.

The other is something that also came up in public comment yesterday and the Dr. Portier asked us to speak to which is the chemical crop combinations. In some cases, it's whole chemicals; in some cases it's chemicals and some uses as to which we have taken regulatory action as part of the individual chemical risk assessment process and/or where the companies have voluntarily changed their registrations materially whether for risk-regarded reasons or otherwise.

And we do have -- we have done that with regard to a number of OPs and their uses. And in most cases, as is typical for a practical way of ending a use, there is some kind of time line. Even when there is a immediate cessation of the sale of the product, there is a period of clearing the channels of commerce. Even after there is a period beyond which there is now allowed use, there is a period for treated foods, for example, to clear the channels of commerce.

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So we are in the glide path for a fair amount of risk reduction. I've looked at the dates, and it would take a while to read all the dates. But sort of the last dates in the list are not, at this point, five more years from now. Most of them end the at the end of '02 or '03. There are some residential uses that go into -- there's one that goes to the end of '05. But even that, of course, is less than four years from now.

Our thinking on this was simply that the risk management choices had been made and that they were on a path of either such expedition as that you couldn't practically make a lot of difference in that or reasonable expedition; and that since risk assessments are conducted among other reasons for the purpose of risk management, that including these in the risk assessment would not materially improve our risk management decision-making. So that's the thinking behind that.

Almost all of the direct food uses have end sale dates or end use dates by the end of this year, especially those on fruits and vegetable. A few go into '03. That gives you a general answer. That information is all available on our web site, but I won't read through each one. If there is interest in a particular one, of course, we could speak to it.

And now maybe Dr. Smith can address the formula and breast milk issues.

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DR. SMITH: With respect to children less than a year old, or for that matter any of them, the potential for contamination of formula is covered to the extent that the survey would adequately reflect what they ate.

What is not in the survey is beast milk, the mother's breast milk. It is our best judgment that that is not a significant oversight on our part. The evidence that we see indicates that there's not much potential of OPs in mammalian milk. We are including cow's milk, of course. And there are no OP residues accumulating in those.

So, basically, that's all I would say on that. It's not included, but it's our opinion that that is not a major oversight.

DR. KENDALL: Any points the Panel wishes to make or ask EPA? Dr. Bull.

DR. BULL: I have a little bit of concern, and I'm going to ask this question kind of publicly. The issues related to the cumulative risk assessment and there's issues that go to OP's regulatory mandate. I'm trying to figure out, if we're really, truly interested in cumulative risk assessment, where you would have to bring in some of these other less frequent contributors to OPP exposure but recognize at the same time if you do bring those in you have to realize that you can't address many of those extreme exposure through your regulatory mandate. It

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probably goes to other places within the Agency or perhaps, or probably in a lot of cases, to other agencies.

So I'm trying to figure out when we're talking about a cumulative risk assessment, are we really talking about a cumulative risk assessment or are we just talking about a cumulative risk assessment that deals with what's in OPP purview?

MS. MULKEY: We are not limited to what is within our purview. I didn't mean to leave that impression. We do not, in the OP risk assessment, other than some drinking-water-related considerations, most of the exposure sources do happen to be within our program. But I didn't mean to leave the impression that that was an inherent element of our approach.

DR. KENDALL: Any other points from the Panel? Are there any other persons who would like approach the Panel for public comment? With none, we will close the public comment period.

I would like now to have Dr. Smith and Miller to go ahead and present the questions to the SAP, and we'll move forward.

DR. SMITH: Question one for food. In the preliminary OP cumulative risk assessment OPP used all available PDP monitoring data generated since 1994 as the basis for the residue distributions of pesticides in treated foods. As a result, some foods multiple years of

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data (as many as five), while others have only a single year of data. All years of data were included to provide the most robust data set possible. These data were extended to cover foods and processed forms of foods for which data are not directly available. Additionally, some other foods were included in the analysis based on other less robust data from FDA.

OPP is conducting a sensitivity analysis in which the residue contributions from specific foods, either one at a time or in combination with other foods, are removed from the analysis. This analysis is being conducted as part of the effort to determine the contributions of specific commodities and chemicals to the upper tail of the exposure distribution. And some of the preliminary results are shown in Table 1 of the addendum which was supplied to the Panel.

Partly as a result of this exercise, OPP has observed -- can I just toss in, too -- that, also, it was shown on the slides in my presentation in a slightly different forms for the sake of other people here.

Partly as a result of this exercise, OPP has observed that the more variables, that is, commodities, chemicals, years of data, that are included in the exposure distribution, the more difficult it becomes to effect the tail of the distribution by removing commodity pesticide combinations from the calculations. While removal most exposure

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contributors results in a demonstrated change in the lower portion of the distribution, the exposures at the upper end of the tail, for example, the 99.9th percentile, are relatively unaffected by removal of a single commodity even if it is identified by DEEM as a frequent contributor to the high end of the exposure distribution.

And so we would like the Panel to please discuss the significance of this observation and its potential impact on the interpretation of the output distributions and the results from highly complex distributional analyses such as the Preliminary OP Cumulative Risk Assessment.

DR. KENDALL: Okay. At this point, Dr. Heeringa, would you lead off please?

DR. HEERINGA: I'll take a first crack at this one and my colleagues can join. First of all, I want to say that simulation tests of the types reported in addendum Table 1 and also shown in summary form in the presentation this morning, they're very important to confirm that the model is performing as we expect. And I think that as we get down to the development of these models and comparison, that these types of simulations play a very, very important role in the work that we're doing.

The simulation tests that produce illogical or unstable results or

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seemingly illogical results. I believe that DEEM-Calendex should provide the ability to tag and replay the inputs for these simulations. So, in fact, you do have data, as I understanding Calendex, to go back and analyze the contributors to these upper percentiles.

So in some ways, I think there's a general problem here of distributional theory and a more specific problem of what happened in your particular simulation; and, hopefully, we can make those two consistent with one another.

Just a little bit on the distributional piece here. I don't want to bore individuals. But in a sense when we create these composite residues in a daily diet, we're compounding multiple distributions. And this yields a very complex composite distribution for daily residues intake. And this is a function of a number of factors. I'll just list those here because they may be explanatory in what's happening to you in this particular simulation.

We have to factor in the child's weight in kilograms, and this could be highly variable for children ages one through two because you're actually sampling people, children from the infants from the CSFII, and taking their weight in kilograms. So that divisor itself could have a factor of twofold.

And I'm not sure, given how diets are reported for these

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children, I mean you put an apple on a high chair tray and about half of it goes to the wall and half of it goes someplace else and a quarter of it may go down the stomach. So those issues I think are there. I don't think that's going to be the answer, though.

The diet for the day, obviously, is very important in determining these distributions of total residue intakes. First of all, does the food appear in the diet? And there are any number of foods that could be considered. It's a narrower set for one to two year olds.

Secondly, if the food appears, is there a positive residue amount assigned to that food in the stochastic draw. If I recall correctly from previous reviews of these DEEM models and others, that in many of these foods, there's a high proportion that come from untreated or presumably zero or no detect residues. So even if the food appears, when we that the stochastic draw for the day of the residue amount, we may get a zero value for it. So there's a tremendous amount of variability.

And then for non-zero amounts, it's actually the value of the stochastic draw that does take place. If we think about the distribution, the means of the these distributions, essentially, because we're treating these foods independently, the means are essentially the sum of the individual expected values for all the contributing

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distributions.

In other words, you have a distribution for every food component that could appear in that diet for the day. Obviously, the only ones that come into play in any significant way are the ones that are consumed during the day.

The mean of that composite for the day is going to be the sum of the means for the individual components that ago into it. Likewise, since we assume independence in our draws of these residue amounts for the foods, the variance of that composite distribution is also going to be the sum of the variances of the individual, non-zero food contributions from each source.

Removing food groups A, B, and C, as you've done in the simulation, changes the mean and the variance of this composite distribution. And, in fact, as I looked at this, my first response to your question is I don't see the problem here because it looked to me that the results from your simulation appear to be very consistent with what we expect, not just the removal of groups A, B, and C, A but even the sequential removal of A and then B and then C appear to produce a logical shift in the distribution of this residue distribution.

So the changes that you observed, and you actually acknowledge in terms of the form of the distribution rate, are exactly

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what we would expect. So I didn't see anything unusual there.

The importance of foods groups A, B, and C to the composite distribution is quite obvious. You get a three-and-a-half fold decrease of mean MOE; a fourfold decrease in the 95th percentile. So, clearly, removing these groups is dragging the body of the distribution back toward the origin here.

Now, a 2.5 decrease in the 95th percentile, which I think is significant in many ways. And even a two-fold decrease in the 99.5th. But focusing on this 99 and 99.5th, which is your problem, the distribution of these quantities in this composite distribution is really somewhat unrelated to the distribution of the composite itself.

In other words, we can do a lot of things to the body of the distribution without being able to influence this extreme tail and really a function of the extreme values generated under of -- and not so much the function of the mean and particular variance of the composite distribution.

If you think about it, if I were to analyze the DEEM inputs to the particular simulation, if you think about how foods A, B, and C can contribute to extreme values, there's really two ways. One of them, is A, B, and C can form a stepladder. They are big. They are prevalent in the diet. They may have large residues. So they serve as

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a stepladder.

And then we come along and we get another extreme value on a less commonly consumed food and added to that A, B, C value, it puts us into the extremes. So essentially, A, B, and C are boosting some other not so extreme values from other into the extreme.

The other way you can get it is that A, B, and C could actually be generating the extreme values themselves. And i think the basis of your question, you're sort of assuming, well, I removed A, B, and C, so A, B, and Cs extreme values aren't there. So why aren't the extreme values changing in the distribution.

Well, the only thing that you really removed is you removed the ability for A, B, and C to boost something else up or for A, B, and C to generate its own. Now the probability that A, B, and C in a mixture of diets is going to generate those extreme values all on their own is relatively small because there are only three groups. And if you think about it, even if the entire residue distribution were based on A to get to the 99.5th percentile, you essentially have to something with odds of almost 99.9th percentile, you have to have something that has odds of one in a thousand of being drawn from a distribution.

So the probability of getting an extreme event from A, B, and Cs residue distributions extremely small; and even in combination, it's

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pretty small. So what happens here is that you've got 69 other food groups which might occur someplace in some child's diet during your simulation run and each of those 69 food groups also has extremes, and so as I sum across all of these children in the particular profile for a given day, someone is going to eat these odd foods.

And although they aren't as prevalent in the diets as A, B, and C, the sheer numbers of them that could be there and the fact that they could each contribute with some low probability an extreme value, essentially the strength in numbers means that you're still generating extreme values from all of these low prevalence food groups; and so these maximums are not being affected as much as you might think.

That's my statistical explanation. In other words, you have several different routes. And that what's happening is because you are still generating potentially with low probabilities but add small probabilities across large numbers of food groups, you generate higher probabilities for generating extreme values from these sort of nonprevelant foods.

I suspect that that's what's happening. This is a guess. And you'll be able to affirm that with DEEM. We can't rule out what I think are more pathological explanations in a statistical sense. That there may be some -- and this is what I think you're hunting for --

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extreme residue commodity potency factor relationships in DEEM that don't make sense and are producing these outliers. Clearly, you want to hunt those down and try to rectify the data there to make sure that it is consistent with empirical data that you have on these distributions.

Also, another factor that occurred to me is that potentially, even though -- and this is really a stretch but I think it's worth looking at in your analysis. If you remove food groups A, B, and C, we're only looking in the simulation at a short one year interval. But most of us know that children's diets change considerably over that one year interval.

So it could well be that what you're doing when you remove A, B, and C is that you're actually removing foods that are eaten later in the interval, like whole fruits and vegetables, as opposed to sort of mushed fruits and vegetables or other types of cereals at the beginning. There may be some time-related dependency between food groups A, B, and C in the year one to year two.

And why would that be important? It would be important because the it affects the weights of the these children. The weights of these children could be actually the kilogram divisor in the exposure could be changed.

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So those are, again, the last is a bit of a stretch. But I think if I had to analyze how to decompose the problem, theoretically, I think what's happening is that, as you draw out A, B, and C, you are in fact contracting this distribution significantly, pulling the body of the distribution back toward the origin, but you're not able to impact the very extremes because you still have this underlying, very thin extreme value distribution for all these other components.

DR. KENDALL: Thank you, Dr. Heeringa. As you can hear, there is music next door. We did not know this. We were only informed this morning that apparently there is to be a concert in ten minutes. So I'm going to -- which started even earlier. And, quite frankly, apologize for this happening. We were just notified a couple of hours ago. So we're going to take our lunch break beginning at approximately 11:30.

I ask everyone to bear with us for the next ten minutes or so. I hope that will work. And they'll be concluded by 1230, and we'll reconvene. So let's grin and bear it. And, Dr. Reed, can you follow Dr. Heeringa, please.

DR. REED: Yes. I just want to commend the Agency for the enormous task and a lot of work put into it. It's impressive.

What Steve was saying, I totally agree. It's a very complex

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analysis. I'm sure if there is an easy way to go back and see what happened to it or in terms of what is the major contributing factor except to do what you're doing. And that's something we do very often in our program, too.

I think even down to look at the CC to identify the high contributing commodities takes some looking around. You've looked at three of them. I want to follow what Steve was saying in that, actually, after you get rid of three of them or even one at a time, look at the CC again and see if you're right on track.

Also, when you look at the CC, as Steve pointed out, see that the H vector would come in to play within that 3-to-5, 1-to-2 bracket. The eating pattern, the distribution of contribution from different commodities, that sort of thing. A lot of times we have to go back and forth and find that high contributing commodities that way.

I'm sure there are many more sets of sensitivity analysis that could be done. Something was mentioned -- and I thought it was worth sort of mentioning again -- was the curiosity of whether chemicals will make a difference. You're looking at commodity; contribution, look at the chemical contribution.

Other things are -- I mean, in that case, you sort of trap the high contributing chemical and then do as you did, removing one at a time

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and to see what happened.

In terms of things to consider, I think there's so many things to consider. But the Agency is under the time constraint to complete something at this time. What I was thinking was as the most important thing is this: From the presentation and the document, it reflects a lot of experience from the Agency in doing what you do and giving the assumption that we assume, for example, dietary exposure does not fluctuate significantly over the year, that type of thing, or even though it's calendar-based in terms of the whole assessment but dietary is not. You know, these assumptions, PDP data, single unit analysis data, will not impact a whole lot as compared to using composite.

I think the Agency has lots of experience with this. It would be good to present it in a way. I think people would like maybe to see some support instead of just a single sentence statement. I think that would help.

DR. KENDALL: Thank you, Dr. Reed. Dr. Zeise, would you like to follow, please.

DR. ZEISE: I agree with the comments earlier, and I think the explanation provided for the finding is very reasonable. And, obviously, we need to explore to see really what is happening in the tail and whether or not there is a problem with the model or whether

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or not that explanation that was given holds up.

In addition to exploring that, I think it's very important to focus on the tails. It represents many individuals in the population. And it's important, I think, to explore other factors that might change the tail significantly. It's not clear the extent to which violated exposure would change that. The extent to which consideration of degradates might change the assessment.

And then the issue -- and I didn't see it explored in the document -- of binge eating and seasonality of fruits coming in in the summer months, and so forth, if CSFII appropriately captured some of the cases where you might expect larger exposure. I think that would be useful to explore.

And the nondetect, I'm assuming that that has been adequately addressed. There was a discussion in the document. It wasn't clear to me the extent to which, if you assumed at the high end of the distribution, if you threw in some nondetects as half the detection level, whether or not it would significantly change the evaluation at the tail.

And the reason why it is so important to look at the tail is that the MOE is rather small there. In fact, if there are even larger exposures than that, that really indicates that there is a problem. So

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really understanding that region is important. And I'll leave it at that.

DR. KENDALL: Thank you very much. Any comments from the Panel in addition to the comments already made on this particular question?

DR. MCCONNELL: Yes. I was struck by the fact that you depend a great deal on the UDSA for a lot of your input in your calculations. I was wondering, and it was suggested by one of the people from the audience, that you have relationships with UDSA. I don't know what they are. Do you have periodic meetings with them to update yourself with what they're doing? Their science must be evolving as is your science, and do you have a way to keep up with that?

DR. SMITH: Yes, we do. In one area, of course, one of the major areas we're discussing today, are the residue data that we're using. That's the PDP program. And we work very closely with them. We advise them as to what our interests are and then things we'd like to see done from year to year. So it's a very close relationship. Also, there has been considerable interaction in the area of the CSFII. I don't know that I can say much more about that; other that I don't know if, David, is there anything you'd like to add to that?

MR. MILLER: Yeah, we do communicate with USDA on the

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CSFII and the food research group that is responsible for it.

DR. DURKIN: Thank you.

DR. KENDALL: Any further comments? Dr. Durkin.

DR. DURKIN: Very briefly, we will be discussing residential exposure at a later time. But this does relate to food and, again, it is the issue of homegrown vegetation. I did not see that in the residential exposure. And we may clarify it then. But it's clearly not in your food exposure. And I'm rather concerned that that could be the 800-pound gorilla.

The concern is with people in a rural area, especially rural south, who may live in a region of agricultural usage that could be very high. And I am a little concerned about what I've heard up to this point that we could have, again, a bimodal distribution of risk that we're simply not addressing.

DR. KENDALL: Okay. Any further comments? Mr. Lewis, our DFO, has informed me that they're running late over there. Therefore, we may have time to go to the next question. I'd like to take an hour break. So could we procedure into the next question as recommended by the best intelligence information I've got. And it's the military next door.

MR. MILLER: The Calendex model can be used in a number of

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modes to develop a profile of exposure estimates. In the current assessment, OPP conducted a series of single-day assessments arrayed chronologically to develop a response surface of exposures. A constant percentile of exposure was selected to represent the potential exposure to a given percentile of the population. For example, the 99th percentile for each day would be arrayed for 365 days to reflect the population estimate across the calendar year.

Calendex can also be used in a multi-day sequential series analysis, asl referred to as a "rolling time frame mode." A rolling time frame provides an estimate of the average of daily exposures for an individual calculated over multiple (7, 14, 21, or 28) days for each multiple day period over the course of a year, (e.g., days 1-7, then days 2-8, then days 3-8, etc.).

In this model, an individual's food exposure is tracked across the calendar year by randomly selecting day one or day tow of that individual's reported consumption from the CSFII and combining each commodity which comprises that consumption with randomly selected residue values for each day of the calendar year. These rolling averages for each individual are assembled to develop a distribution of rolling average exposures.

During previous SAP meetings, the Panel has expressed concern

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about the use of CSFII records to represent longitudinal consumption patterns for individuals. Concern arose as a result of the design of the CSFII study, in which two nonconsecutive days of data (separated by 3 to 10 days) were collected for each individual.

Please comment on the use of CSFII data to support each of these two modes of Calendex as they pertain to the cumulative risk assessment of pesticides in foods.

DR. KENDALL: Dr. MacDonald, can you lead off, please.

DR. MACDONALD: Well, I guess to begin with, I'm under the impression that CSFII is about all we have that's relevant. So we don't have a lot of choice here. I guess there would scope for doing some kind of sensitivity analysis to see what the impact would be of having, say, you could make up some data on longer term records and just see what impact it would have on the estimates.

As far as the different modes of running the Calendex model goes, I think Dr. Portier's remarks earlier were very relevant. And I hope they'll get into the response for this question.

But, basically, I think the effect of using the rolling average is it will mitigate effects of sampling nonconsecutive days to some extent; but, mostly, it will just reduce the extremes in the simulation.

Is this relevant? I don't really know. I think we have to know

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more about the metabolism of the OPs in humans at different life stages. I think the limitation here is the margin of exposure computed as the point of departure divided by exposure, so we have to make sure that the exposure measure and the point of departure are both relevant.

For example, what we saw yesterday in the adult rats, the dose response curve, we saw there was a shoulder and in many cases in that suggest in some situations a moderate short-term exposure is totally innocuous. But that's for adult rats. As the NRDC has pointed out, it might be totally different in humans; it might be totally different in human infants and fetuses. So it's really hard to say what the effect of changing your exposure measure is going to be if we don't really know what type of exposure is most relevant in the population we're considering.

I think to conclude, the rolling average is probably a good idea if the main concern is chronic low to moderate levels of exposure. But if the real concern is acute levels, than reducing the extremes is perhaps going to be missing some of the more dangerous episodes.

DR. KENDALL: Thank you, Dr. MacDonald. Dr. Freeman.

DR. FREEMAN: The two methods used with Calendex, you can almost think of them as bounding examples. The use of a single-day

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constant percentile of exposure for every day provides an exceedingly conservative estimate of exposure. It is clearly not representative of individual exposures over time. And I find it difficult to understand what it actually means in terms of population exposures. And, also, I'm not quite sure how you're going to use that.

In contrast, the second method which uses the rolling averages, is not only less conservative, but for very young children when you only have two samples of food, may actually reflect what young children over a limited time period, as Dr. Heeringa was suggesting, is fairly realistic. Young children tend to have very narrow food habits. So that while you only have two samples to draw from, they probably aren't that different from each other because the children aren't eating a wide range of foods. So that may actually be useful in representing sort of the average young child with fairly limited ranges of foods in their diets.

On the other hand, that same rolling average, because you only have two food samples to work with, may underestimate or suppress the high-end exposures from diets in the same children. And I'm not sure what you can do about that.

A concern of mine is in the application of all this stuff. In the examples that you give, you suggest that diet is treated as uniform

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throughout the country. And unless you have already done so, I think this is a hypothesis that needs to be tested, particularly in areas such as Region 3, the Texas Fruitful Rim, which are predominately Hispanic. I wonder whether the diet for based on the CSFII for the total United States is really appropriate. And one thing that you could do is to compare the diets associated with that region from one such as the Easter Upperlands or the Northern Great Plains where the demographics are very different.

Another alternative -- that also assumes that the CSFII has not under represented minorities in their sampling, which may also be the case. And if that's the case, you may have to go back and look at census data for those areas and do some sort of proportional weighting based on census characteristics.

So that adds more complexity to your model.

DR. KENDALL: Thank you very much. Dr. Reed.

DR. REED: I want to follow up on what Natalie was saying. I think, basically, if we take a sort of a common sense way of thinking, we would think that the diet has seasonality and has regional differences. Again, I think it's partly I think because of the Agency's experience in this area, knowing the impact of parting them out into region and season, and maybe it doesn't come out to be a whole lot in

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terms of impact. And it's time consuming and it's not readily available in terms of tools right now with DEEM and Calendex. I'm not sure about that part.

But what I'm trying to say is that I think it would be good to give some support to that assumption or, as Natalie was saying, run some data sets. Remember, we've in the past looked into things that are important to children. For example, apples, they do have seasonality and also regional differences. It could be up to about 20-percent differences. So it's something that probably is worth looking into.

In terms of using that data for modical day sequential analysis, you have already presented the pros and cons. But I remember -- I just have one simple comment. I remember in September 2000, when we look at Calendex, there was the recommendation to look into this method. And I'm still very interested in following up on that.

That is instead -- I think maybe the overriding desirable idea right now for you is to trace an individual. And, therefore, you think that perhaps you need to stick with these two data points. But I think there's somewhere in the document that emphasizes that you're not actually tracing individual exposure pattern. So in that case, it is still possible, as what we recommended before, to base on demographic

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characteristics, to pull the data together so that you would have a larger sampling size of population to draw from instead of just two points.

And I don't know how difficult that is. But I think that's something that's still worth looking into. I don't know if I'm clear on that point.

DR. KENDALL: Is that clear?

MR. MILLER: Yeah. I think what you're saying is when you say "pool the data," the way it's done now is each individual's diet is connected to that individual.

DR. REED: Right.

MR. MILLER: Each of those two days worth of diet.

DR. REED: Right.

MR. MILLER. What you're saying is maybe draw from, essentially a pool that has demographic similarity to that individual.

DR. REED: Right. Three to five pool with different seasons, four seasons.

MR. MILLER: Okay.

DR. KENDALL: Very well. Dr. Heeringa, anything to add?

DR. HEERINGA: Just briefly to Dr. Reed's comments. I think the idea -- right now, the way that you're using the CSFII data, is

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essentially you're locking a child's body weight and gender and age into a particular diet or maybe at most three diets if in the CSFII and two diets for the infant and child observations in the '98 CSF.

And what we're doing there -- I don't think of us believe that this child is going to eat macaroni and cheese 365 days a year. But in your sample someplace else, there's a child eating green beans and a hamburger or there's a child eating oatmeal. So what you do is even though you're focused on an individual child, what you're assuming is exchangability among children of the same age and same gender. And the thing you're doing is you're locking a particular body weight to a particular diet.

I think that's a constraint you don't need to use. Dr. Reed's suggestion is essentially sample the child. You need to get a representative samples of children with their body weights and their genders and their ages. But then, among children in your national sample, which you're assuming to be exchangeable anyway, sample their diets to link to those on a daily basis.

So I think that breaks one sort of false correlation in your current input structure that is unnecessary and doesn't contradict in any way.

Now, on the other response to this question, you are

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constrained by the fact that you have two or at most three days of diet for any individual. By putting things in this pool, you've sort of unconstrained people's diets a little bit. But you haven't actually built in realistic patterns. You still have to assume, if you go Dr. Reed's route, that you have random eating and that there are no consistent correlations over time in consumption patterns. Which we know for a bag of oranges or a bag of apples or a bunch of bananas or even things like green beans, you might be eating them two or three times during the week in which they're bought. I think that's another level of sophistication that you might think about bring in at least in terms of simulation.

And this is what Dr. Portier brought out, yesterday or earlier this morning, that you might look at some testing in the model where you do two things. And that is you have a lag factor in the consumption in the dietary intake for some of these commodities that we know are going to be in the household for a protracted period of time. And I don't think macaroni and cheese is going to be one of them. But apples and various fruits that are bought in larger quantities than vegetables, and see what that does.

And if you do that, then I think you, in addition to sort of introducing a lag in people's dietary consumption during the period of

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a three- or four-day average, also preserve the draws on the residue amounts because it's only realistic if you do that that these commodities that came from the same source would be expected to have nearly similarly residues amounts. We know there will be variability, but much less variability than a completely random draw.

So I think with the data that you have available and some assumptions -- and, again, I would only put this in simulation context right now, to look at what happens when you introduce not only lagged consumption from one day or time-correlated consumption of some of these commodities for short periods. And I would say three to four days would be fine on most of these or a week. And then, also, to preserve the residue amounts associated with those.

Now, that's complex, I know. But I think that would add a little bit more reality. Now if you do that, then I think this whole issue of whether you use these rolling averages or individual days, the rolling averages make sense as a measure of sort of short-term chronic or maybe steady state impacts of the residue consumptions; but I think they only make sense if you do these other steps. And that is allow foods to have time correlation over short periods of time and that the residue amounts on those fruits are also preserved as draws from your residue distribution. Then I think these rolling averages do approach a

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better reflection of what the sort of chronic exposure over a 28-day period is more likely to be.

I think if you're doing fixed diets for kids, random draws of residues everyday for each child. I'm not sure that you're getting from these rolling averages what you would really like. It's not a good reflection, I think, of chronic exposure. And the one-day stuff gives you the acute exposure in a better sense, I think.

DR. KENDALL: Any further comments from the Panel? Dr. Portier.

DR. PORTIER: I agree with all the comments that have come forward, starting with the one that said you guys did a great job on this. But presuming something we can look at and comment on is really pushing the edge of what's been done previously.

I was sitting here trying to think about my question earlier concerning the conservativeness of this particular method. Especially, the two-day flipping back and forth. And your observation that you think this is going to be somewhat conservative. And we had several questions about that from lots of the public yesterday, both the grower's side and the environmental side asked a question to what degree can we assume this is conservative.

So I'm sitting here trying to ask myself how do we assess that

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without doing a full independent resampling scheme where everything is independent. As Ruby pointed out, you sort of have two extremes that you could do. The first extreme is the individual day data, run it for 21 days. But that's exactly the same as the distribution for the individual day. Taking the average of that over the 21 days is going to give you exactly the same distribution. So you've got that one. That's one extreme.

The other extreme is everything is random. Every day a new draw, a new diet. Everything is completely random. That's the other extreme in the sense that we know there are probably some correlations in there.

But we know something about the other extreme. If your distributions are normal, which they're not. Them I'm going to choose the simplest case here. If your distributions were normal, you know that by averaging over 21 days, independent normal random variables drawn on a day-by-day basis, the 99.9 percentile, in fact, any percentile except the 50th percentile, is going to change by a factor of 4.6; the square root of 221.

If it's log normal, you can actually calculate the same things. The 99.9th percentile. But it's not a constant. The 99.9th percentile change is about a factor of 12. The 95th percentile change is about a

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factor of 6.

But the point there is you can look at your two-day consecutive draws, compare it to your extreme single-day case, and ask yourself, have I dropped the 99 percentile and the variances by some number that appears to be in this range or less. So is it on the conservative side or on the independent side?

Judging from your quick graphs there, David, it looks like it's on the independent side not on the conservative side in terms of a very consistent redraw. But I'm not sure because I don't see the full distribution for that.

But I think you could address it that way. You might see some mean shifts as well which could tell you something about theoretically how conservative that approach might or might not be.

But I agree with everyone that you need to try some other things, potentially theoretical or to resampling technique.

DR. KENDALL: Thank you. Any further comments from the Panel? Dr. Rhomberg.

DR. RHOMBERG: Just briefly. And I hope this is the right place to raise it. On the single-day analysis, you know, in the end what that is able to show is seasonality. Otherwise it's just doing the same thing over and over and over again and they're just replicates.

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The only thing that's really different between one day in January and another day in May is seasonal differences.

And I guess I was struck by the fact that there didn't seem to be many, that if you looked at those graphs, including the one that's right on the front of the report there. Yes, there's some variation up and down; but there's no big sway, no big seasonal sway of going up and down.

And my question is why is that? I would really have expected at least some such effect. And the only reason that there wouldn't be any is if seasonal effects are at all important, that they are somehow excluded here. Would that mean that seasonal effects are driven maybe more by seasonal effects on food choices than they are by seasonal effects on residues or what? I guess I'd just like some discussion of why there isn't more seasonal effect there when one would expect some.

MR. MILLER: I'll say we're not -- when we use the PDP data, we're not taking into account -- and it's just clarify it. We're not considering the seasonal effects of when the food is sampled. So there is no seasonal component.

When I said we start with January 1, it's not necessarily a diet that a person reported eating on January 1. So for example, when the

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CSFII went out, they didn't -- the January 1 diet is not specifically a January is 1 diet. It was essentially the seasonality component is added to the assessment by means of the drinking water which is seasonal. We take into account the season there and the residential uses.

DR. KENDALL: Any further comments? Yes, Dr. Zeise.

DR. ZEISE: I just want to reinforce the idea that when you consider the averaging period, you carefully look at the pharmacokinetics in humans and determine what makes sense to do. It might make sense to actually build in a pharmacokinetic parameter to address the issue of persistence across time.

DR. KENDALL: Very well. We understand now the program next door may go as late as 1, so I'd like to try to move into 2B. We are tracking their program. I think somebody is speaking at this time, to be followed by a concert. The concert is going to blow us out of this room. So let us push forward.

Today's one of those challenges. We will take a break for one hour. And I will see you for 1 o'clock. Thank you very much.

[Lunch recess.]

DR. KENDALL: We'll go ahead and get started. This will reconvening the SAP. The point at which we are currently is

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addressing Question 2B. Please read that question, Mr. Miller; and we'll go on from there.

MR. MILLER: The random PDP residue values assumes that the residues in foods consumed across a series of days are independent of each other. In other words, foods consumed are from unrelated sources and there is no carryover from one day to another. This assumption may be inappropriate given that many consumers obtain food in bulk (i.e., multi-day) quantities that may have similar treatment history and would typically consume this food over a short multi-day period (e.g., leftovers). In such a case the residues contained in the foods would violate the assumption of independence.

Please comment on the use of PDP data to support each of these two modes of Calendex as they pertain to the cumulative risk assessment of pesticides in foods. What issues are likely to accrue from the assumption of independence in residue data?

DR. KENDALL: Dr. Reed, can you lead off, please.

DR. REED: In terms of single-day exposure mode, I don't have a lot of problem with it. As long as it was clearly stated, you know, what the announce is about. I think the only issue that we're been throwing about is the composite nature of the data.

We knew that from single-eating-size analysis that you would

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have essentially higher, possibility to a higher, residue in a single-eating-size sample. But that's for a single chemical. And I don't have any feel about what is it going to look like for index equivalence-type of residue data base.

So I would really appreciate that, again, I think that assumption was that there's not a substantial difference in it. And I think it would be good to present something like that in the documents so a reader could understand and follow.

In terms of multiple day rolling average, I think PDP data is suitable for that, especially when the composite is not a problem. I'm not sure -- or I am sure that this does not really address the carryover, leftover, or same batch exposure scenario. I would go about and find the heightened contributing commodities and see if linking days would make a difference. I would not offhand go in and link everything from day-to-day yet.

The reason I say that is because I think linking days would be really specific to certain foods. You know in the past we talk about Thanksgiving meal and that kind of thing, also the buying-eating pattern; people buy a bag of apples and eat for how many days; shopping pattern and all of that.

That being so, I think what I'm thinking is it's important to find

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places where it might make a substantial difference and not just shotgun and go in and do all of that. And I'm thinking of that mostly in terms of resources. And I'm thinking of now of approach and risk assessment is about. You decide when and why you want to go in and refine something so that you're more focused and you're not spending a lot of time and effort.

That goes back to the comment that I made earlier that it is important to make a clear presentation in terms of what are the assumptions and why you think so; and so when it comes to the steps whether we link days or not, it would be much clearer as a choice or not.

DR. KENDALL: Thank you. Dr. Heeringa.

DR. HEERINGA: I very much agree with what Ruby has just presented. Just a few added comments.

In response to the earlier question, I mentioned exploring the issue sort of continued consumption of a single food item over several consecutive days. Again as Ruby has just pointed out, it requires modeling, buying, and retention patterns within the household. My sense is that even has something sort of three to five days retention of a fruit or vegetable batch would be an appropriate bound to set on testing that.

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Clearly there if you do that, then I think you want to preserve the sampled residue amount over those three to five days, also, to preserve that correlation which you would naturally assume in the purchased food product.

With regard to the independence on a single-day analysis, I think the independence assumptions, since you're doing it on a daily basis, it really doesn't come into play. It's more when you look at sort of chronic or accumulating over multiple day analyses that I think you need to take into account the correlation, not only in foods eaten, but also the residues on those particular foods over the days.

One additional comment to, I guess, related to the question, that is, the use of OPP residue data base. I believe that most of these are composite amounts. We're not only compositing the servings over the day, but we're also compositing the residues over multiple articles. If anything, I think that would tend to attenuate the extremes that we would observe on a daily analysis.

So if anything, it's probably a little bit anti-conservative to use the composited, samples as opposed to some strategy which I know we've investigated in the past to try to derive a single serving or a single-serving residue amounts for use in these analysis.

DR. KENDALL: Dr. MacDonald. Thank you, Dr. Heeringa.

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DR. MACDONALD: I don't have a lot to add to Dr. Reed and Heeringa. But I will express my sympathy for what I see what must be a very frustrating situation because there are just limitless ways to start making these models more complicated and you'd really like to know ahead of time which of these ways are going to be worthwhile.

I guess all I could suggest here is if you -- I don't think you even have to do a pilot study. If you could make up some the data with the consecutive days or with the correlations built into it and just try some small simulations and see what kinds of differences it makes.

Certainly, that in the other context, the study you did with the A, B, C gave some -- it seemed to be a very simple thing to do, but it gave a very useful results fr what would happen if you change some of the data. And maybe you could devise something like that with the correlations.

DR. KENDALL: Dr. Zeise.

DR. ZEISE: I don't have a lot of add to the comments that already been made. We've talked about this this morning as well.

The one thing I would add is that there are likely to be differences across the different age groups in terms of the extent to into which this comes into play. And particularly for the younger age groups, one would expect a lot more similar behavior from day to day.

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As an upper bound kind of analysis, one might assume that every day they consume the same value or sample between the two days.

Another possibility comes to mind along the lines of -- I like the idea of the correlation analyses that have been proposed. And another possibility would also be to do some scenario plane to kind of test and speculate what could be happening at the extreme by looking at different scenarios for some high consumption of foods, say, during -- I don't know -- watermelon season or when you might expect very large consumption of fruits more so than other part of the year among certain subgroups.

DR. KENDALL: Good point. Any further comments from the Panel on this issue in food exposure? Dr. Portier.

DR. PORTIER: Not specifically on this. Well, let me ask a question on this one first.

Steve was just asking me, and I guess we're both a little confused about the issue. If the PDP data set has a residue that exceeds the limit, you still include that in the analysis? Yes or no, you take those out?

DR. SMITH: We take out residues that exceed tolerances, yes.

DR. PORTIER: Then I think from my perspective, I would recommend you not do that. I think it's going to be there's two

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reasons. One is it's going to happen no matter what the tolerances are set; there will be samples that exceed the tolerance. That's the first.

The discussion we had of where PDP data comes from and the question of what happens when people buy things in the market or from not necessarily the large commercial sources, there may or may not be higher residue levels depending upon when and where, et cetera, where they buy it. And those things are just unknown. My recommendation would be that you include them in your over all analysis. And I don't know how the rest of the Panel feels about that.

The other point I wanted to make, which is more general, is yesterday we had a discussion about point of departure for margin of exposure from the point of view of hazard. And much of our discussion pertains yesterday pertains, also, here especially to some of the public comments which had to deal with the quality of an estimate of the 99.9th percentile.

I think one could argue that choosing a distributional point from which to compare margin of exposure could be driven by the science, find some optimal rule for deciding what seems supportable by the science that you're working with, and the margin of exposure process is adjusted based upon where that percentile is and the quality of the science that went into that exposure percentile.

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I think that would potentially be a better solution than the continued debate about the quality of the 99.9th percentile. And I think I'll add that to my comments to you.

DR. KENDALL: Would EPA like to respond to that? Dr. Roberts.

DR. ROBERTS: Yeah, Chris asked how the rest of the Panel feels about the issue of including the violative residues from the PDP in the assessment. And I guess I would weigh in in favor of including them.

I think that as a follow up to some of our earlier conversation, I think that this probably is an unavoidable consequence even of the lawful use of pesticides despite everyone's best efforts. It's a human exercise, and there's going to be a small percentages of times when those levels are exceeded. And I think if we're going to make the argument that our cumulative risk assessment reflects reality, I think it's probably important to go ahead and include those small percentages in our assessment.

DR. KENDALL: Any further comment or agreement? Dr. Durkin.

DR. DURKIN: Yeah, I would like to simply endorse the idea of putting the residues in. I understand why they're not there in terms of

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not being able to address them perhaps from a regulatory perspective and that does make a great deal of sense.

But we seem to have two tracks here, and we discussed this. Are we dealing with a regulatory tool, or are we dealing with some sort of a public health risk assessment? Do we have a problem here? And if that second part is important, and I believe it is from what I've heard, then I don't see a reason to exclude those residues. In fact, I see every reason to keep them in whether or not they make a great deal of difference. We're trying to reflect reality.

DR. KENDALL: Dr. Bull.

DR. BULL: He said it much better than I, but I agree with that.

DR. KENDALL: Okay. Dr. Rhomberg.

DR. RHOMBERG: I guess I'd like to take an agnostic position on this, but with a little discussion.

It seems to me that the purpose of doing the risk assessment is to serve risk management ends. So the real question is what risk management options that are available and what kinds of analysis would most inform them?

Now, you could imagine violative exposures, that being an argument for including or for excluding violative exposures. And in a way it sort of depends on some things about how inherent they are in

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any kind of use of the agent as Dr. Portier was suggesting. Obviously, to some degree that's true.

But if you put them in, you have to be very sure that you then interpret the analysis accordingly. And if it happens that those violations are driving the upper percentiles, it has to, then, be acceptable to do a risk management solution that sort of takes that into account and takes into account what perceived responsibility there are for different parties to deal with the fact that that kind of things occurs.

So if we put it in, we have to be very clear that the analysis means sort of something different from a risk management point of view. We can't play it this way one time; and then when the Agency is going and making the risk management decisions, playing it the other way and to try to say, Oh, it's incumbent on the Agency to make regulations such that those things don't occur as well.

Whether they are not, is a complicated question that isn't really about exposure analysis anymore. I think that if we put them in, the analysis means something else; and it should be clear that we are expecting a different use and interpretation of it by the EPA in the regulatory arena as a result of that.

DR. KENDALL: Dr. Adgate.

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DR. ADGATE: I mean not to beat the dead horse too hard. I think it would be useful to point out the fact that tolerances are in fact not health-based and that should provide you with some cover. And I think that fact you are all quite aware of often gets lost in these sorts of analyses. At least in theory what we're doing here is health-based.

DR. KENDALL: Dr. Portier.

DR. PORTIER: Following up on what Lorenz said, I guess the only regulatory control that would convince me you should throw out the violators would be one in which you were continually monitoring these products, and if it exceeded the tolerance, you threw away the product. If you didn't throw away the product but in fact mixed it with product with lower bounds, lower levels, then that could, of course, be incorporated into the sampling strategy for the PDP to look at the question of what impact could would that have. But I think the reality is those are the data and I would really encourage you to use them.

DR. KENDALL: Would EPA care to respond to any of the points made, or were they clear enough?

MS. MULKEY: I think we would like to encourage a little more elaboration if there is going to be a discussion of some sort -- and I'm over simplifying this -- trade off between choices about what part of

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the distribution to consider regulating at and what kind of acceptable or target MOEs we might work with. And we are mindful that that is that's a mixed science and policy decision as you seem to be mindful. But if you're going to discuss the idea of the intersection between those two, do so in more that identifying it as an intersection, I guess is what we're trying to say.

DR. KENDALL: Okay. Anybody like to comment on that? Chris, do you want to comment? Lorenz? Go ahead and start, Chris.

DR. PORTIER: You know we've discussed this from the other direction before with the SAP in terms of using the benchmark dose and what happens with 1 percent, 5 percent, et cetera. On the side of exposure, I think it's got to be the same thing. And I don't have any fixed factors for you. I think it's a debate you have to have both publicly and internally as to how you do the margin of exposure and what constitutes a reasonably acceptable margin of exposure.

It's driven by a lot of things. In this case, instead of looking at a directly toxic endpoint, you're looking at potentially a biomarker of a toxic endpoint. And that weighs into your decision about how big or small you want the margin of exposure.

I think the same thing is true on the exposure side of that distance. In terms of, if you only have 10 or 20 or 13 samples from

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which you're making your distributional assumption, you would want a larger margin of exposure against a fixed point. And that pertains -- it pertains to the variance of the estimate of the point.

If I choose a 99.9th percentile, I know the variance is going to be large; and I know, to some degree, that my choice of that percentile is driven a lot by tail behavior of my data set. So the bigger the data set, the less of a margin of exposure I would want if I believe 99.9 percent is really safe.

If I believe 99.9 percent is safe and I'm going to set it at 90 because that's the best thing I can do with the data set that I have, then I'm going to want some sort of factor in my head for this margin of exposure that makes it a bigger margin of exposure. Because I know chances are 10 percent of the population is somewhere above is, but I'm not sure what, how far above that actually goes.

There are no easy answers in that question. But I think we have to be as a Science Advisory Panel, we have to be clear where the science can take you and where it can't. And by deciding on a margin, deciding on a point of departure that's based science per se with reasonable objective rules and recognizing that sometimes the science pushes us closer to the tail of that exposure distribution and sometimes it doesn't, I think that needs to be factored into the margin

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of exposure rather than always choosing a fixed point, 99.9, regardless of the quality of the information and a fixed margin of exposure against that.

DR. KENDALL: Okay. That's pretty clear. Dr. Durkin.

DR. DURKIN: I was going to weigh in with something a lot more simplistic. I think basically philosophically agreeing with what Chris has said here.

We are talking about margins of exposure and talking about these as things that can be basically set as a matter of policy. But I think it's good to keep in mind that for a very, very long time, the EPA and others involved in human health risk assessment have sort of looked at the reciprocal, the hazard index of chemicals, that was in turn based on a ratio of the exposure to the RFD, where the RFD was something that was pounded out as a matter of science to the extent possible.

And I think that this is -- you can still handle it as a margin of exposure if you're comfortable with that; although I think the hazard index approach is much more elegant. That's just my bias.

But I think the point is that we know a great deal about the organophosphates. You have picked yourself an index chemical, and we have, I think all, agreed that this is a reasonable approach and that

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the relative potency method is reasonable. I don't think it is beyond the scope of OPP to look at whatever choices that they would like to make in terms of do we regulate at the, you know, 99.9 or the 99 or whatever, and then to look at both animal and the human data that we have, not simply methamidophos, but on the whole class of chemicals, and come up with what is functionally an RFD or, if you're old an ADI. That would indeed lead you directly to a margin of exposure that is more science-based than policy based. And I think that would probably be a reasonable way to go about this.

DR. KENDALL: Dr. Reed.

DR. REED: Maybe this is a good time for me to get something clear. I really appreciate in this, whether it's uncertainty or a sensitivity analysis or the material that we received, that you actually present not just one slice of the distribution, 99.9th or whatever, but that you actually present modical points.

I don't know. Are you thinking of doing that in the final document, or are you thinking of just presenting it one point?

MS. MULKEY: In almost all our risk assessments, we present these multiple points.

DR. REED: That's my understanding. Because to me, that's important. I think a lot of problems or lack of understanding about

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when you read a document is that it's really bothersome if somebody just presents one point to me. It depends on how you slice it. The high end gets sliced off or high end gets included and that kind of problem.

Thank you for that clarification. I would like to see multiple points being presented.

DR. KENDALL: Dr. MacDonald. Okay. Dr. Bull.

DR. BULL: Just a quick point. I think it's building on what Chris started off here with. But one of the reasons I asked my question related to this earlier was I think you pick your point on the distribution, you may find that regulating at the 90th percentile will have absolutely -- taking your margin of exposure at 90th percentile, no matter what it is, the way I see the data there is some possibility you'll never affect the upper end of that distribution because those are going to get every more rare events as you get out. And when we come to the drinking water thing, that's what concerns me. If there's a hazard in drinking water, it's a very extremely rare event. And might be an important event.

But you're probably not going to change that by either adjusting, you know, within some reason between the 90th and 50th percentile on the way you deal with residues on these different fruit

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crops. It's probably not going to effect those extreme values.

DR. KENDALL: Okay. This will conclude our food exposure assessment, unless there are any further questions from EPA for the Panel.

Okay. At this point I'd like to move us to drinking water exposure. And, Dr. Perfetti, would you like to introduce your scientist.

DR. PERFETTI: To do the water presentation, we have Nelson Thurman and Kevin Costello.

DR. KENDALL: Welcome.

MR. COSTELLO: Thank you give everybody a chance to get a hand out.

Good afternoon. I'm Kevin Costello and today with Nelson Thurman here we'll present a summary of the work we did designing and performing the drinking water exposure assessment OP cumulative risk assessment.

First, a road map of today's presentation. First of all describe the preliminary results of our assessment so that everybody can consider the rest of the presentation in that context. I'll describe the background which led up to our assessment, first reminding you of the data requirements we had for the exposure assessment. And then I'll

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describe the knowledge we already had about the organophosphates in drinking water, what data we had available, and just briefly review the guidance we had received from the SAP in the past on the building blocks we used for this assessment.

Finally, Nelson and I will discuss the drinking water assessment as it appears in the December 2001 Draft. As we do, keg in mind the two questions that we posed which deal with the two issues basically presented here. First, the watershed modeling approach that we took for the drinking water exposure assessment; and, second, the regional assessment approach that we took which differs from the nationwide assessments we've done for individual chemicals.

We'll try to do our presentation in a way that clarifies, builds on those questions so that everybody understands better what it is we're looking for.

Although Nelson and I are the ones giving the presentation today, we're actually part of a much larger team that worked on this basically from March until the December legal deadline and completed it in time.

You can see that on the team from EFED beside us that we had ad hoc teams that worked to come up with new modeling scenarios. And Ian Kennedy worked to get the model development together. We

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have some folks working on a separate track for an SAP on water treatment effects. There are people from other divisions such as HED and BEAD helped us with all the usage data and with building regional assessments.

Now, the preliminary results of our exposure assessment indicate that drinking water is not a major contributor to the total cumulative risk from organophosphate insecticides. In fact, the assessment showed that the exposure from drinking water was up to an order of magnitude or more below of the food exposure.

Because of this result, it's very important to us that the Panel think in terms of whether, as we give the presentation and from what you've read, are there any systematic flaws in our approach that would lead to over estimations or underestimations of possible drinking water exposure. This is really important not only for the OPs, but this is the tool, this is the first shot at the tool, that we intend to use for future cumulative risk assessments for other pesticides families.

DR. BELL: Can I ask a question? I can't read this either there or there. And I'm trying to figure where we're at. Is this dealing with some level of residue?

MR. THURMAN: Actually, I think the whole part of that was just to illustrate. Basically, when you get above the 95th percentile,

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you see the similar trend.

DR. BULL: So it's above the 95th percentile.

MR. THURMAN: It's a higher percentile. And the whole intent of it was just to illustrate that.

MR. COSTELLO: So as Dave Miller presented before, and as SAP has seen before in the case study, the cumulative risk assessment was done using a calendar-based approach. And daily exposures in water are one of the building blocks of this approach.

Now, for the OP assessment we used the daily time step as described before. But in future assessments, it could be -- that an error there. Calendex will allow the 7-, 14-, 21- or 28-day rolling averages we've gone through. And, also, as described earlier, Calendex is the tool used to combine these exposures from the different routes.

This is important especially for the drinking water and the residential exposures because they have seasonal differences, they have pulses of exposure that we consider in the assessment as opposed to the food.

So we knew that in order to work with Calendex our water assessment had to provide a distribution of daily concentrations for the probabilistic exposure assessment. We had to account for

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variations in time, daily, seasonally, yearly. We had to account for variations in place because drinking water is much more of a local phenomenon than food because of how food can be distributed the around the country. And we needed to reflect the possibility of co-occurrence of multiple OPs for cumulative assessment as they occur together in place and time.

When we started this, we were not starting from scratch. We already had, from the previous five years, more than 24 individual OP assessments in the interim routes that had been done. From those, we were able to derive the pesticides properties, the physical chemical properties of the chemicals that we used to figure out environmental fate.

And on top of that, because of those, we had regulatory actions that had been taken voluntary cancellations, use rate changes for many of these pesticides. And as was described before, as uses were taken out, they were no longer considered in the assessment.

On top of that, we had a great volume of monitoring from surface water and ground water; and to a lesser extent -- I'm sorry. Can you go back one.

And we had the individual drinking water assessments that were done in the aggregate human health risk assessments done for each of

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these routes.

And finally, very importantly, we had SAP guidance along the way as we refined our process for doing drinking water assessments.

Now, as we look through the available monitoring which had in fact grown in volume since we did the individual assessments, we found that in fact the OPs are found in drinking water sources. Although this is not frequent, and they're usually not at high levels. When considering all kinds of water monitoring, not just drinking water, surface water sources, generally, seemed to be more vulnerable to contamination by the OPs in a pattern that was seen not only in nationwide programs like the NAQUA Program, but also in the state programs because we actually contact all 50 states to see what kind of monitoring they've done over the last 10 years or so.

Chlorpyrifos, diazinon, malathion were the most frequently included; but they were also the most frequently found in surface water studies, ground water studies and drinking water studies. We found especially from the NAQUA Program that co-occurrence of the OPs in water is likely. Multiple OPs were detected together in individual samples. And this is not surprisingly related to usage in a particular watershed.

In looking another the monitoring, however, we did find that

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there some limitations to what was available for our purposes. Most importantly, there is no single definitive study that can answer the question what OP exposure is in drinking water. So we knew we would need to look in monitoring in a weight-of-evidence approach from several sources.

In looking at all the sources, we found that the monitoring covering a number of sites but not all high use areas for the OPs. Even in the largest programs, the ones that had the most intensive sampling, sampling was not frequent enough to account for daily fluctuations. And those programs, all of the programs, also have been done because of constraints of how much they cost for a limited number of years.

Now, I mention that the chlorpyrifos, diazinon, and malathion were the most often included OPs in monitoring programs. But not all OPs were included in monitoring at all. In NAQUA Program included nine currently registered OPs. State programs included some more that weren't in the NAQUA Program, but some of the lower use OPs were not in anything.

Few or no OP degradates of toxic concern were included in most of the studies. Some of the very most recent studies are starting to include those such as the pilot reservoir monitoring study that EPA is doing with the USGS. And the monitoring that was available, even

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the most recent data, does not reflect the most recent regulatory actions that were taken. Like I mentioned, voluntary cancellations, although they have been made official, still have the time before they phase in.

So in the end, after looking at all the available monitoring that we had, we concluded that we would not be able to base our exposure assessment solely on available monitoring.

So if we were going to have to make up for the holes in the monitoring assessments, the monitoring programs rather, with computer modeling, this is where the guidance from the SAP we had gotten in the past was particularly helpful. And I'm just really going to run really quickly through some of the highlights of what we learned along the way, what the guidance we received along the way.

In 1997, first taking our model, the PRZM-EXAMS model to the SAP, we were told that it was a good tool, the best tool available, to do our screening assessments. But that in the future, we should devote resources to refining our assessment and concentrate on surface water impacts, and as we go along, to use both modeling and monitoring data in our assessment.

In 1998, we took a first refinement of this model to the SAP, bringing our index reservoir scenario for consideration. This

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adaptation of PRZM-EXAMS includes a scenario based on an actual watershed, an actual reservoir, in the Midwest. Then having done that, we moved from working with the watershed to trying to consider what portion of a watershed would actually be cropped to get a maximum idea of what portion of the watershed could actually get treatment by pesticides.

The SAP actually approved of this, especially for major crops. But due to concerns about scale differences, the size of the hydrologic units, the eight-digit HUCs to drive these percent crop area factors, it was not recommended that we use the PCAs for smaller crops or that we considered percent crop treated with the pesticides without getting further monitoring.

Now, this is important. As Nelson will describe before, although the SAP did talk to us about this when considering aggregate assessments, this was something that we felt we had to adopt to some extent in order to do a cumulative risk assessment.

And then one last thing that was on the last slide, the SAP recommended that we consider regional modeling, something that we have done for this assessment.

In 2000, we went further in presenting proposed regression modeling approaches that the USGS was and is developing which show

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promise. But, again, it's just another step in the continuing refinement of our assessment. These are still in process. And the SAP recommended that we shift our focus to monitoring programs to support model development and evaluation.

This is led up in December to the case study for the cumulative risk assessment. That used WARP, the regression model; but we were told at the WARP, while showing promise, was not ready for this kind of assessment because it couldn't also do the daily time step. So WARP was not used in our assessment at this time.

Finally, one more please. Something not directly in that line but another ongoing and very important issue that we're looking into is the effect of water treatment on pesticides. And the SAP recommended that until we have enough data for any particular assessment to really know what removal of a pesticide might occur and how much of degradates, especially toxic degradates, might be formed, that we should do our assessments based on raw and not treated water but that we had to consider the impact of transformation products.

This is important for the OPs because we have limited evidence that OP residues are in fact likely to not be reduced. But let me see, the concentration reduced not speaking chemical by water treatment, especially not reduced because we're talking mostly about chlorination

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and oxidation processes.

There is, also, evidence for transformation of products that are of toxic concern. However, as consistent with the SAP, because there was not enough information for us to make quantitative adjustments to our assessment, either to figure out how much of the parent goes away, how much of toxic products are formed, and are how long they last, we were not able to quantitatively include the transformation products in, the water treatment transformation products, in our assessment.

So with this guidance in our head, we went forward with a watershed modeling approach for the cumulative exposure assessment. We adapted PRZM-EXAMS in an attempt to estimate pesticide levels in a small drinking water reservoir. By doing that, we derived daily distributions over multiple years with weather being the variable for 12 regional assessments. By doing this, we're able to look at multiple chemicals used on crops in multiple fields within the watershed.

For the cumulative assessment, we adopted typical use patterns, typical rates, looking at the area that is actually treated with pesticides. This is something that we have not done in our individual assessments and we have to actually decide whether it's appropriate to do in our individual assessments.

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And, finally, for each of the 12 regions, we looked at region-specific inputs. And I'll describe how we choose our scenarios in just a moment.

Basically, when we decided that we were going to take a look at regional exposure assessment for the cumulative assessment rather than the national assessment that we did before, the first time we considered how we were going to do it we sat around the table and decided what would be the factors that would be important in figuring out what these regions would be. And the very obvious ones that came to mind were the OP usage. It's important to have an regional assessment because some of the chemicals in the assessment aren't used nationally. Some are. But some are used in very specialty crops or just certain parts of the country. So we had to see which crops were there that OPs were being used on and how much was being used.

Then we decided we really need to consider what the source of drinking water is if we're going to do a drinking water assessment. And some parts of the country, say, Florida, Southern Georgia, ground water is the predominant source of drinking water; whereas in other parts of the country, surface water was the main source.

Then we had to consider what the vulnerability of the drinking water sources were. Some parts of the country, while having great OP

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use, may not be all that vulnerable to runoff or to leaching. And we wanted to take a look, on a regional basis, what the likelihood of actual vulnerability was.

It just so happened that our friends in the Health Effects Decision knew of a regional framework that had already been developed by the USDA Economic Research Service. These are their farm resource regions and this had the advantage we thought right away of pretty much corresponding with what we were thinking about.

But on top of that, these are based on different farm types and on previous work that the USDA did for separating the country in ways that made sense, both for farms and for climate and for usage. And, of course, they had advantage of ready-made names that we could adopt.

Now, as you look at that, you can see that we have, we have more than 12 up there. We did, in the end, combine some of the regions based on the vulnerability. The basin and range was subsumed into the Northern Great Plains as much as anything because of the amount of OP use and where in that region the most vulnerability seemed to be.

Now, once we had the regions, we still had to determine how to do a drinking water assessment for an entire region. It does represent

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a refinement over doing it for the entire country, but it still was a problem that had to be addressed. So in building the cumulative assessment on a regional scale, the first thing we did was to identify high OP usage areas within each of the regions.

You can see, if you look at the regional boundaries, that say in the Fruitful Rim Northwest you have multiple regions that have high OP use, say the Wallamet Valley, the Yakima, and then along the snake river in Idaho. So this was a good first cut.

But then if we go to the next slide, we built on top of that. We took a look at how vulnerable areas were in each of the regions. How vulnerable they were to surface water runoff and something that wouldn't have come through on the computer. You see the dots. On top of the vulnerability, we, also, took a look another where surface water intakes were for drinking water sources.

So taking all of that into account, in the end for the modeling approach, we came up with a set of areas within the regions, watersheds that were going to represent each of the 12 regions. These areas, then, have high apparent potential for cumulative exposure based on the OP use, the number and the pounds of OPs being used in those areas; they coincide with those areas high runoff potential; and where surface is an important source of drinking water.

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It is important to recognize that, although we choose those areas to represent the highest cumulative exposure, they don't necessarily represent the areas that have the highest exposure for any single pesticide. But we still expect that the combined OP exposure to be among the highest for each region. And on top of the four regions like the Fruitful Rim Northwest, where we chose the Lamit Valley, we did consider as best we can in our characterization, we attempted to describe other important areas in those regions.

So for the Fruitful Rim Northwest, for instance, we went into a discussion of the Snake River Valley, the geology, the hydrology of the area, the type of use, the source of drinking water, which was ground water. So that in an attempt to try and explain, again, why we thought that the regions we choose were the best representation of risk if the drinking water was a risk driver for any particular region, which as it turned out, they were not, we were prepared to go to a finer resolution than the regions and to try and look at what those watersheds we choose actually represented within those regions and try to get a more refined assessment.

So what we ended up doing by choosing these watersheds was to tailor our assessment to selected areas. We used location-specific enviornmental data for the regions that we chose -- the soil, the sites,

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the local weather and the crops that were grown there -- and we considered the major crop OP combinations within that area. And by doing that, we looked at crops that actually occurred together. We were able to look at different OPs used on multiple crops. And if OPs were actually used in those particular regions for usage data. And there the end, we did enough scenarios in an attempt to account for about 95 OP use in each of the areas that we choose.

And Nelson will take over from that to give more details on how we did the assessment.

MR. THURMAN: What I'm going to touch on here is not so much how it built upon the SAP guidance in terms of what we were doing for the individual screening assessments and how we tailored these tools for use in the cumulative assessment. Kevin's already talked about a regional framework, one of the big differences.

If you compare our individual assessments, we started at a national level. We tried to pick one site that represented a high-end exposure across the nation. In this case, we're starting in a regional level and we're looking high-end exposure with each region with a concept of, if we're okay on that site within the region, we're okay in the rest of the region; if not, we need to burrow down further.

I'm going to talk about how we did our watershed-based

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modeling and talk about the way we use the data which is a little different than what we have in the individual assessments and how we took a look at usage information.

There some people in this SAP that have been on some of the water SAPs we've had and there are some of you folks are, at least to me, new faces. So I wanted to briefly give you at least a concept of what type of model we were using. For those of you who've heard this, it won't be too long.

Essentially, PRZM, which is the Pesticide Root Zone Model, is something that was developed out of EPA's ORD. It takes a look at what happens when a pesticide is applied to a field. And it basically follows the pesticide from the application to the field to the runoff right to the edge of the water body. It's a field-scale simulation using chemical movement, hydrologic factors. Accounts for ways chemicals are transported, and it is very useful in terms of using it uses a lot of chemical specific. We included both OP pesticide and those toxicological concern it was primarily the sulfone (ph) and sulfoxides.

We did not include degradates that were not formed in the environment, for instance, the oxons were not something we saw in the environmental studies; that is something that we do see as a result of the water treatment. But it is not formed in the environmental studies

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we saw.

EXAMS, which is the Exposure Analysis Modeling System, is another model developed by ORD. Basically, it takes over when PRZM leaves off and looks at what happens once the pesticide reaches the water body..

We had a few fixed inputs. The primary fixed input was the geometry and hydrology of the reservoir itself. Essentially, as Kevin mentioned, we used the index reservoir. Essentially, what we did for each of the regions we picked up the dimensions, the hydrology, the geometry, the size, and plot them in each of the regions.

Now this is going to be representative more of drinking water reservoirs and drinking watersheds in the wetter parts of the country than in the west where you're going to need a larger watershed to supply that reservoir. It's also not going to be as representative where you have artificial drainage or controlled drainage conditions, which you also tend to see in the west.

It is a reservoir. It is not a flowing water body. Based on what evidence we have, we expect the reservoirs tend to be a little bit more vulnerable. Once again, we're looking at a site that, if we can make the conclusions we did based on this site, we're not worrying about other sites. But we do no know there were some limitations in terms

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of that as we move in different regions in the country. And that's one of the reasons why we continue to go back to feedback on what the monitoring showed.

We had a number of variable inputs. As I mentioned early, the chemistry, chemical properties, were specific to those chemicals. The weather, the site, environmental crop, and usage information are specific to each of the assessments areas. So in that way, we are tailoring to things that actually occurred in the area where we did the assessment.

What you see here, in case you can't see -- what you have is concentration on the Y axis, and you have time on the X axis. And, basically, you're looking at a 10-year span here. What we get as an output of a PRZM-EXAMS are daily distributions of concentrations in water over this ten-year -- in this case, a ten-year period.

I want to contrast a little bit because NRDC raised a concern about one thing we do differently, which, as they pointed out, we use a peak estimate individual screens. Actually, what we use when we do a individual screen is a higher percentile what reflects a one-in-ten-year concentration that we would find over the period.

And I forgot to mention, most of these sites we had up to 36 years of weather data. So we would run this simulation over a 36-year

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period. In effect what we're doing when we do these simulations, we're holding use constant and varying the weather from year to year. So the variations you see from year to year reflect differences in the weather and runoff that we get as a result of that.

For an individual screening assessment, we might use this one value. And this red line there. And in effect what we're doing for that assessment is we're assuming that this is a concentration that occurs every day. What we're doing in this more-refined assessment that we're doing and looking at multiple chemicals is we're realizing that that concentration doesn't happen every day. You get your daily and seasonal and yearly variations. So we're capturing that full range of concentrations that you get.

We're also preserving the time component. We do know that in any given year the concentration of pesticide you might see in water on June 1 is going to be related to the concentration you had the day before and the concentration you had the day after. So there is a time relationship that we're able preserve by going to this yearly distribution; and we're able to preserve Calendex to pull those exposures in.

This one did not come out very well. I think we were so ambitious to make sure that you could see it that we overloaded the

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memory on the computer.

You should see at second distribution superimposed in here. The intent, the point of that, I can tell you is that with a cumulative, we're looking not just at one chemical; we're looking at multiple chemicals that are going to have uses on different crops; their timing of application is going to be different. We have to find a way to take all of this into account.

Kevin mentioned briefly how as we use the use information and zoomed in on an assessment area in each of the regions, we tried to make sure that we captured all those OPs that would actually be used in the same watershed. For instance, to use as an example, the Northwest Fruitful Rim, we found that OP use on potatoes tend to be concentrated primarily in Idaho. And OP use in apples tend to be more in Washington. So we're not combining those two areas since they don't actually physically occur.

The other component the co-occurrence is the time of use. As I go forward in this, I will try to explain how we did try capture those windows of application so that we could separate that timing as much as we could accurately do with the data we had.

One of the big departures between what we have brought before this SAP in the past and what we were bringing forward in terms of

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this cumulative assessment is how we use the PRZM part of the model. PRZM is a field-scale model. That basically carries a lot of baggage with it. It assumes that we can take the field scale and scale it up to a small watershed and not loose too much in the estimates.

We know that there are some assumptions that go with that. We're assuming a single soil in the watershed, the crop and the management practices are homogenous in that area.

For the cumulative assessment, we basically went back and used PRZM as a field-scale model. But what we basically did is we simulated multiple fields in the watershed. One of the things to keep in mind is that, while we did this approach and we feel it's something that does reflect what you might find is happening in the watershed, we still don't have any way of giving a spatial distinction within the watershed.

If you remember in the earlier slide of the pictures, the conceptual drawing of that watershed and reservoir, we basically don't have location-specific information there. We're assuming the crop that's used covers a certain percent of that area, but the percent of area is evenly distributed throughout the watershed. So we're not distinguishing between crops that may be grown in the upper end of the watershed versus those crops that may be concentrated in lower

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end.

It also assumes that all of the runoff flows into the water body. We know those are the two limitations that we in that. We do feel that by simulating multiple fields, it better reflected what we needed to do with the cumulative.

We, also, had to have a way to take in the fact that we understand that not all of any watershed is going to be treated with OPs. Those areas that are treated, you're going to have different crops treated with OPs at specific times and specific rates and specific frequencies. I'll say right now, the tools to do that are probably a lot easier to do than getting the data that can do that. And one of our challenges was how to pull this data together and use it to the best we could. And in response to, I think, Daniel Botts comment, we're hoping that we used the appropriate data. And we'll try to explain to you what we did use. And we hopefully used it appropriately as we did that assessment.

One of the things I do want to say is the advantage of simulating multiple fields in a watershed, as we did, is each field may very well have a different soil and a different crop. And so we are getting a little bit more a reflection of a little more heterogeneous watershed than we can using it as we did before.

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This picture happens to be in the document and it looks better in color than it does in black and white. Essentially, what I can tell you is that that map shows a percent of the crop areas taking a look at, by on a watershed basis, what the percentage of each of those watersheds are in agriculture.

You can't tell whether the gray tones there, but your highest concentration prejudice of agriculture occurs in the watersheds that are in the Midwest. And the lowest is, obviously, in the Basin and Range. This is where your highest concentrations are.

We used something we've called a cumulative adjustment factor approach to account for the relative contribution of each OP in crop use. We did this in terms that we had to take into consideration both the recommendations and the concerns of the SAP on the percent crop area factor that we brought forward to them. And I'm going to explain to you how we did this so you can take a look and see whether it makes sense. We think it makes sense, but it's one thing we want your feedback on as we go along.

One of things I will say is that one of the earlier recommendations of the SAP was that, when we started looking at percent crop areas, we should do this on a watershed basis. And it makes sense on a physical basis because we're looking at, we're

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dealing with watersheds.

The thing to keep in mind the data is collected on the basis of geographical and political boundaries. In other words, most of it is collected at a county or state level, not on a watershed level. So you need to take some way to translate that.

We brought forward an approach in 1997 for applying a percent crop area factor starting with county level ag census data. In the '97 presentation, we used the 1992 ag census. We now have the 1997 agriculture census available which is one of the recommendations the Panel was, as soon as it was out, to use the most updated information.

We, basically, overlaid those with watersheds and used GIS to get that spatial distribution within the watersheds. Kevin mentioned what we had available for GIS were 8-digit hydrologic units, which tend to be fairly large. They average 367,000 hectares in size. And you compare that with 172-hectare watershed we were using, you can see that, at least for the smaller drinking watersheds, you get a lot of them and you can get lost in those large HUCs.

One of concerns of the SAP was that while you may have minor uses that don't add up to a big percentages in these large watersheds, those minor uses are often clustered and they may be clustered in a smaller watershed where they have more of an impact then they did on

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a larger scale. So that was one of the challenges we had in trying to convert this data.

We, also, were trying to keep in mind the caution against doing too small a PCA for that reason. What we decided to do is come up with a cumulative OP-PCA. So for each of those 12 regions as you saw, we derived the percent crop areas for the total agriculture using the '97 ag census data.

We then took a look using the latest national agricultural statistics service data which is collected on the county level. We took at look at agriculture land that were in crops that had registered OP uses in that area. And we came up with that percentage. So we essentially adjusted your total agricultural PCA by your percentage of the aggregates from the OPs and came up with a cumulative OP-PCA.

This is an illustration that the numbers you see down there are based loosely on an earlier version of one of the regions we were looking at. I round them off to make it easier for me to do the math and to explain what's going on. One of the challenges we had, if you look at these total acres, they are total acres in the assessment area, which is a lot larger than what you're looking. This is one of the reasons why we went to a percentages so we could use that percentage as a way of scaling down based on the area.

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In this particular area, we're looking at a cumulative OP-PCA of 50 percent. Basically, 40 percent of that area in that region were in crops that had registered OP uses.

Now, if you keep in mind that not all -- we know that in any given year, not all of those crops are going to be treated with an OP.

It's further complicated by the fact, if you go to the next slide, that these crops may be treated with multiple OPs. Some OPs may be used on more than one crop. We used a second concept which was a percent acre or percent-acre-treated factor. This basically used the acres treated, which we collected state-level data, as a way of determining how many acres of the total -- for instance, how many acres of total corn were treated with a particular OP.

Now, this acre-treated doesn't take into account the fact that you may have more than one application that goes in that area. And if you were to look over at, for instance, the beans, which you see here, is a particular case we had two different OPs that were basically used on the entire crop at different times.

What's not reflected in here is timing and I'll get at that again in just a little bit. But we used this concept to derive a cumulative acre cumulative adjustment factor which combined both the percent-crop area and the acres treated based on the slide that -- based on the one

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that had the map that you couldn't see.

I know you can't read all of these. What I want to just point out is that when we did this, by combining both the acre treatment and the percent-crop area, this gave us a way to distinguish between the relative contributions of each OP and crop use within that watershed. And so we use this cumulative adjustment factor as a way of making that adjustment.

So what we did is that we ended up with each of the crop OP uses that we identified in the assessment area, we ended up with daily distributions. And we still needed to combine these individuals distributions for different chemicals together. So what you see here in each of these distributions is that we put them on equal area. We use a crop-area factor, the cumulative adjustment factor, to put these on equal footing in terms of the area contribution they made in the watershed. We used the relative potency factor, we talked about earlier, to put them on a comparative basis so that we could combine this so that we'd end up with any regions a single distribution over up to 35, 36 years in methamidophos equivalence.

And so what you see there, in fact, you will see in these multiple peaks in a given year, which basically reflect different timings of applications of different pesticides.

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Now, there are some assumptions and issues that come out of the way we did this approach. One again, we tried to address the SAP concern about the fact that data came in different scales. We're trying to take county and state level data and apply it to a watershed. And the fact that the size of the watersheds we had that we could work with to do this are a lot larger than the more vulnerable drinking watersheds. And we're trying to address the fact that some of those crops cover small areas.

Our feeling was that by using a cumulative OP-PCA, starting with the total agriculture and adjusting for total OP uses, we don't end up with a number of small, separate percent-crop areas that may introduce more error into it than the combined PCA in that regard.

Secondly, we said we still have some issues on applying an acre treatment adjustment. The percent-crop treated is complied to state level. And there's a couple exceptions in that one is California where they, California Department of Pesticide Regulations, basically has a census in that they require all users to report what they use and when.

The other one is whenever we were looking at the Willamet Valley, we also found some use data specific to the Willamet Valley Collective, actually folks at Oregon State, that we were able to use.

When we take this information to state level and we try to apply

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it at a watershed within a state, there's a number of assumptions embedded into this. And one of the big ones it that we've assuming that the data that's collected at state level, the percent-acres treated, is uniform across all watersheds in the state. There's also an assumption of uniformity i time. I'll get to that if in a little bit.

What we know is that pesticide pressures are not necessarily uniform. And so what you're going to find is that where pesticide pressures are great in a particular year, you're going to see more acres treated, possibly at higher application rates. Where they are less, you're going to see less acres treated. So there are some concerns in doing that.

One of the other things as we took a look at that is we, also, realized that crops aren't uniformly distributed across the entire state. So in those areas where your crops are clustered in a certain area and where your use is clustered together, there may be less of a variability than in other cases. And that may be one of the differences between some of the minor crops and some of the crops like corn which tends to be more uniformly distributed in the Midwest.

Our assumption in doing this is that this is probably more of an issue when you're looking at a single crop, single OP use in an single pesticide than when you're looking at an area where you're looking at

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multiple crops, with multiple pest pressures that are going to vary, not necessarily all at the same time and over multiple OP uses.

We did take a look in one area to see -- and one effect we got some reflection of maybe some of the variability we might see in this. In the Northern Great Plains we focused on the Red River Valley which tends to be where the highest total OP use was in that region.

We identified high OP use areas on either side of the Red River in North Dakota and Minnesota. As we start taking at look at some of the OP use information, you could see a difference, both in terms of application rates and the percent-acres treated between those two states. Our feeling was that difference was more of a reflection of the data collected at the state level in those two states then of actual differences on either side of the river in that Red River Valley.

We did do comparisons using North Dakota information and then using the Minnesota information to see how much of a difference that makes. And what we did find is that at your highest percentiles -- in fact, anything above 90 percent, there was roughly no more than a 10-percent difference.

And we're talking about single parts-per-billion concentrations, so we're looking at no more than a fraction of a part per billion difference with that. A lot of that was the fact that, once again, we're

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looking at a combination of uses. So there was not just one single use that was pulling together.

We used survey data to get at the use. We uses USDAs National Agricultural Statistic Service information on pesticide usage to give us the information on use. We did not attempt to forecast. Except for the fact that we did exclude any uses for which regulatory action has been taken to cancel.

We also focused on the most recent year of the use data. One of things, if you look at the data, and particularly if you look at each of the regional assessments, you will realize that some of those dates -- you have different dates; different years. That's because the NASS collects the information at different times.

Field crops are collected every year, but fruits and vegetables are collected in alternate years. We may have had to go back more than one year to get equivalent data. The other thing to keep in mind what we did use was not your maximum application rate, but we used an average. And that was basically the average of the respondents of the survey within that assessment area.

We took a look -- a number of OPs have more than one method. They can be applied to either aerial or by ground. We focused on the dominant method of application in that area. While our primary source

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was NASS, we did, where we could find local sources, we did supplement that information in those local sources and we have documented that in the assessments.

We still need a way to account for the time component of the co-occurrence and in the timing of pesticide applications are going to have a big influence, particularly the timing in relation to when a runoff event occurs.

So we took a look at what information we had. This is a distribution for the Central Valley, California, which we use the in the Southwest Fruitful Rim assessment. This happens to be the area that had the most OP use and the most crops with OP uses.

And as you can see here, you got a distribution of applications the different colors are the different pesticides, have a distribution of applications throughout the year.

One thing to keep in mind is the data in California is a little different than what we had elsewhere in the fact that California does require reporting of every user in terms of how much you used, when, what, where. So we could get that at a county level, and we could get that across the year. So that data reflects more of census than a survey.

And that's the one differences that we had there. This, in effect,

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made it a little easier for us to do an assessment in California terms of timing.

DR. BULL: Quick question on that. Those are cumulative curves. I mean you've got one shade.

MR. THURMAN: Yeah. Those are cumulative curves. It may have been easier if we'd had another one where -- but this just shows you the more complex end of it.

In other areas, we only had surveys. So we had to find a way -- we didn't have this type of distribution information. We usually had something tied to a window of application. We had to find a way to find that window in a way that would try to as accurately as we could, reflect those actual differences in applications.

What you'll see when you look at the document is there are different ways we accounted for this temporal variability. In California, where we had the census, it showed a distribution across the year. What we ended up doing was we selected five dates along this distribution with each date representing 20 percent of the total applied use. So, essentially, you had quintals for each of your crop OP combinations.

In the other regions where we didn't have that specific timing, what we usually had was information reported by a particular window.

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It was either management windows or times of the year. We used USDA chemical usage information, their planning harvest reports, crop profiles; we talked to regional specialists or local specialists in those areas to try to define that window of the application as narrowly as possible.

If we had a pesticide that had a single application of a crop but we had no distribution information, for instance, if we had a pesticide that we knew was applied at planting, but there was no other information on the distribution of those applications, we would take a look, go to the local area, find out when the window of planing was. And then we would apply this pesticide at the beginning of that use window.

If we had a single application but we had some type of distribution window and we were able to define an active window within that, then we would select the midpoint of that active window to apply the pesticide. If we had pesticide that had multiple applications, then we tried to distribute that evenly across the use window.

Once again, this is given the fact that the information we had. We felt this was as tight as we could get the windows to do that. And given the data scales, it was difficult for us to get tighter values.

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There is some conservatism when you saying we're applying all that single application on a given date on the same data in a given watershed as opposed to saying, well, we're going to distribute that application out using a uniform distribution within a use window.

However, we don't think that was unreasonable conservatism when you start looking at the size of the watershed we were looking at. When we're looking at adjusting those fields for the percent crop area and the percent acres treated, it made more sense that these fields were the size that all those applications would actually occur on a single day rather than at different days on there. So we felt like there was some conservatism to it, but it wasn't an unreasonable assumption to make.

What we found is that when we did these and in each of the regions we generally found that there were one or two chemicals that were drivers in terms of the water exposures. This is also in the Central Valley of California. One of things that we found here is these cumulative distributions that we pulled together in methamidophos equivalents, once again, were a function both of the concentration of the pesticide in water and the relative potency factor.

Disulfoton, which is the one that you see dominating the curve, and once again this is a cumulative curve, has a higher relative potency

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factor than these other OPs that you see here. That helped skew that curve. We did find, as we went back through there, is that we were able in most of these regions to get some separation of peaks and time so that we weren't artificially adding peaks together that wouldn't actually occur together. And the fact that in each of the regions, we were pretty consistent that there were only a handful of OPs that were drivers. And these tended to be the type of OPs that we saw in the monitoring data suggested that we weren't too far off.

Okay. You'll be happy to know this is the last slide before the questions.

We kept trying to go back and compare what we did in the modeling to the monitoring data. When you look at the report, one of things where the comparison occurs is in each of the regional summaries, each of the regional write-ups we wrote up a comparison. What we're planning to do to make life easier, because of some comments we had, is to try to pull that together in one place for all the regions together to make it easier to find it all at one time.

One of the challenges we had when we were comparing what we did in the modeling to the monitoring is that, A, there is no single definitive study. A lot of the monitoring studies we had were on running water from streams and rivers. There were a few, a couple of

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studies, that focused on reservoirs. But these did not focus across a broad geographic range or across a broad time.

We took a look at everything we could. We tried to compare as much as we can, particularly looking at the peaks that we estimated for each of the individual pesticides in those regions to the highest detections that were reported. We also tried to take a look what I would call an "equivalent frequency detection." Each of those, in the monitoring studies, each of those OPs has a limit of detection.

When you're in PRZM-EXAMS, it can carry it out well below the limits of detection. But we could, basically, take a look at what percentile fell above or below that limited detection you would see in the field to see whether or not how we were doing in terms of estimating or overestimating.

One of the things, because they're not necessarily easily comparable, it's difficult to draw definitive conclusions and point this tells us one thing or another. Because we looked at 12 different regions, we were -- give us a chance to take a look at what each region tells us.

So if we were looking at something -- it gives us another way of kind of discerning whether or not we were having a function of compensating errors or fortuitous results or whether we may actually

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be on to something.

What we found is the other thing that we need to keep in mind is we did not have monitoring data for every OP. So we had to assume that what we had reflected in comparing for the monitoring that was there would also be have been reflected for the others that weren't monitored.

In each of the regions, we did find a few known detections of one or more of the OPs that occurred at levels that were higher than what we would have estimated. We were looking roughly at order of magnitude differences, in part because the results that we had showed the drinking was and order of magnitude or more lower than food exposure.

So we took a look at order of magnitude differences. And to be honest with you, when you're doing some of these comparisons, getting much closer, gets a little queasy, anyway.

We did find that some of these had reported monitoring values that were higher than what we estimated, but there were also some where our estimations were an order of magnitude more greater than what we found in the monitoring.

We did not find a consistent trend in one way or another. We also found that there were a number of OPs that were fairly close to

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each other in each of those regions.

In the questions that you're going to respond to after the public comments, we were asking you about whether you say anything where we may have significantly underestimated exposures, in part, because that's the way the results of the study came out. We're just as interested in anything you see that might suggest that we're significant overestimating exposures, too, so that we can take that into account on future assessments.

And I think the next ones comes to the questions.

DR. KENDALL: I don't want to have those read at this time. First of all, any points of clarification from the Panel for the presentation?

DR. MCCONNELL: I'm sorry. I missed the first few minutes. Maybe you covered this, Mr. Thurman. I noticed in your geography plots up there that one of high use areas is in Florida. And I got to thinking about in a situation where you have soils, poor soils, shallow water tables, have you looked at the ground water; or did you cover that and I missed it?

MR. COSTELLO: We considered it. We made the decision looking at it first -- well, one step back. Again, one of the reasons why we separated regions the way that we did, was to separate those

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regions that had ground water as the major source of drinking from those that had surface water as the major source.

Next, we came to the conclusion that surface, generally, would be more vulnerable as a drinking water source to contamination from the OPs. For what data was available, there was clearly a lot more contamination of surface water and, just as importantly, much more cumulative co-occurrence of OPs in surface water. Something that we don't have evidence for in ground water.

But compounding that is the fact that beyond the fact that the monitoring is not enough for ground water to allow us to get the daily distributions, we actually don't have a tool like PRZM and EXAMS that would allow to us do the same thing for ground water. So it is one of the uncertainties of our assessment, especially for places like Florida, that we had to do a surface water assessment and assume that the concentrations that we would come up with, the exposure we would come up with, would exceed it.

There are reasons for certain individual chemicals that calls that into question to some extent. In Florida in particular, one of the OPs has, in certain regions, been found at higher concentrations that we had in our surface water assessment. This is one thing that we describe in our risk characterization as one of our uncertainties.

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On top of that, in all of the regions, including the ones in which surface water is the dominant source of drinking water, there is still a significant portion of the population that derives drinking from shallow, private drinking water wells.

Again, this is why we are hoping in the way that we did our modeling scenarios that we have come up with what is likely to give the highest cumulative exposure to OPs as opposed to potential individual higher exposures to individual OPs in shallow drinking water.

MR. THURMAN: One other thing I'd add to that is this is where the relative potency factor also comes into play when we're looking at cumulative impact.

In Florida it turns out that where we did focus on surface water -- and there are not many surface-water intakes in Florida; we know that -- there happened to be a couple of OPs -- and I'm going to blank out on which ones -- that are used on sugar cane that have relatively high application rates and had a much higher relative potency factors than the OPs that we were finding in ground water. So when you started looking at it from a cumulative impact and you take into account the relative potency factor, we did feel that the surface-water assessment is going to be protective in that regard.

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MR. COSTELLO: And this is one of the reasons why I described -- when we figured what areas had the highest OP usage, if we had not chosen them to be representative of the entire regions, we made some attempt to characterize the likelihood of drinking-water exposure in those regions. So if you take a look at the Mississippi Portal, for instance, which, like Florida, is an area that has much more of a population deriving its water from ground water than surface water, a detailed discussion of the geology of the area of the aquifers in the area will let you see that the greatest portion of people that derive their water, at least from other than private wells, are getting water that is protected by confining layers between the aquifers.

It does not write off the risk especially to people on private wells. But just to say that we made our best attempt to account for the vulnerability of the drinking source other than the surface water that we used in our models.

DR. KENDALL: Dr. Bull.

DR. BULL: A couple points of clarification. The issue you raise at the end, wouldn't you want -- since this was a conservative approach that you were taking, are you a little bit surprised that you had some things that are higher than what you predicted because I would have guessed this scenario would have been more protective.

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MR. THURMAN: We are going --

DR. BULL: I would expected most actual monitoring data to come in lower.

MR. THURMAN: We are going back through and taking a look at each one of those and trying to come up with a rationale, see if can identify a reason why there may have been up.

In some cases, we do know that they are from uses that -- they're uses in the area that are being canceled. So we know that there is that type of a contribution. In some cases what we found that they are in areas were not necessarily, the monitoring was not necessarily directly located where the major use, where our cumulative impact was.

In one or two areas we do find that there were some watersheds where the monitoring came from that are high ag use but are not representative drinking water -- they are not drinking water sources. So those are some of the things we are going back and taking a look at to see if we can...

MR. COSTELLO: But if I may. Some of the monitoring that I did find, although not direct drinking water monitoring, something to keep in mind how limited direct drinking water monitoring is for the OPs. But even if they were not drinking water samples, they were in

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potential drinking water sources or in small streams that fed them.

DR. BULL: I'm going to try to keep this to points of clarification.

One of things that impressed me is those areas that you got are pretty heterogeneous within those I areas. I live in one of those areas as everybody else in the room is. But I know what they are.

I heard you talk about weather patterns, but I didn't hear you talk about irrigation. And irrigation is a big issue on runoff because you're going to get runoff from irrigated fields. And if you're just using -- are you taking that into account?

MR. THURMAN: We did take irrigation into account. There were a couple of regions where, you know, PRZM does have an irrigation routine. And in some cases, we've had to do some calibration of that irrigation routine. So particularly in the Central Valley, but in a couple other areas --

DR. BULL: In our part of Washington State, you don't get runoff if it's not from irrigation.

MR. THURMAN: Yeah. To be honest with you, one of reasons why we are looking at that is taking a look at where your runoff was going to occur. And we do realize that -- that's one of things we know that, where you have controlled drainage or human influence drainage,

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and in this case irrigation, is this is going to be weaker in terms of trying to capture that effect on it.

DR. BULL: And there's probably limited places you can actually measure it.

MR. THURMAN: Now the thing that helped us on that is we did do -- we were able to do some comparisons from USGS NAQUA data and different -- particularly in the Northwest Fruitful Rim, in each of those major use areas, there were some NAQUA studies that were conducted at the same time. And so we were able to do some comparisons with the monitoring data to see where the relative impacts were likely to be. So that helped guide us in selecting the site.

DR. BULL: There's another kind of issue that runs in a funny way, too. You mentioned the potatoes in Idaho. I've heard -- I'm not sure it's true, but I think we do more potatoes in Eastern Washington than they do in Idaho now.

MR. THURMAN: I apologize for that. But that's true.

DR. BULL: But the issue of shifting crops, I mean, there's also a good -- you can also get applewood which is very good for the fireplace in Eastern Washington because a lot of people are taking orchards and they've shifting to different locations along the river.

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MR. THURMAN: Certainly that's --

DR. BULL: How do you take that into account? These are big shifts going on.

MR. COSTELLO: Well, you know, the usage data that we had, the attempt was to have it for as recent as possible, and the monitoring data as well, to keep it somewhat recent. You know, along those lines is why we described how things such as -- we know that the uncertainties say that in the usage that is reflecting a certain number of years that the monitoring can't reflect canceled uses or other OPs that might come in to replace cancelled uses.

DR. BULL: That's what bothered me about taking out the canceled ones.

MR. THURMAN: Once again, we weren't forecasting. But I will say that in each of the regions, as we were looking at the sites, we were laying out what are the crops and what are the uses. And the one that strikes my mind, comes to mind right now, in Eastern Uplands we were looking at an area in Kentucky which did have tobacco use. That is a crop in, at least in Kentucky, is going down in acreage and OP use is going down.

And the other alternative was apples which is in another part of the area which was steady or going up. And so that's one of the things

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we did take a look at. It was more of in each of the regions as we're trying to decide where do we focus the assessments. We would look at that, but sometimes that's hard.

DR. BULL: The final question I had along the same kind of line is you said the state usage rates are state wide but you only spread that over crop areas; right? You didn't spread that over --

MR. THURMAN: Only over crop areas.

If you look at the use information that is based on surveys. So they are selecting farmers across the state that reflect -- they're reflective of different farm types and sizes and they're actually asking them what is your application rate, and how many times do you apply it on this. So that survey -- so what we're getting and let's say we get an average is actually a reflection of actual survey response. And it's aggregated at a state level.

DR. BULL: But the apples in Washington, in Yakima, but most of them are probably up in (inaudible) Valley and up in Columbia and up into Canada which is another. The (inaudible) Valley up in Canada. So those are all very concentrated. And then you get out in other areas and they're grains and potatoes and things up on the flat.

MR. THURMAN: Did it does take into that.

DR. BULL: It does?

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MR. THURMAN: Yes.

DR. KENDALL: Any further clarification from the Panel about this issue?

DR. CAPEL: Yes. As part of the introduction you showed up a watershed exposure plot for drinking water. I'm not quite sure exactly what that represents. I have two question. One is: Is it the output of PRZM-EXAMS with no adjustments for treatment?

MR. THURMAN: Okay. It's actually more than -- the output of PRZM-EXAMS, we did not adjust the treatment. So basically we're -- we did find anyway to quantitatively do that.

But it also takes into account where Dr. Smith Mr. Dave Miller were talking about the CSFII dietary data. Part of that data includes drinking water consumption. So you get your levels in the water, which are your residue part of that, but you also have a consumption part of that to take into account in that MOE plot that you saw,

DR. CAPEL: So I guess the other half of the question is: Is it based only on the parent compounds, or are the transformation products also included in that?

MR. THURMAN: It is based on parent compounds and transformation products as it occurs in the environmental transformation products. So basically the parents...

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DR. CAPEL: So it's part of the PRZM-EXAMS model that you've got --

MR. THURMAN: Yeah, yeah. And there were a couple of other transformation products that were included in there. But those are the major ones that were included in that.

DR. BULL: This is --

DR. KENDALL: Dr. Zeise.

DR. ZEISE: I was wondering if you could speak to the drinking water consumption assumptions that were made. And then how you dealt with it. If we turn back to the food case, it looks as if a good deal of the high-end exposure coming from perhaps high consumption and high residue levels. And I'm wondering if in this example where the equivalent is sort of trying to address that high-end exposure group.

For example, did you address one subgroup that gets basically all it's fluid from water, bottle-fed infant? How did you deal with these more extreme cases?

DR. PERFETTI: As part of the food consumption data, the CSFII survey, the latest one, the 94-96 and even the '98 children level, directly asked the question how much water did the individual drink under those two nonconsecutive days. So those consumption values

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are for water the same type, reflecting the same survey that the foods consumption was collected.

DR. ZEISE: Did it capture -- did that sort of capture bottle-fed infant? And did you look at that in particular as a special case where you might have a high exposure? Did you make sure that --

DR. PERFETTI: Water consumption of the bottle-fed infant or the formula consumption.

DR. ZEISE: Well, you would --

DR. PERFETTI: Well, okay. There's two components to water. There's water you get in your food, and there's the water you actually just drink to drink water. Both of those are in the CSFII but in different forms.

DR. ZEISE: Okay. Well, I'm just talking about this one particular subpopulation where you might have very high exposure. Do you think they were adequately captured in this analysis?

DR. BULL: The extreme would be formula made from water.

MS. MULKEY: I thought I understood Dr. Smith as saying -- he's here. Do you know the answer to this question, Bill, the formula that you make up, the power the water in the powder formula.

DR. SMITH: Yes. As I understand it, the current survey, it breaks out the different forms of water, as Randy was saying; and they

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are separately listed as water and then there's water that's used in preparing, for example, formula and all the other food components. And it is a fairly high consumption item as you would expect.

DR. ZEISE: Okay. Thanks. As we saw earlier this morning, we looked at different plots for different age groups. And in this case, if you think analogously, this might be an age group where you might see -- I mean, it's very upper tail high levels. And I wonder if you did any of that kind of disaggregation to look to see whether there were some subpopulations that could potentially have higher levels, both on a consumption and then from, perhaps, abnormal use applications.

DR. PERFETTI: Do you mean in terms of the water?

DR. ZEISE: One side the consumption is for the water, and the other side is the different assumptions made with respect to application of pesticide.

My understanding is you've used average application that you obtained from surveying. And I don't know the extent to which that might address things like outbreaks and so forth.

DR. PERFETTI: I'm not sure I understand all of the question. As far as based on the water consumption and the residues observed from the PRZM-EXAMS run, there was none of the subgroups had -- there was hardly any -- well, the MOEs were in order of magnitude

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above the food and sometimes three or four orders of magnitude. So you will even -- that subgroup zero to one, which, I assume is what you're referring to, that the water was not playing a major part in that even though, as you pointed out, both from water consumption from the formula plus any water the individual drank would be a high consumption of water.

MR. COSTELLO: And I think understand what you're getting at when you say "the outbreaks." You're talking about pest pressure and using higher than typical rates. And we choose for the cumulative assessment to use typical, that is to say average rates, where we might not before for individual chemicals because we thought it unlikely that the highest rate for each of the pesticides, for all the pesticides on different crops, would be used at the same time.

To attempt to look at -- again, because remember, these are different crops, so pest pressure wouldn't be uniform over all the ones we have in their assemblage. But to attempt to alter some to be higher would introduce another dimension of probabilistic assessment, and it is not something that we attempted.

DR. KENDALL: Any further points? Dr. Portier, you stand, then, between the break and closing this session.

DR. PORTIER: The average rates question, you answered a

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question I was going to ask. You didn't consider any variability in what you got out of PRZM-EXAMS. You simply ran it and got sort of an average for each region.

MR. THURMAN: Yeah, actually, that was one thing. We held the application rates constant. So what you see in terms of that variability in time is due to weather differences. There was no attempt to try to -- and, actually, part of the problem is with finding the data to do.

DR. PORTIER: And the other question, since it's not in front of me and one of the questions you're asking us about, is whether we believe that the water component is a trivial part of the organophosphate exposure. I have to ask the obvious question. How bad were your estimates in the worse case? Since I can't see all the data you looked at in deciding the water concentration levels you observed, give me some indication of the magnitude. Is it less than an order of magnitude? Is it two orders of magnitude?

MR. COSTELLO: You mean compared to monitoring.

DR. PORTIER: Yes, compared to monitoring data.

MR. COSTELLO: I think the important -- I could give you a yes-no answer, but that wouldn't be serving you.

In the case of some of the exceedances that were significantly

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higher and I think they were at somewhere at least an order of magnitude, you have to consider, again, what the monitoring represents. And this is, again, one reason why we couldn't use the monitoring by itself.

In looking at the available data, it's an assemblage of monitoring studies designed for different purposes. And some of the highest concentrations that we saw, the best example is an area near Salem, called Solter Creek, from the NAQUA program, where there were several of OPs that exceeded significantly when they came up in our cumulative assessment.

But Solter Creek, beyond the fact that it is not a direct drinking water source, also has a small watershed with 99-percent agricultural. Again, a question of scale. The percent-crop-area factors that we come up with are based on OP crops in these large 8-digit HUCs.

So to compare what we come up with there to actual monitoring near the time of application in very high-use area in an area that's got 99-percent agricultural, we have to actually stop and think what does this mean that it exceeded our output.

I mean you have to consider both what does our output really mean, and that's part of one of our questions. And then what does it mean once we figure that out to compare to monitoring with...

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MR. THURMAN: With those caveats in mind, I can tell you just from going back and going into a little more detail in each of these and figure out what it is.

In each of the regions, there's no more than a couple of OPs where we found monitoring that was greater. Most of it was around an order of magnitude type if it was greater. It was not much more than that. And once again, at least as I was doing initializing, you look at once we found our overestimates, first of all we found our underestimates and started taking into account the relative potencies of each of those and looking at that. We didn't see anything that suggested a consistent, you know, that we're missing that by an order by what would effect the assessment by an order of magnitude.

I know that's a very general. And I could probably give more details, but I'd have to go back and dig for those.

DR. PORTIER: That's fine. I'm not sure you haven't just answered your own question. But when we get to the discussion, I'll do that.

The other question is the frequency examples. I didn't get a feel for what's the magnitude of the monitored data in terms of, you know, a given region or a comparison to your model. Are we talking about 30 points, 3,000, 20 on an average? Give me some feel for the size of

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what you're looking at.

MR. COSTELLO: The very best monitoring that we might have would be a very small area from the NAQUA program, say, bi-weekly over two years. And that's not common. And on top of that, again, then you have to go deeper. Did that monitoring represent target monitoring for OPs? Was it in a high OP use area? Not usually.

DR. PORTIER: Thanks.

DR. KENDALL: Okay. I'm going to go ahead and close this clarification session. We will take a 15-minute break. When we return, we will have two public presentations as registered currently. And then we'll begin the questions at which time the Panel will have full opportunity to address additional issues and concerns.

Thank you.

[Break.]

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CERTIFICATE OF STENOTYPE REPORTER

I, Jane F. Hoffman, Stenotype Reporter, do hereby certify that the foregoing proceedings were reported by me in stenotypy, transcribed under my direction and are a verbatim record of the proceedings had.

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JANE F. HOFFMAN

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I-N-V-O-I-C-E** ****I-N-V-O-I-C-E****

JANE F. HOFFMAN

849 S. Irving Street

Arlington, VA 22204

SS#305-52-5988

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METHODS USED TO CONDUCT A PRELIMINARY CUMULATIVE RISK ASSESSMENT FOR ORGANOPHOSPHATE PESTICIDES

February 7, 2002

[8:30 a.m.]

SHERATON CRYSTAL CITY HOTEL
1800 Jefferson Davis Highway
Arlington, Virginia 22202

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PARTICIPANTS

FIFRA SAP Session Chair

Stephen Roberts, Ph.D.

Designated Federal Official

Ms. Olga Odiott

FIFRA Scientific Advisory Panel Members

Dr. Herbert Needleman, M.D.
Christopher J. Portier, Ph.D.
Stephen M. Roberts, Ph.D.
Mary Anna Thrall, D.V.M

FQPA Science Review Board Members

John Adgate, Ph.D.
William Brimijoin, Ph.D.
Richard Bull, Ph.D.
Rory Conolly, Sc.D.
Patrick Durkin, Ph.D.
Natalie Freeman, Ph.D.
Jean Harry, Ph.D.

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Dale Hattis, Ph.D.

Steven Herringa, Ph.D.

Ernest McConnell, D.V.M.

Peter MacDonald, D. Phil.

Nu-May Ruby Reed, Ph.D.

Lorenz Rhomberg, Ph.D.

Lauren Zeise, Ph.D.

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DR. ROBERTS: Good morning and welcome to the February 7 meeting of the FIFRA Scientific Advisory Panel. This is the third day in a consultation between the Panel and the Agency topic of cumulative risk assessment of organophosphate pesticides.

My name is Steve Roberts. It's my pleasure to serve as chair today. Before we the Panel for today's session, I'd to introduce our designated federal official for today's session, Ms. Olga Odiott. Good morning, Olga.

MS. ODIOTT: Good morning, Dr. Roberts. I want to welcome everybody to this important meeting of the of the FIFRA Scientific Advisory Panel. For the benefit of those who are you joining us today for the first time, this meeting is being conducted under the provisions of the Federal Advisory Committee Act. And all background materials and all documents related to these meetings are available from the Office of Pesticides Programs docket. And many of the materials are also available from the EPA web site. Your agenda lists the contact information for both places.

I would like to thank the Panel members for their commitment, for their contributions, and for their willingness to be with us during this process and to provide to the Agency the much appreciated feedback on these issues. And we're looking forward to very good

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discussions today. Thank, Dr. Roberts.

DR. ROBERTS: We have a new Panel member with us joining us today and there's possibility that there are some folks in the audience who have not been with us previously. So I think it would be useful for the Panel to introduce themselves. So let me ask the Panel, beginning on my far right, and then proceeding around the table clockwise, and for each member to state their affiliation, and the expertise they bring to today's discussion.

DR. BULL: I'm Dick Bull from Washington State University. My expertise is in toxicology.

DR. DURKIN: I'm Pat Durkin. I'm with Syracuse Environmental Research Associates. I do pesticide risk assessments for the USDA, and I've been involved with the EPA in risk assessment issues.

DR. HARRY: Jean Harry. National Institute of Environmental Health Sciences in North Carolina. My background expertise is in neurotoxicity.

DR. CONOLLY: Rory Conolly CIIT Centers for Health Research in Research Triangle Park, North Carolina. I'm toxicologist with a strong interest in mechanisms of toxicity that underlie the shape of the dose response curve and in the development of computer models

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of those mechanisms.

DR. RHOMBERG: I'm Laurez Rhomberg from Gradient Corporation, also, adjunct professor at the Harvard School of Public Health. And I'm interested in several aspects of quantitative modeling and risk assessment.

DR. MCCONNELL: I'm Gene McConnell. I'm veterinary pathologist and toxicologist from Raleigh, North Carolina, Toxpath, Incorporated. My are of expertise, as I said, was in comparative pathology, toxicology, particularly as they relate to bioassays done in experimental animals.

DR. KENDALL: I'm Ron Kendall. I'm a member of the Science Advisory Panel. I'm from Texas Tech University. I'm professor and chairman of the Department of the Environmental Toxicology. And I also direct the Institute of Environmental and Human Health at the university. Area of interest is toxicology and risk assessment.

DR. HATTIS: Hi. I'm Dale Hattis from Clark University. I do a fair amount of pharmacokinetic analysis and I focus on issues of variability and uncertainty in risk analyses in general.

DR. ADGATE: I'm John Adgate from the University of Minnesota School of Public Health. And my area of research interest and expertise is in exposure analysis and risk assessment methodology.

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DR. REED: Mu-May Ruby Reed from California Environmental Protection Agency, Department of Pesticide Regulation. I do pesticide risk assessment.

DR. FREEMAN: Natalie Freeman, Robert Wood Johnson Medical School and the Environmental and Occupational Health Sciences Institute in Piscatawy, New Jersey. I look at residential and children's exposure.

DR. MACDONALD: Peter MacDonald from Mathematics and Statistics at McMaster University in Canada. I have a general expertise in applied statistics and model fitting.

DR. HEERINGA: Steve Heeringa from the Institute for Social Research at the University of Michigan. I'm a biostatistican with specialization in epidemiology and population-based studies.

DR. ROBERTS: And I'm Steve Robert. I'm a professor at the University of Florida in the Colleges of Medicine and Veterinary Medicine. I'm also director of the Center for Environmental and Human Toxicology. My research interests are in mechanisms of toxicity, particularly pertaining to the liver and immune system and toxicokinetics. And I have a working interest in risk assessment.

I'm delighted that we have with us for our session again the Director of Office of Pesticide Programs, Ms. Marsha Mulkey.

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Good morning, Ms. Mulkey. Welcome. Did you have comments or would you like to address the Panel before we get started today?

MS. MULKEY: I will just a moment in the midst of this marathon -- I feel like I should offer some water bottles to the Panel -- to thank you just in case the latter part of the day doesn't offer that opportunity for this extraordinary session. And, of course, it's a culmination of a number of important and indeed critical sessions. But this is very important to us, to our work, to our credibility, to our service to the American people.

And I think, as many of you have noted, it also lays a groundwork for the work of many others, us and many others, as we go forward trying to understand ways of thinking about sources of exposure that are beyond a single chemical.

So we are very gratified by the value that has already been added. We look forward to today and to your report and to our continuing collaboration and consultation as we go forward. Thank you.

DR. ROBERTS: I would like to add that your input during our discussions over the last couple of days have been very valuable to the Panel. You've been a real asset to our discussions having you here with us.

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MS. MULKEY: That's very gracious. I feel it has been modest at best but thank you.

DR. ROBERTS: Margaret Stasikuwski of OPP, welcome this morning. Would you like to introduce the presenters and the scientists you have with us today?

MS. STASIKUWSKI: Yes, this morning's presentation will be made by Jeff Evans. And sitting to go my left is Dr. Randy Perfetti, also from our division, deputy director.

DR. ROBERTS: Dr. Perfetti, did you want to give us a recap? I think was originally on the schedule for the morning.

DR. PERFETTI: Only insofar as to again welcome the Panel and then give our sincere thanks for the previous two days and the sessions and the great advise you've given us. We really appreciate it.

Other than that, as Margaret said, Jeff Evans will be providing the presentation for the residential nonoccupational exposure part of this risk assessment. And this afternoon, Dr. Beth Evans and Dave Miller will provide the presentation for the risk characterization part of this assessment.

Thank you, Dr. Roberts.

DR. ROBERTS: Welcome, Mr. Evans. We'll be delighted to hear your presentation on the residential aspect of the cumulative risk

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assessment.

MR. EVANS: Thank you very much. This morning I would like to go over some aspects of the residential assessment. Today we would like to talk about, briefly, how we used our calendar-based model to address the temporal aspects of the OP uses, in particular, for the residential uses.

I should note that this approach is similar to the approach we took to the OP Case Study presented here not that many months ago it seems. And, also, I'd like to talk a little bit about the data we used in our cumulative assessment.

Not all of it, but certain aspects of it that are a little difficult for us to get our thoughts around and to discuss with the Panel use of distributions of our available data and, also, additional ways to incorporate survey data that's recently become available.

And, also, on Tuesday, there was a presentation suggesting the types of survey data that we will be getting in the future. And it's going to be up to us to decide how to use it. And we are really looking forward to your comments with respect to those possibilities.

This is something very new for us, the use of survey data and, also, using distributions to accompany a wide range of exposure variables. So this is our first stab. It is a beginning. As time goes on,

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we're going to have to get more sophisticated. So with that in mind, I can proceed to the next slide, please.

Now, just to lay out the use, I think anybody that does risk assessment, and particularly a large one like this, wrapping around all the uses is always difficult. The minute you think you have it, something else shows up. And it was also very difficult with the single chemical assessments still in progress, what was in, what was out, what were people going to support. And it's important for the Panel to know that the DDVP strip use that's presented in this assessment is no longer registered and that's going to change.

The pet uses for DDVP and Tetrachlorvinphos were not included in this preliminary assessment primarily because we're still, I think all of us, are really still working with the difficulty of modeling our relationship with pets, both the receptor and the source are constantly moving. And it's very difficult for us to model, I think, effectively without just having a screen that once loaded into a model would obviously swamp every other use.

So, also, perhaps in our conversations when we talk about the various aspects of exposure to maybe also think about what it would be like to model exposure to a pet wearing a collar or a pet that's been recently treated with a spray or a dip or some sort of top-spot

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treatment.

We have home lawns. And the major uses are bensulide, malathion, and trichlorfon. And some of those uses are no doubt going to change as time goes on. Golf course uses. There's nothing like finding out that something isn't registered by someone in a public meeting. And that's certainly been the case for some of our golf-course uses. And we heard you. So if you would limit your comments to other aspects rather than that, we'd appreciate it.

Home gardens. We have in the ornamental sense, we have acephate and disulfoton. And for the vegetables and other edible crops, we still have registrations of malathion.

We also looked at the specific public health sprays for mosquitos, fenthion and malathion. And then also the use of naled for black flies up in areas of Minnesota.

I've been told that your slides have got this very simple equation backwards that we use every day. We know what we're talking about here. And the only point of the slide is to, obviously, point out the fact that we're looking at inhalation exposure, dermal exposure and oral exposure through the mouthing behavior of young children. So that is somewhat separate from than the dietary and drinking water assessments. Now.

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For our age groups, we picked what we feel we have the best information with respect to the hand-to-mouth behavior. We have children in one-to-two years old and three to five. And those groups, the one-to-two-year-olds are 12 to 35 months. And the children three to five are 36 to 59. And, again, those are what we feel we have the best information for the hand-to-mouth behavior.

For the adults, we have all the other age groups. And I think that probably the big difference is the body weight surface area of children that has impact on the dermal exposure values. You know, they're shaped a little bit differently than we are. Obviously, their heads a little bit bigger or their trunks, arms may be a little shorter, things like that. And of course, as they get older, they become a little bit more like we are.

Again our focus in terms of having the number of files that went into the model, we focused on those children and adults. But in a sense we feel we really covered everybody.

Just briefly, we've conducted assessments for 12 distinct geographic regions. And we hope that we've reflected climate and pest pressure differences. In California, we just -- one region was put into two residential assessments. We may reevaluate that based on some of the comments we get from the public and regulator

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community.

It includes, we believe, are the remaining residential OPs that have significant uses and appropriate exposure data. And, again, I just want to say that we have not, at this point, included the pet products; but we intend to by the time this is all over.

You've all seen this map many, many times over. And I think it really does point out the facts that there are differences where we live and the climate and the climate influences the types of insects that bother us. I think our main goal, really, was to, first of all, keep it simple and also really try and figure out why people were using pesticides. And I'll get into a little bit of that later. And, of course, you've seen this many times over.

Here's an example of the Eastern Uplands. This was the area we used in our pilot. Now this time you get to see some of the pesticides that we addressed there. We really mainly address malathion or trichlorfon.

And on golf courses, acephate, bensulide, fenaminphos, malathion, and trichlorfon. Ornamentals, those three as I mentioned before, the home garden, malathion, and the indoor uses of the DDVP.

Now this matrix, I think, is really important for people to think in terms of the files. Think of each of those as a file for a region.

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What the slide does, also, is indicate the time in which something might not applied.

So for each and every one of these there is a AGX file that deals with all of the residue data, all the contact values, the pesticide application schedule, the percent of houses that are treated. All those things are boiled into those AGX files. And it is all those files that are then loaded into the program. And it, also, works with the DEEM.

And it's a lot of data to manage as you can possible imagine. There's a number of people that worked on this, Sheila Piper, Sherry Cenard, Jennifer Tylor, Dave Herd. There's an awful lot of work in managing these kinds of files. Seeing how the model goes, checking out your schedules, making sure things line up, there's obviously some things that we need to go back and fix. And we're in the process of doing that. But it was a lot of work to manage, and we really appreciate their efforts.

And so with those temporal aspects you do then see the efforts. The seasonal aspects in the middle there, the lines, that really is your garden uses, your lawn uses, public health happening in there. There's the use of the strips up there, your food, and this is your drinking water.

So this was really probably the strongest reason to do certainly

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something that's, you know, geographically and temporal-based because you really want to be able to line up the possible uses and concurrence.

So with that said, our road map today will talk a little bit about the distribution selected for some of these key scenarios, obviously, lawns and golf courses, public health, and the garden. I'll also go through a little bit of the characterization and our feeling on how we kind of addressed it. And then, also, with a future view towards the consideration of survey data that's going to be coming available to us.

Now for the lawn use information, as I've said many times before, we rely primarily on the National Home and Garden Pesticide Use Survey. It was done a number of years ago, but it still is probably the best data we have available now that is related to the use of pesticides in homes. And we're able to determine the percent of households using a given pesticide. And there are regional distinction.

Treated lawns, there's also regional differences in the percent of the population that hire lawn-care services. So this would be important for chemicals that may be are no longer registered for application by residents but may be applied by the LCOs so that we can address the post-application exposure to those.

And, also, lawn sizes. Having an idea of how large someone's

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lawn, which is a variable for assessing applicator exposure is difficult for us to determine, and it's going to continue to be a challenge for us.

And for that we selected a uniform distribution of 500 to 15,000 square feet, a third of an acre, which was the median for homes, you know, throughout the country. But I think it's important to note that that only considers the lot size minus the footprint, and it really doesn't consider other things such as decks and, of course, the fact that there are gardens and other things that we are also assuming people are spraying pesticides on.

But all of this started out with the label. That still is kind of the legal document. And that's where we find our site-pest relationships. This is where we get the application rates. And some of them are more descriptive than others. Sometimes they'll just have a list of thousands of sites and thousands of pests and not all pests get on all sites. So it's really important to find out what is going on in the various regions.

And a very good place to go is the State Cooperative Extension Services. A lot of really great stuff on line, a lot of information about the timing, when to look for pests, when to spray, also recommendations on the number of applications, when to look, when to scout. Also, sort of the landscape as far as what they're

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recommending. And obviously this ties into what people may use, what kind of information they'll get at garden centers.

And, of course, timing of applications is very important with respect to all the other aspects of potential exposures from other sources.

And I also looked at efficacy data that is also broken down into regions. Certain pests just don't occur in other areas. And that was an important consideration.

Now, for applicator exposure data, we have some pretty robust data from Outdoor Residential Exposure Task Force. This is addressing two major lawn application methods. Obviously, the push-type rotary spreader for granular formulations. That would be for bensulide and trichlorfon.

And then hose-end sprayers which are available as a ready to use where the concentrate is already mixed in and the person doesn't have to really handle the concentrate and the proportion is already calibrated.

And there is another one for those that still have the old fashion one where you have to add your own concentrate and make your own settings to determine how many gallons per thousand square feet of lawn area.

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The data also address a range of clothing, which include short-sleeved shirts, short pants, up to long-sleeve shirts and long pants.

Just by way of example or just for people to understand what the unit exposure is, it's really the amount of pesticide that gets on an individual as a result of an activity and how much they actually used. And this would be used in our simple algorithm unit, exposure times how much the individual applied and divided by body weight. Sometimes other metrics such as dermal absorption are used. But we had a dermal endpoint for these scenarios, so we didn't make any adjustments.

Now the hose-end sprayer, we have for this go-around anyway, we used uniform distribution. Obviously, there's quite a range there. And we've also done the same thing for the granular applicators.

Now as far as an activity pattern, this is pretty easy to understand. And it's also easy to measure. We selected a uniform distribution that would reflect a range of clothing to be worn because we did see some survey data that suggests clothing worn will change over the season. And the survey data were temporal based on formulation type. And we only have percents with respect to application type.

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So even though, normally, we would have -- in our typical screening level assessments we would use the short-sleeve shirt, short pants. And those we've already determined to be log normal. We would use a mean or some other statistic. But in this case, since we have in some case two application types which we may need market data for, we have a sense that as time changes, people are going to shed off a few clothes while they're making those applications.

We had a little bit of difficulty really trying to wrap my mind around that, so I took the flag of convenience of a uniform distribution. And I don't know if it really is going to make that much of a difference in this assessment. I think with a view towards the type of the data that we may be getting where you're going to actually have longitudinal survey information about what people wore while they made that application, then we can probably do a better job of developing distributions for those specific clothing types. But it will take many more files to load that into the model, so we want to make sure it's worth it.

Post-application becomes a little more difficult. It becomes more difficult to identify an activity pattern that is representative. Many years ago before this Panel some of you members may remember, we had an activity pattern or macro activity pattern as we would use in

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this case called "Jazzersize" which would be a series of exercises on the floor or on the lawn in which you can roll around and do exercises that put you in pretty good contact with the treated area but for a short period of time.

It was a very reproducible study. It gave you very uniform results. The standard deviation would be less than the mean which was, you know, really great from a person designing a study, but it was really difficult to communicate to people what it really meant.

In the meantime, we decided to look at other studies which were a little more understandable anyway. So we looked at two studies, one with a spray and one with a granular formulation of choreographed activities but more believable kind of activities. They used crawling in one sense to mimic adults that still weed the old-fashioned way and edge or dandelions and things like that but also to perhaps mimic a child crawling, also playing touch football, Frisbee, things like that.

But there were activities like sun bathing on a blanket, which really are not all that intensive but perhaps maybe more representative of a picnic at a park or typical activities with the family on the lawn.

For children we took a look at a study that was done really as someone's dissertation. But it was a very interesting one that they used a nontoxic substance that's used to whiten shirts, other types of

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clothing, safe. And you read with a short of a UV technology that measures florescence. And these kids were really nonscripted. They were just given toys and a half hour to just mess around, really, on a treated lawn. And that really seemed like a really valuable thing to also include with the children's transfer co-efficients.

So here they are for addressing post-application exposure. I should, also, add that we use the up to two hours and up to three hours -- well, two hours for adults and up to three and a half hours for children. The two hour value if the Exposure Factors Handbook. And that's actually time on a lawn.

There is a similar value for children, but with concerns about them being other places, other lawns, at the park, at the school, other places, I bumped it up to the three and a half hours so for time outdoors for that age group. But again that was a cumulative distribution based on the statistics and the Exposure Factors Handbook.

The adult transfer co-efficients range from 2,000 to 13,000. We used a uniform distribution. Again, you know, these are representative. Is it really what people do? Is it really something that's deserving of a log normal distribution? I'll leave that to the Panel.

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And, also, for the children, you know, we're combining kids transfer co-efficients scaled down from the adults and, also, the inclusion of the nonscripted activities. You know, these may look like small numbers to most people, but they're fairly descent compared to what we've seen.

For the lawns, we have transferable residues. Often these studies are done in a number of locations. In this particular assessment, some we have a number of sites that are appropriate for the geographic regions. So we did a range of the distributions, uniform distributions, for values for each day that could include as soon as dry up to 8 hours, 12 hours after the application is made.

It, also, includes such factors as watering-in or not watering-in. And it also includes days that there's also the potential for rainfall.

And nondietary ingestion is even harder. Again, applying, that's pretty easy to measure. That's pretty easy to understand. What do we do on lawns? That becomes a little more difficult. And then what do kids do while on they're on lawns, hand-to-mouth behavior, it becomes even more elusive and difficult for us to address. It's very important pathway, obviously.

So we looked at a number of things. We looked at, first of all, frequency, which is based on observational data. But that really

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doesn't tell us very much about how much gets on their hands. So we had to think about how much gets on hands by looking at some data that was done on behalf of ORD for this particular aspect. Also, how much comes off once it's on the hands.

Now for the hand-to-mouth frequency of events we continue to rely on Reed. And this includes 20 kids in day-care and 10 at home. I selected a uniform distribution of .4. I guess one can obviously say 1 to 26 would be a little bit better. But in that study, the mean was nine and a half; median was eight and a half; and the 90th percentile was 20.

Some issues for consideration is the differences in hand-to-mouth behavior that may happen when we're indoors or outdoors and, also, the differences between active and quite play. I know this Panel has touched on this before. And just to go even further into discussion, some recent information that Dr. Freeman has looked at. Again, a small subset of children, but there's differences between the indoor and outdoor frequencies of hand-to-mouth events.

Now, if their mouthing, the hands are wet. So we wanted to make sure that we accounted for perhaps the increased transfer to the hands if the hands are wet. There was a comparison of wet-hand efficiency and dry-hand efficiency with three surrogate compounds.

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And it was very helpful that these data had a very similar transfer efficiency as the available data that we have.

The turf-transferral residue data that we have measurements of. The range there was .9 to 3 percent for two chemicals. And we noticed that the chlorpyrifos was much, but it showed the same percent transfer.

So we would take the turf-transferable residue and increase it one and a half to three times higher to account for the hand-to-mouth behavior.

Now once the hand goes in, how much comes off. And that I think that's also fairly difficult to look at. One study by David Camann showed 50-percent removal by saliva-wetted sponges. And this struck us a sort of a vigorous wiping method. So we used that as our high value.

There was, also, another study in which people grabbed test tubes that were spiked with a know concentration and then a more passive sort of removal technique of hand wash with ethanol and with water was also used and they recovered 20 to 40 percent of that which is spiked on the hands.

And then, also, since outdoor play may also include, you know, residues and grass stains and smashing into the soil, you're going to

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have kind of gamish of soil and residues. And so took a look at soil-removal data in which people had a certain amount of the soil on their hands and they measured how much was removed from various mouthings events, thumb sucking and the like. So that's kind of the basis of the removal efficiency for the hand-to-mouth.

Getting into golf, that's a little bit easier. But for the percent of individuals, we looked at a study that has statistics on the percent of people that play golf also the number of hours playing golf. I mean I pretty much left it for four, unless there was some indication that only greens were treated and then two to four hours. I didn't really mess around with that too much.

The percent of golf courses that were actually applying those pesticides is available, you know, in proprietary-type data available in Doane very recent. And this is also an activity pattern that is pretty to understand. You can just put people in dosimeters and go out and measure after they played golf on a treated golf course. That's a lot more easier to understand than what kids do and adults do when they're playing on lawns.

Although with it being that easy, you'd think there'd be a little more data. But we were able to get round 10 transfer co-efficients that addressed the playing golf, walking around, using a cart. There

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really wasn't that much difference. Typically, fairways and the greens are treated. So if I guess if you're a duffer, you have less exposure if that helps anyone when they're having a bad day on the course. Again, we use chemical-specific turf-residue data.

Public health gets back into the difficult. And that is, you know, how much gets on the lawn from these applications. In the single-chemical assessments, the reviewers relied on information for how much actually deposits on to a lawn as a percent of the application rate. And that ranges considerably, depending on ground equipment, whether or not it's being applied by aircraft, you know, nozzle size, all those kinds of things, how much is evaporating. So we used that just to get a concentration to the lawns.

And once we had our deposition on the lawns, then we pretty much addressed it the same way we would a lawn chemical with the same transfer co-efficients, same hand-to-mouth values that we used and I just discussed previously.

To determine the number of population, we looked at statistics suggested how many people have lawns. When these things are applied, we spoke to people responsible for making these applications. And, obviously, part of the comment period we are certainly expecting a lot more information: Where, when, how, and why these things are

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being used.

Now garden, again, this is pretty easy to understand. Application, and we have a number of studies to address the uses. We have a chemical-specific. For disulfoton we used a shaker can and this is just a systemic insecticide so you apply it to soil, rake it in, and it's great for roses and those types of things. We also have used the garden duster for vegetable gardens and also small tank sprayers for gardens and spraying trees and those types of things.

It has the same issues with the types of clothing. You start with long-sleeve shirt and long pants and as the season begins. And as summer progresses, you find yourself wearing less and less. But, again, to address that, we simply left it with the uniform distribution for this time.

The area treated for gardens, this was a fairly difficult to determine. So we simply used a median home area and assumed a certain perimeter. But in this case, we made sure that whatever the area that was treated, everything was treated. We didn't really make any distinctions there.

Vegetable gardens there was data suggesting it was log normal. There was a survey conducted by the Outdoor Residential Exposure Task Force with the Gallup Survey people. Vegetable gardens are a

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little bit easier for people to understand, how big it is versus their lawns which is obviously complicated by the structures and green spaces and shrubs and trees and those sorts of things. And we went ahead and used a log normal for this statistic of garden sizes.

Now post-application dermal exposure, that, again is a pretty easy thing for us to understand in the agriculture region anyway. Someone is going to pick apples all day; that's great. The problem is when you get into home garden there's a certain number of crops that people have. There's a number -- they'll have trees. They'll have strawberries. They have grapes.

So, you know, with that, knowing there's so many difficulties, we just simply selected a uniform distribution that would represent a number of activities. And it includes hoeing and weeding, harvesting, staking tomatoes, picking apples, those kinds of things.

The duration of garden activities, survey data suggested five minutes to an hour, a couple days a week. But we went ahead and set it for every day.

And we also have a chemical- and regional-specific residue data which would most importantly impact the dissipation and how long it's actually in someone's garden.

For inhalation, for the indoor use of DDVP, we have standard

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work horse, unit exposure from the pesticides handlers exposure data base. We just simply used the uniform range there.

For post-application inhalation exposure for adults and children, we had the pest strip data. But then, again, that use is no long registered. Crack and crevice from Gold. These aren't the most recent studies in the world, but they are what we have available to do this assessment with.

The duration of time spent indoors and breathing rates, we used readily available statistics in the Exposure Factors Handbook, obviously, up to 24 hours. And we used rest to moderate breathing rates.

Just simply, we discuss the majority of the data that we used for the major uses in this assessment. For example, we have the lawn residue data for all the compounds, and we made regional adjustments where feasible. We addressed a wide varieties of activity patterns. Some are more straight forward. Application, that's pretty easy. But it gets more difficult as you get into post-application in lawns, and the hand-to-mouth is still proved to be difficult for us to address.

And if it wasn't clear in my presentation, I'll simply say now that we tended to use uniform distributions our flag of convenience when we were presented with scenarios that had a lot of confounding

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variables and it was a little bit difficult for us to address.

Now to characterize, again, for us the hose-end data, there's a lot of replicates. And we have the mix-your-own and ready-to-use. So, you know, we think that's pretty realistic with some further thought, you know, on developing distributions of the types of clothing that we have indicated by the survey or, you know, some other way to really handle that. You know, perhaps determine what percent of people are applying understand a certain clothing scenario and develop distributions for that.

For the push granular, 30 replicates of, again, high confidence. And these studies were performed by people that, you know, they don't work for chemical companies. These are just regular people that belong to garden clubs. So those type of people are recruited and they just went and did what they did without any coaching.

The lawn size, you know, is fairly reasonable considering the equipment used. It might be a slight underestimate in areas that have larger lawns. You really would be a deal breaker wouldn't have a huge impact on the assessment to make that variable larger.

For post-application on lawns, we do have activities that are representative. But, you know, the distributions may really reflect the study design rather than the actual activities. We are really more

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interested in if we had a realm of activities that are representative or that can at least cover some of the other things, say, if you're just walking across the lawn. We were fairly confident that these cover things that are less than that. And, again, it seems like a reasonable suite of activities that people might be doing.

For the children, again, we have a combination of scripted activities. And then also there are unscripted activities, just kids being kids hanging out on the lawn. So we feel pretty good about that.

We have turf-transferrable residues. And it reflects a range of high values immediately after. But it also, you know, in the real world, it does rain and that's also a possibility on the second or third day or so after application.

The turf-residue hand-to-mouth, it's based on surrogate data; so there is some uncertainty there. It would really be a whole lot nicer to have chemical-specific data on that.

The frequency is, you know, it may be an overestimate; it may not. But, again, these are based on kids indoors, so there may be differences with kids outside.

Duration on lawn, for kids, again, we bumped up the value to beyond the times they spent on lawn. If the lawn was treated, you were reentering. So that's an aspect of this assessment.

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For public health, it's a distribution of -- the uniform distribution of aerial ground equipment values. The percent of applications made by ground equipment and aerial. The population exposed to the public health we limited it to those having lawns and, you know, those having kids.

For the home gardens, you know the applicators, again, high confidence. Again real people making applications. The same deal with the home gardener and the granular application as well.

The garden, that area treated was pretty descent. We thought a pretty decent survey data. And, also, an outfit that's been collecting this kind of data for a long time.

Vegetables, you know, certainly a well-studied variable for individual crops. It gets a little complicated when you realize that in gardens people don't just have one thing. And it's a pretty high available exposure scenario.

Frequency applications. For frequency for the applications, again, you know, we used survey data. That's based on generic insecticides and it's not chemical-specific.

The post-application in the garden. We're assuming all the plants are treated. What it would also be reasonable to assume that you're only going to treat certain crops, certain types of year, certain

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pests, that sort of thing.

The residues, we're pretty confident with those. Again, they're regional chemical-specific.

The indoor air is chemical-specific.

The duration, breathing rates, those sorts of things are pretty well-established factors in the Exposure Factors Handbook.

The population exposed, for the pest strips we based it on the use of all pests strips including those sort of hideous sticky strips that just catch flies. And the use patterns for all scenarios were based on the percent of households that were actually using that particular pesticide.

So, you know, now we're going to get into survey data. And that, also, presents, you know, a number of possibilities. So we're going to, first of all, look at how, you know, how we put people together in our assessment. And then, also, just by way of example, what one might do with survey data. And also to discuss a little bit about the upcoming pest use survey data that was discussed just this past Tuesday.

So survey data, you know, primarily to look at what they would like to call "human activity patterns." And these are macro activity patterns. This is, very simply, in the garden. Obviously, that's a

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macro activity pattern. And the types of transfer co-efficients are macro activity based. You know, driving to work, time at school, those sorts of things, you can track an individual during the day.

But our basic approach for this assessment was kind of an independence/dependence. First of all, we identified households based on their reported use of an OP for a given scenario and relied pretty heavily on the National Home and Garden Pesticide Use Survey. For example, 6 percent of households in Region 5 used lawn chemical A.

Then we identify, from the Exposure Factors Handbook, how much times do people spend on lawns. And those values were taken from surveys such as the National Human Activity Pattern Survey, a pretty large cohort survey. Not necessarily addressing the use of pesticides. I think it was primarily designed for addressing secondhand smoke. But, again, it was useful as far as where people spend their time.

So in our simple step-wise process, you have your food exposure calculated from DEEM. And then you would select the residential treatments for an individual on a given day; and this, of course, is regional-specific. You know, where the pesticides applied are in or around the home, and if so, what are the treatments, what are the frequencies.

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So that's why it was really important that we had that early matrix be the windows of exposure possibilities. So for each day, as it works its way through the year for each individual, it is going to go does this house, a certain percent of houses are using a pesticide. And so it will pick statistics from those libraries that have all those exposure values for that scenario. And you'll just keep repeating this step until you've addressed all the uses that are available, again, going back to that large matrix.

So for this assessment, co-occurrence is driven just by random probabilities. So, again, largely the percent of the houses being treated. So 6-percent lawn use, 10-percent crack use will give you a certain percent that has both. And, again, we just want to stress, whatever household is selected, the probability of -- you know, you're going on that lawn and you are in that house. So we don't really mess round with, at this point anyway, of looking at the people who responded that they didn't go on the lawn. But there is data that suggests that people just don't exactly go running right out there. But for this assessment, if you have a lawn and if you have a lawn chemical applied to your house, you're going out there.

So now this very nice new web site that's available to us all, the Consolidated Human Activity Data Base. There's a lot of survey data

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that's suddenly available to us all. And it's a compilation of lot of human activity pattern surveys. So you can look at the questionnaires and you can look at the responses. So there's now the possibility that you can develop a daily activity patterns for individuals. You can kind of track their life in a given day.

But, again, these surveys are mostly cross-sectional and they're not longitudinal. We do expect a pesticide use longitudinal survey one of these days from the regulated community.

And with all apologies to Drs. Zartarian, Xue, and Ozkaynak, I just pinched a couple of their slides that suggest, just by way of discussion, a strawman, if you will, and how one could approach using survey data.

And this would be that you could get individuals and track their time. So you could actually identify how much time they spent in a given room. And this may be important for the crack and crevice uses. It could be important for other uses of pest strips if it's simply being used in a garage or something like that. You know, how much time did they spend on the lawn. Those sorts of things. So you have an accounting for all the time they spent in the day.

And then possibly you could assemble diaries that would simulate a person. You could use a number of surveys to address what

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they might do seasonally, what they might do on the weekends. And I would imagine that we would have to also somehow tie it to the type of person that we also selected from the CSFII. So, again, this is just the kind of thing that's going to be available for us to address perhaps this assessment, perhaps more likely future assessments.

You know, finally, the Residential Exposure Joint Venture is collecting data longitudinal in nature that actually address the application of pesticides in and around the household. We're going to have information on when and where the applications of specific active ingredients are made. We're going find out whether or not multiple applications are made.

In our scenario, it might be very likely that, based on the application treatment type, you could treat your garden and your ornamentals in one day. It would be nice to have survey data that suggested that that is exactly what people did.

I think what's really important is we also have what they wore while they were making those applications. So it would make our management of those log normal distributions of clothing scenarios a little more of a fit for the seasonal aspects. And it's also going to discuss the demographic information. Do they have children? A lot of people who garden are a little bit older, the kids are gone, and they

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need something to do, so that isn't necessarily figured into this assessment. But that might be something that may be of importance in future assessments.

So with that, I'll conclude my presentation and would be happy to answer any questions of clarification.

DR. ROBERTS: Thank you, Mr. Evans. Are there any questions from Panel members clarifying from your presentation or your methodology?

DR. BULL: This is probably in here, but I was not able to find it nor did I catch it out of your presentation.

You got these transfer co-efficients in turf-transferable residues. Transfer efficiencies is kind of different unities that you go after this. But I didn't see -- is, say, dermal absorption included in one of those? I saw no mention of the absorption rates.

MR. EVANS: Yeah, a lot of times we do, obviously. But in this case, our endpoint is from a dermal study; so we have made no adjustment.

DR. BULL: But how do you relate that to the amount that's absorbed from the area that's exposed?

MR. EVANS: Do I have that data?

DR. BULL: That's what I'm trying to ask.

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MR. EVANS: Well, the endpoint or the effect is based on a dermal application to the laboratory animals.

DR. BULL: I see. Okay.

MR. EVANS: But a lot of times we have endpoints from oral studies that we do.

DR. BULL: So it's purely empirical.

DR. ROBERTS: Dr. McConnell.

DR. MCCONNELL: Yeah, a quick question. Are these different procedures you're described to us today written out in SOP form, and are they available?

MR. EVANS: The --

DR. MCCONNELL: How you --

MR. EVANS: How do we calculate all those things? Those are, first of all, our standard operating procedures for residential exposure.

DR. MCCONNELL: For how you collect this material, are those in form of a standard operating procedure?

MR. EVANS: We have a standard operating procedure for how to make the calculations. And we also have guidelines on how to conduct those studies to get those --

DR. MCCONNELL: That's what I'm more interested in.

MR. EVANS: Yeah, very much so.

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DR. MCCONNELL: Okay.

MR. EVANS: I believe some members of this Panel actually may have been on a guideline-related subject.

DR. MCCONNELL: I recall the guidelines for post-application.

MR. EVANS: Yes.

DR. MCCONNELL: But that's the only one I recall. There are guidelines for other things.

MR. EVANS: Right. Not this Panel, but previous panels have addressed the application aspects as well.

DR. ROBERTS: Dr. Durkin then Dr. MacDonald.

DR. DURKIN: I see that you cover the public health use of chemicals in that sort of indirect sorts of exposure. What I didn't see -- and I may have missed it -- did you address pesticide exposures to populations that live close to or adjacent to agricultural areas? You know, cotton fields, tobacco --

MR. EVANS: No, we did not.

DR. DURKIN: Okay.

DR. MCCONNELL: Isn't that your spray drift?

DR. ROBERTS: I'm sorry. Dr. McConnell.

MR. EVANS: I believe you're referring to spray drift.

DR. DURKIN: Drift from agriculture.

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MR. EVANS: Right.

DR. MCCONNELL: Excuse me for interrupting, but they have guidelines on how to measure spray drift.

DR. DURKIN: No, I'm not talking about how you measure drift; I'm talking about those populations who their residence is close to an agricultural area where pesticides may be applied over the course of the season, so folks living next to tobacco fields, cotton fields. I know they have methods to get at the drift. I wanted to find out was that drift factored into the risk assessment.

MR. EVANS: No.

DR. ROBERTS: Before we get to Dr. MacDonald's question, let me remind the Panel that our proceedings are being audiotaped; and it will be very use for someone listening to the tape if they can sort of make sense in terms of who's commenting. So if I haven't just called on you or it's not otherwise obvious who's making the comment, I'd appreciate if you could just briefly state your name before we dive in. And that way, we'll be able to sort it out later on.

Dr. MacDonald then Dr. Bull.

DR. MACDONALD: Just a couple of questions. Very clear presentation. But 4-19, Lawn Applicator Exposure Data, you said you selected a uniform distribution. It's not clear what this is a uniform

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distribution for. What's the variable being considered there?

MR. EVANS: You unit exposure is the metric that describes how much gets on you on a per AI basis on the amount of AI used.

DR. MACDONALD: And, also, considering that you've accounted for the amount of clothing worn, but do you also consider what happens to the clothing afterwards? They'll come into the house. They'll sit on furniture. It will be handle by someone doing the laundry. So I don't think wearing clothing is necessarily the end of it.

MR. EVANS: Yeah, I mean, that's true. There's a number of -- I mean pesticides migrate. That we do know. But how do we actually model that is really difficult. We're really focusing right now on what we sort of think of as "big ticket items," the actual handling of the concentrate. That's certainly one aspect.

Probably over the course of -- at least my experience in this is that, you know, our guidelines are not -- you know, they're conditional. So we've always had a sort of step-wise view of things. The old days of agricultural applicators were okay, you know, in even probably home garden people were. But as time goes on, we get more sophisticated; we ask more questions.

For the residential, we're beginning to become comfortable with the application or beginning to come a little more uncomfortable with

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post-application. But some of the more elusive and arguably smaller concentrations of pesticides that's still on the horizon for us to consider.

DR. ROBERTS: Dr. Bull, do you have a questions Mr. Evans?

DR. BULL: Just a quick. The past question about public health spraying brought up a question in my mind. That at least in some geographical areas lawns would not be sprayed for that purpose. I don't know how wide sprayed it is that you spray residential areas in other parts of the country. But where I am, it's most likely the guy that's got his kids on the boat running up and down the Yakima River that's going to be exposed rather than someone being exposed on the lawn.

I'm a little bit worried about the issue of identifying lawns as the major determinate of exposure for public health spraying. It actually might be drinking water exposure in some cases because that's the drinking water source, too. so I'm questioning that a little.

MR. EVANS: Right. Again, just thinking how we approach some of these things. There's an infinite number of exposure scenarios. But if it is applied to one's lawn and then goes out and performs activities, that's a pretty good hit. I think a random flyby is, you know, in my view, a little less of a potential.

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DR. BULL: No, it's deliberately done in specific areas, not in lawns; that's what I'm worried about. Along the river, for example.

MR. EVANS: Right. I mean you're suggesting more of a refinement of our assumptions.

DR. BULL: Yeah. It may be true for the nation as a whole; but certainly in the area I'm in, it would not be sprayed over residential areas.

MR. EVANS: Right. I think I could say, fortunately, that none of these are used from a public health perspective in Manachi, Yakima area, the Washington area

DR. BULL: Tri-city area, yes.

MR. EVANS: Yeah. At least to my knowledge, these are used more in Florida, East Coast, you know, places like that down in the south. At least these pesticides are used in this respect.

DR. ROBERTS: Dr. McConnell.

DR. MCCONNELL: I just wanted to state that Dick lives in an unusual area. My neighbor, for instance, he subscribes to one of these outfits. And seven times a year, they're putting something on his yard. And, in fact, they put a little sign up to let you know when you've been there so that you don't let your pet run over on their yard. I mean in the neighbor I live, this is about every second or third yard has one

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ever these signs in it, seven times a year. So this is not unusual at all.

DR. BULL: Not unusual in North Carolina.

DR. ROBERTS: Dr. Adgate.

DR. ADGATE: I just want to make sure I've got this straight. And as I've been thinking about this, and it's a very good presentation.

The question I have: This model as we look at this and try to fit all the pieces together is essentially cross-sectional. Right? You can -- I'm worrying about you got a bunch of different scenarios and how is it constrained so if you have a lawn you're more or less likely to have a garden, I would assume. And there's certain things fit together and certain things you wouldn't as you look at this. And I'm wondering how the model deals with that particular issue.

MR. EVANS: Yeah. We deal with it totally randomly at this point. So the percent of houses that use this pesticide on the lawn, you know, you're going to have a certain odds there. And just totally independently, you're going to have a garden.

DR. ADGATE: So there's no sort of correlation made --

MR. EVANS: Right. That's why the type of data that's bandied about every once in a while about the longitudinal, what people actually do, that would really be the key to really identify that co-occurrence. Right now, it's just kind of a roll of the dice.

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DR. ROBERTS: Any more question before we move to public comment? If not, thank you very much, Mr. Evans, for a very clear presentation.

We have two individuals who've indicated an interest in addressing the Panel on this subject. One is Dr. Jeffrey Driver, from infosciencs.com. Dr. Driver. Welcome. Can you introduce yourself for the record?

DR. DRIVER: Good morning again. I'm Jeffrey Driver with infoscientific.com. I'm making some comments this morning on behalf of the Implementation Working Group, but also beneath that Residential Exposure Joint Venture, the group conducting the survey that Jeff mentioned, the temporal survey; also a group called Sound Science Policy Alliance that represents some of the OP manufactures.

A very good job, Jeff. And I have a theory that some of our hair loss may be associated with this cumulative risk assessment.

The comments that I want to make this morning really reflect my position and I think the position that I think many of us share. If you want to make comments, you should also be part of the solution. So some of the issues and next steps that I'll be suggesting are things that EPA has already recognized, is addressing, and also other stakeholders are addressing.

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Some of the issues, I think, also as I'll point out, are work in progress or things that we need to do in the future. But I'll try to distinguish those.

I think, as Jeff's given you an appropriate impression of the complexity of residential exposure analysis. It's truly multi-route, multi-pathway issues of interdependence or dependence versus independence rather, conditional probabilities. There's a lot that we don't understand. We're ostensively trying to simulate human behavior across time. So we're all sort of residential experts in some sense and we all have an appreciation for the dynamic of that.

So you know, again, as Jeff said, we try to keep it simple but with the caveat that all models should be as simple as possible but no simpler. So I think that's kind of the state of the science and the challenge that we face.

What I'm going to do quickly is just give you a quick overview of some of the issues, next steps. First under the rubric model input and output quality assurance review. As Jeff mentioned, some of these issues have already been recognized. So I won't belabor some of it.

Label application rates, just checking our accounting system, making sure things are correct. Product-use scenarios, Jeff mentioned there's kind of an ongoing understanding of what's registered and

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what's not. I give an example of a scenario that is not registered as we understand it, but it is included.

Exposure duration corrections at some of the upper percentiles. It appears that we have greater than 24 hours per day for some individuals. That is, they might be spending 24 hours inside the home maybe inhaling DDVP and then they go outside and spend a couple hours on their lawn. That's another quality occurrence check.

The evaluation of the impact of alternatives of uniforms distributions under the guise of sensitivity, you know, as Jeff has requested the Panel's advice in this regard, I think we do have some opportunities to explore distributions other than uniform, which, of course, assumes that every value within that range as an equal likelihood of occurring. Most data sets have some shape and some inferred probability at the upper and lower tails, typically, of occurrence.

So, you know there are some examples that I mention there. The hand-to-mouth, I'm particularly interested in. And I'm hoping Natalie and others can give us some advice there. We mentioned the indoor versus outdoor differences.

The unit exposure distribution as Jeff indicated, we have some fairly good data sets for those. This is getting an applicator exposures

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for different methods of application, clothing configurations. I think that's a ripe opportunity there.

We, also, recommend that EPA and other groups for that matter, too, really investigate this temporal product use and single-day co-occurrence prediction. As Jeff mentioned, you know, what we have is a predictive algorithms that allow us to do this. But I very it's very important that we have explicit understanding. I challenge us to do this.

We need to understand how the algorithm is structured and is working. And very importantly, what's the interpretation quality of the underlying data. For example, Jeff mentioned this generic sort of general market share values by scenario. What's the percent of uses versus non-users in the U.S. that use lawn-care products.

But underneath that, there are other conditional probabilities that John Adgate was sort of getting at. For example within, you know, this general market share, what's the relative market share of using one OP versus another. If you have multiple OP products that could be used for the same scenario, say, to treat the lawn, which one do you pick within that group?

There are other examples of conditional probabilities. You know, if you have a lawn, is there an associated likelihood that you

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also have a garden, a vegetable garden.

The REJV survey and other survey data I think allow us to get at some of those conditional probabilities that otherwise we have to kind of piece together as a patchwork quilt from various data sets.

Timing and frequency of application by region. I think as Jeff pointed out, why do people use pesticides? That's kind of where we have to start. You know, you're managing pest population dynamics which, of course, can change from year to year. But, again, temporal survey information, I would submit, is what we really need to understand this in a realistic way.

Explanation of the peak exposures observed in graphical outputs. I'm sure you all looked at these three 65-day plots of different percentiles. And, of course, those each day might be a different person. You know, it's a 99.9-, 95-percent person represented at that percentile. And sometimes you'll see peaks and features in these plot schemes.

Well, understanding what's driving those peak exposures, what's the underlying demographic of that individual, their activity pattern, the scenarios involved that are driving their residential assessment; you got to really investigate those peak exposures. Obviously, they have important regulatory implications.

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That kind of leads to the next theme of contribution sensitivity and uncertainty analyses. And I think, again, under the guise of sound science, transparency, stakeholder involvement, we have an obligation to pursue this, to give our risk managers the best information and advice we can.

One of the things that concerns us is I think EPA, and we have an obligation as well as others of us who are interested in, evaluating the biological plausibility and statistical representativeness of some of these upper percentile values. Are there people who are spending more than 24 hours in the day? Are they consuming, you know, if you look at the dietary, same issues really apply. Are they consuming plausible amounts of foods? So are the combinations of various input values resulting in simulated people who are understandable and within the realm of reality.

Meaningful drill down. As I implied with the previous slide, contribution analyses. Trying to figure out what's driving these peak values or for any given person or population strata, what chemicals are contributing, sources, scenarios, lawn care, garden, et cetera, even which specific products they're using. Which specific OP product they're presumably using, pathways and routes.

This type of uncertainty contribution sensitivity and uncertainty

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analysis, I would submit, is really needed prior to determination of an appropriate percentile regulation. I mean, what confidence do you have at what percentile that you're looking at. I think you've got to establish that before you can really decide on a percentile regulation.

I'd also submit that you need these analyses, again, for meaningful risk management. If you're going to do mitigation, you really have to decide what you're mitigating. You know, what products are involved, what scenarios are involved. Particularly with the residential, you know, again, it's a variety of inputs that create this exposure estimate. So we've got to be able to drill down. We can't just look at methamidophos equivalents. We have to drill down to figure out if mitigation is necessary and what it would be.

An issue that has been raised previously that I think deserves careful consideration is what's the most appropriate exposure metric. We're looking at route-specific exposures right now, external exposures, and comparing them to methamidophos benchmark doses and going through relative potency factors. That's fine.

Another alternative altogether is to look toxic equivalent dose in terms of total absorbed dose. With the current situation, we're looking at route-specific external exposure and comparing it to some bench route specific benchmark dose, should we be looking daily

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exposure metrics or should we be looking at some time averaging, moving average metric.

And I think that's if you look at the underlying kinetics and I think the Panel can hopefully give us guidance in this regard, what should we be exploring in that situation. I think there's a relevant opportunity to look at some type of moving average here.

Finally, it's important, you know, for all of us to review and participate in and also review the upcoming revised version of the cumulative risk assessment.

Thank you very much.

DR. ROBERTS: Thank you. Are there any questions for Dr. Driver? I don't see any, so thank you very much.

The second individual who's requested the opportunity to address the panel is Dr. Judith Schreiber from the New York State Office of the Attorney General.

Welcome, Dr. Schreiber, and could you, also, introduce yourself for the record.

DR. SCHREIBER: Certainly. Good morning. Nice to see you again. I'm Dr. Judy Schreiber, senior public health scientist with the New York State Office of the Attorney General.

Again, a very commendable effort by EPA and certainly a very

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clear presentation. These are clarifications and questions, observations I had during the presentation. My office will be submitting formal comments to the EPA on the cumulative risks.

The first question I had was with the regard to the pet products. It was mention, I believe, that that has not yet been assess but the intention is that EPA will be assessing exposure from use on pet products. Particularly, I'm concerned about potential children's exposure to hand-to-mouth activities in playing with their pets.

How does the EPA intend to assess this, and will the public have an opportunity to comment on that portion of the assessment prior to the document becoming final? That's one question I have. Should I just continue and --

DR. ROBERTS: Sure. Would you, please.

DR. SCHREIBER: Okay. Thank you.

Another question that came up. And I'm taking these in order of the presentation that the EPA made. What about inhalation exposures during the scenario of children playing on lawns? There was quite a bit of discussion about the rolling around and dermal absorption and clothing contamination that sort of thing. I think that's very good.

But I believe there could certainly be a possibility that the child might, also, inhale some of the material as they're rolling around with

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their nose to the dirt in the grass and so for the. So I think that really needs to be assessed, at least a ballpark assessment of whether that's a significant contributor.

Also, ingestion of both soil and grass by young children is a common phenomenon. I know my kids were little they definitely dug around in the soil and often tried to put it in their mouths. Was that assessed with regard to the rolling-on-the-lawn scenario?

Another comment about the golf scenario which I thought was quite interesting. I've read a number of recent reports in the popular press in the popular press about increasing numbers of children playing golf. Tiger Woods has inspired a whole generation of kids to really like golf and go out there. And there's been a lot, I understand from my golfing colleagues, in golfing magazines they're talking about the increasing number of children and, also, the effort to try to include more children in playing golf.

So has there been any effort to assess the percentage of the population of children that might be actually on golf courses and potentially exposed to government treatment chemicals?

One particular area that I didn't hear and maybe I missed. It's possible it was included in another section. School exposures to pesticides, I didn't hear that mentioned at all; and I think that's

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potentially a very large area. I know certainly in New York State we now have a pesticide notification regulation where schools that treat their indoor environments and their outdoor fields, soccer fields, football fields and so forth, have to notify parents. There's been a lot of concern from parents about potential exposures in school settings. And I didn't hear anything about that. But I think there probably are some data that are available that talk about the percentage of schools that treat either indoors or outdoors with OPs.

And I think it's a great concern to parents and especially for young children, are they being exposed to OPs in their school environments that could cause them to have undue exposures, especially for young children, but also for sexually maturing teenagers, I think that's probably equally an area of concern. And I didn't hear that discussed.

Two final points. One, although, I certainly understand the need for these mathematical manipulations, they're also a little bit troubling in some regards. For example, it was mentioned that -- and it might have only been an example but let me just carry it through.

For instance, 6 percent of homes and lawns are treated in a particular geographical location in the country. While that may be true and one can figure out what the overall average population

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exposure could be if 6 percent of the lawns are treated. But if you are a child playing on that lawn, your exposure probability for that child is a hundred percent. That child is definitely being exposed. And I would like to see an analysis that in terms of the children who actually being exposed, how close is that child's estimated exposure to the point of departure for cholinesterase inhibition? How close is that exposure to the point of departure for neurotoxicity and neurodevelopmental effects. I think that's something that really needs to be looked at.

You know, if we take this room of people and only one of is exposed and we divide by the number of people in this room, well, then that number is very low. But if you're that one person who's exposed, you could be exposed to a very high level that can actually cause health effects. And I think that's a very serious oversight. At least in my reading of the documents, I haven't seen anything looking at that.

And then finally the public health uses. In New York State we have had experience using -- you have to forgive. I forget which chemical it. But for the control of West Nile Virus in New York State where there was quite a bit of public health spraying to control the mosquitos carrying West Nile. And we received a lot of residential complaints about inhalation exposures as well as concern about

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exposures of lawns, gardens, and people because the spray would come down in areas where people were located.

And so I think that's a big concern that should be addressed even though it might be sporadic and it is necessary for public health protection, I think that's something that the EPA ought to consider.

Thank you.

DR. ROBERTS: Thank you, Dr. Schreiber. A long list of the questions. I guess, would the Agency like to respond to those?

MS. MULKEY: Well, I think that for most of this, that we will treat these as public comments. And we will be sure that we include them in our docket from these comments as well as from any that the Attorney General's office may subsequently submit.

I would say that if any of the issues give rise to questions in panelist's minds, we would welcome hearing that as you go through.

The only thing of this list that might be useful to spend just a few minutes on, because it comes up in a lot of context and I know that we've done some thinking about, is the school exposure situation. So, Jeff, if you just want to spend a minute on how we've thought through that issue. But beyond that, I think, in short of panelist's questions, we will treat these as public comments for our docket as well.

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DR. ROBERTS: Thank you. Mr. Evans, did you want to respond to that one?

MR. EVANS: Right. I think, if I remember correctly and I know you always do a good job of refreshing my memory when it fails me. I think with the schools, we did look into the use of these pesticides, and we pretty much came up empty. Also for lawn uses, again, we stretched the time that someone could be on a treated lawn to include all time outside which, you know, at this point in time is at least a way to address time at school in which a soccer field or something like that may be treated.

You know, when we get a little more sophisticated and move people around in this model, we'll be able to do that. But right now, we just jam up all the time on the lawn to include the time at home and also time in other places.

DR. SCHREIBER: So I guess then you're assuming that the schools -- their use patterns will be similar to what the residential use patterns will be?

DR. ROBERTS: That was a follow-up question by Dr. Schreiber for the record. Go ahead, Mr. Evans.

MR. EVANS: Right. Right now, again, since we're not moving people around, we're just extending their time on a treated lawn to

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account for other places.

DR. SCHREIBER: That would be a yes.

MR. EVANS: That would be a yes.

DR. ROBERTS: Let me just ask the Panel members if they have any questions for Dr. Schreiber or for the Agency in view of Dr. Schreiber's questions.

DR. HATTIS: Do you have any sort of documentation about insecticide use in school's day-care centers? I'm thinking of sort of cockroach treatments and things of that sort.

DR. SCHREIBER: I do believe that we could probably generate some. I think in New York State, because of the notification requirements, we probably do have some data that I could try to provide for the EPA. Sure. Thank you, Dale.

DR. ROBERTS: And Dr. MacDonald.

DR. MACDONALD: I'd just like to say the contact I've had with this work it still leaves me wondering why institutional exposure isn't taken more into consideration. I'm thinking back I think it was the Lifeline, for example, which was looking at the residential exposure but not institutional. And it was showing that when children started to spend more time hanging around in malls and schools and places, that their apparent exposure levels dropped. And I really had a

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concern. Was that simply because the model wasn't taking into account the exposure they would find in the places they were hanging in.

MS. MULKEY: It may be helpful to remind all of us that many, though not quite all, of the organophosphate have been canceled for these public-setting uses. So the remaining compounds that lawfully used -- or will be at the relatively short time line -- are only those that are identified in this assessment. I need to make absolutely sure about that. But I'm pretty sure about that.

So we don't have a different group of compounds. And the number of compounds involved is now very small. Nevertheless, the rest of the answer was the one Jeff gave, that the attempt to have and, in fact, have home setting be a surrogate for the institutional setting by extending the time.

DR. ROBERTS: Thank you, Ms.Mulkey for that clarification. And thank you, Dr. Schreiber, for your comments.

Let's go ahead and take the first question under this section. Could you pose the question to the Panel, Mr. Evans.

MR. EVANS: I do have to confess. This is a little difficult for me so bear with me. I'll be visiting the eye doctor in two weeks. I'm at the trombone phase of reading large and small print. I'll do my best

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here.

Historically, the Agency has relied on means (primarily arithmetic or geometric) from residue and exposure studies for key input variables in exposure assessments. The recent development of calendar-based models and others having features to incorporate distributions of exposure values has presented the Agency an opportunity to consider using all available data points from existing exposure and residue studies.

In the Cumulative Risk Assessment Case study presented to the FIFRA Scientific Advisory Panel in September, 2000, most of the exposure variables were presented as uniform distributions. The exceptions were for variables that are reasonably well established, such as exposure factors taken from the Agency's Exposure Factors Handbook.

The data used in the Case Study and the preliminary CRA are believed to be from well-conducted studies of generally high quality. However, these data sets tend to be small (e.g., n = 10 - 30) and are being used to address wide variety of exposure situations.

The uniform distribution appears to be the most appropriate for these relatively small data sets because it relies on easily established values such as the minimum and maximum and provides the most

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conservative estimate of the standard deviation.

Does the Panel have any additional comments or thoughts on the OPP's use of the uniform distribution in general on OPP's selection of the uniform distribution of the specific parameters chosen? What criteria, if any, would SAP recommend for parametric input distributions from available data? Under what circumstances, if any, would it be appropriate to use available data empirically?

Does the Panel have any recommendations on how sensitive analyses could be performed to determine if the assumption of a uniform distribution is responsible for a majority of the risk at the tails of the exposure distribution?

DR. ROBERTS: All right. The first question is, of course, in fact, a lot of questions. Dr. Adgate, would you like to lead off the panel discussion on this.

DR. ADGATE: Fortunately, I have lots of answers or at least attempts at answers.

I want to say just in starting out a couple of things. This is a very nice presentation, and I got a much better sense having seen this presentation what this was about than I got if from reading the document. Clearly, there's a lot of things going on since that was written in December.

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And I particularly like that table that though sort of lays out all the key assumptions and what you thought about their quality, the uncertainty associated with them. And I think that's an important thing that goes into the document in it's next iteration.

You know, that said, I think one of the things you're going to hear, I think, from a lot of us is problems with -- I mean we're the ones that told you to go and use the uniform distribution. Which brings to mind, the old analogy about when you have a hammer in your hand, everything looks like a nail.

And I think in this case, while the uniform distribution is a good idea, you know, it's the simplest tool you could use. And I think, as a group, we're probably -- I can't speak for everybody, but I suspect for conversations I've had with people that we're all going to sound something along the lines of you need to talk about characterizing the shape of the distribution based on even the sparse data that you have. So that's a quick summary of it.

We recommended the use of uniform distributions in the cases where data were sparse or uncertain. This is distribution which sets the minimum and maxima assumes each value within the range is equally likely and simplest model input. It's use is appropriate if you can -- which you seem to have done and all the values equally likely to

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use as an analyst.

To me, a first step in a continuum as you move from a uniform distribution to a well-characterized distribution, in your question you're calling that fully parameterized or something along those lines, a well-characterized distribution based on large unbiased data sets.

As complex distribution, I think the next more complex is the triangular distribution. You can make use of here and make use of certain statistical testing techniques that will tell you something about shape that I think you could incorporate relative easily and that that would make your presentation of this fairly complicated model a little more convincing to me.

Changing from a uniform to a triangular distribution, for example, is one type of sensitivity analysis that you could performed based on residential exposure scenarios. You've taken away my example. I was going to -- now do I understand correctly that the DDVP scenario has pretty much gone away? Because that was the one where it was most obvious that I think the use of the uniform distribution was a bad idea because you had a case where you have decay over time which I think you could come up with a physical explanation for that that would be much more convincing to most of us. So I won't dwell on that.

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In terms of criteria for developing what you call parametric input distributions from available data, I think you need to use an iterative process that's familiar to the Agency from a lot of other things, you know, good laboratory practice protocols and SOP and things like that. Things that ensure studies both are done in scientifically defensible manner and are statistically defensibly.

In the first case, I'm talking about things that have to do with performing the study using standard scientific methods, using QC protocols that characterize measurement error and variability. An example of this would be like chemical measurement use of appropriate methods, field lab, and calibration blanks, development and tracking of calibration curves over time, repeat analysis, standard reference materials and things like that.

There's analogous processes for a lot of the survey instruments that you're -- really, I think, is the nut of the problem is longitudinal tracking of behaviors, human behaviors, that really most of us recognize are one of the key uncertainties in this risk assessment, cumulative risk assessment.

Statistically defensible data is not a just question of sample size but of characterizing the important features of the study design that ultimately effect the derivation of data useful for this cumulative risk

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assessment. This means using studies that have large enough sample sizes to characterize temporal, spatial, and individual variability.

It also means that the resulting empirical distribution to data are good estimators because they're consistent, they're unbiased, they're robust, and, hopefully, in the end practical.

To get back to your question about sensitivity analysis. I think that what you need to do is along the same lines of what you've done in other analyses that have been presented at this is you need to block either by the scenario or the compound and systematically remove either a chemical or a scenario and see what it does to your outputs. And that with possibly changing distributions or shapes of distributions to see what happens are sort of the standard things you need to do to figure out what's going on and what's driving your analysis at the upper bounds.

In previous Panels, we've recommended, you know, an explicit analysis where variability and uncertainty are treated as separate entities and doing a two-stage probabalistic analysis and there are people here who have more expertise on this that I do on this topic.

But in simple terms, the first would state the variability distributions, i.e., measurement error, while the second would get away from or characterize the uncertainty distributions. And this

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would allow you to get to what I think is your ultimate goal is being able to describe the confidence intervals around your final estimate. It's nice to look at those traces over time, but I think what we all really want to know is what's your confidence in those estimates at the end of the day.

Apart from that, I have a couple sort of minor points. I agree to the exclusion of exposures that have been -- registrations that have been removed. And I do, also, think that the process would be a little more transparent if you present all the age groups that you've looked at. A number of people have commented on this. And I just think for purposes of being complete, folks need to see that.

And this whole issue, what I was asking before and couldn't articulate really well about conditional probabilities and co-occurrence. You know, whether or not somebody treats 100 percent of their lawn and then 109 percent of their lawn is 50 percent garden, but 100 percent of the lawn is still treated sort of questions are things that people are going to have questions about over time whether or not it's realistic.

And I, also, agree that this institutional exposure levels, schools, day-care centers and all that, has to be looked at in a systematic way. Although, I agree that there's -- I don't know how

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much those right-to know laws are going to be helpful to you because a lot of the data that they generate won't necessarily be useful in this analysis in my experience.

DR. ROBERTS: Okay. Thank you, Dr. Adgate. Dr. Freeman, do you have any comments to add?

DR. FREEMAN: Yeah, a few.

First, I'd like to compliment Jeff and his colleagues on the work they have been doing. This is really an amazing undertaking and very, very challenging. One of the things that I found very interesting was your figure of residential scenario application and use schedules over the seasons for each of the regions.

I think this is an approach to take because it gets away from the idea of treating all of the United States as a single entity, which it isn't. There's enormous diversity in this country in terms of what you're going to use, when you're going to use it, and why you're going to be using it.

I'm not sure that I'm adding much more to what John has already said about the uniform distributions. My concern is that if you rely too heavily on it that it may, in fact, seriously distort the characters of the distributions that exist. The impact of uniform distribution on an exposure estimate will be determined to some extent by the

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characteristics of the original distribution and the size of the data that provided it.

With some of the data -- what I do when I have a data set is I go use my Kolmagorov-Smirnoff test to try to find out what sort of distribution it has. And if it says that it's not uniform, I won't use uniform. I'm a very happy to use medians rather than means if it better characterizes shapes of distributions. And as John was saying, triangular sometimes is a really good way to go.

You asked the question about when it is appropriate to use empirical data. As a field person, my counter-question would be when is it not appropriate to use empirical data? I have colleagues who are model people who say, you don't need any data; all you need is physical principles and you can do everything.

The problem with that is it is the data that is drawn from the field in terms of what people do, what their exposes are, what the biomarkers are that actually tells what's happening. So I say use empirical data whenever you can with great comfort.

I would suggest that -- I think in your study you mentioned something like 11 different variables in which you were using uniforms distributions. When you're looking at the average individual, I don't think that's a problem. But if you're look at the 90th or the 99th

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percentile, you may be having extreme effects, creating a high-level exposure that's not really there.

And I think for some of the regional things that seemed to be the case, that the residential was driving these exposures. And I think that may be at these high ends because of this multiple magnifications created by using too many uniform distributions at the same time.

And I guess that's what I have.

DR. ROBERTS: Thank you, Dr. Freeman. Dr. Hattis, do you have anything to add?

DR. HATTIS: Yeah. I, unfortunately, have a relatively comment that's going to conflict to some extent with the advice you got in September 2000. So I'm sorry to be inconsistent. But if you ask more than one person and they say the same thing, at least one of them is redundant.

First I want to that the EPA staff is to be commended for what appears to be an initial effort to apply the techniques of distributional analysis to represent the population variability of residential non-occupational exposure to pesticides. Unfortunately, the choice of the uniform distribution for generic application to limited data sets and summary statistics is very ill-advised.

In my experience reviewing probabalistic assessments in the

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past several years, I found that the uniform distribution is the single most over used distribution and nearly always significantly distorts available information about the variability or uncertainty to the parameters to which it's applied. It is particularly the case where there are limited directly observed data.

Analysts often give the perceived simplicity of the uniform distribution as an important attraction. Moreover there's often an impression as stated in the text paragraph introducing this question, that quote, "it relies on easily established values such as the minimum and maximum." In fact, it's not to so easy to appropriately establish true minimum and maximum values from observed ranges from limited data sets of empirical observations.

It's completely incorrect in general to assume that the largest and smallest values of a group of 10 to 30 data points or fewer represents the true minimum and maximum values that that parameter can assume. Moreover, there are few cases where the mechanisms that cause measurement or estimates of exposure-related parameters to vary among people to create situations where there is no greater chance of producing a case near the center of a distribution than at extreme ends as would be required for the uniform distribution to be correct.

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Much more commonly, factors that cause exposures to differ from one individual to another tend to interact multiplicitively leading, when this factors are numerous, to expectations of a log normal distributions.

Sometimes where categorical factor of two is likely to have a strong influence like wearing short-sleeved shirts versus long-sleeved shirts or short pants versus long pants influencing dermal exposure from hand spraying on page 14, it's good to create mixtures of log normal distributions weighted by their expected frequency to represent the influence of these different known cases.

The uniform distribution is appropriate in cases where, one, it's physically impossible for the parameter to take on values outside the limits; and, two, there's really no greater likelihood of values close to the center of the range than at either end. For example, I have no problem using the uniform distribution to represent the probabilities of when the meteor is likely to hit, which day of the week for example. That's not a problem.

But my experience is that uniform distribution is often selected in cases where there's -- anyhow. The other generic difficulty with the uniform distribution is that it plays into directly into over-confidence bias which is one of the most reliably established phenomenon in the

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psychological measurements of people's misconceptions of probabilities.

And that same things applies to the triangular. Then my prejudice would be to say you ought never to assume a defined limit unless you have a reasonable physical basis to impose that limit. Otherwise you should tend to expose unlimited distribution.

I'll get to ways in which you can put in reasonable limits where they we must be there in a couple of paragraphs.

I want to refer briefly to 1994 paragraph of mine that gives a series of rules and examples of mechanisms that give rise to different distributional forms.

Experience and the basic idea that variability is often the results of combined actions of many factors adding multiplicatively indicates that the log normal form is the most often the best choice for exposure-related data where there are limited information. Both normal and log normal distributions have just two parameters, so they're in fact statistically no more complicated than the uniform distribution. And there's, you know, relatively straight forward methods to estimate the parameters of normal and log normal distributions.

The current document doesn't, unfortunately, provide a detailed

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description of the data underlying it's various choices of uniforms distribution. Nevertheless, I'd like to make some specific comments on particular cases to which you've applied this distribution.

Page 9, you talk about this distribution of sizes of lawns, and you've applied this uniform distribution from very small value to something that's slightly over the mean that was observed in the cited paper. And I understand why you might want to have the mean of the distribution you select be slightly smaller than that mean there because of the presence, as you said, of stuff that takes up area that's not lawn that isn't included in the calculations that they made.

But I would rather you be faithful to the original data and then have some variable factor for the rest of the thing. As you say, ranging from 10 to 50 percent, you can easily put that in as a second variable factor depending upon what your information is that leads you to believe that it takes up that lawn, those fractions.

Pages 11 and 13 give 14 applications of the uniform distribution. In general, the ends of the ranges provided differ one from to the other by many fold. Sevenfold, for example, in the case for inhalation exposure from a hand-pump sprayer to over 1,800-fold from a hand garden duster. Such large multiplicity ranges are based presumably on data sets with limited number of observations strongly

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suggest that you better be selecting something like a log normal skewed distribution.

A modified Poisson distribution can also be used in cases for which there is, in fact, a defined upper limit to a process, for example, the fraction of pesticide in soil on fingers that's removed by inserting a child's fingers into his or her mouth. In this case, the fraction clearly must have an upper limit of one or 100 percent.

I handle cases like that by postulating a log normal distribution of basic transfer rates K among children and then modeling the fraction of soil particles or molecules transferred as the fraction that receive one or more quote "hits" in a Poisson formula. And the formulas in the thing is very simple.

Basically, the fraction absorbed is the 1 minus the fraction of soil particles that get more than one hits which is 1 minus E to the minus K where K is log normally distributed. As K goes to higher values, then you get toward this natural upper limit.

And then I had a comment on of the DDVP that I won't say because you're going to take that out anyhow.

Thank you.

DR. ROBERTS: Thank you, Dr. Hattis. We seem to be of some consensus that too much use of the uniform distribution but some

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differences in advice on what to proceed and what to use elsewhere. Dr. Bull, what do you have to add?

DR. BULL: Not much. This is a little outside my area of expertise, and I bow to the folks that went before me because they're much more schooled in this area.

I did notice one other question I'd just like to ask. Did I understand in your presentation that the 1 to 2 year old age group is actually 12 to 35 months?

MR. EVANS: Right.

DR. BULL: So why don't you call it that? Or is it just -- I have real simple questions.

MR. EVANS: I wish I had a simple answer. But we did go around and around on this and those are just the little boxes that we tick in the model. But that's exactly misleading as can be.

Dr. Freeman had that question, and I made sure that I found out how many months that I was. And I'll get that back to the people that outline it that way.

DR. ROBERTS: Let me open it to other members of the Panel for their viewpoints. Dr. MacDonald and then Dr. Durkin.

DR. MACDONALD: Just a few comments on the uniform distributions. I think I'd take a little more pragmatic approach than

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Dr. Hattis has suggested. But just have some general principles. If you got especially a small sample and distribution that really has a long right tail, then you fit a uniform distribution using the minimum and maximum, you're going to overestimate the mean and the median. So that's pulling the values up a bit.

But then when you go to generate data, you're precluding getting any generated values higher than what was observed in the small sample. And that sort of pulling your answer down in the other direction, you're going to avoid generating really extreme cases.

I'm assuming that your simulations here are all set up in a way that's fairly easy to tweak because you're expecting a lot of suggestions for tweaking them. It would seem to be fairly straight forward just to replace your uniform random number generators by log normal, gamma, Y-Bole, or for discrete data, negative binomial.

I would think that just fitting these by moments and using mean and variance of your small samples rather than maximum and minimum and just finding the log normal gamma Y-Bole negative binomial that matches and trying that and just see how sensitive the results are to the change. And I think that would be a fairly straight forward exercise even just to try for a few scenarios.

DR. ROBERTS: Thank you, Dr. Durkin.

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DR. DURKIN: Well, Peter, really just made my point. Although I didn't understand half of words that he used. But I seriously do want to strongly endorse what Dale has said I think very, very well.

People like to use the uniform because they think it is simple. They think it's conservative. None of the distributions are all that difficult. And the log normal is no more difficult than the uniform. And the uniform, I think, can run the risk -- and I believe I heard Natalie make this point -- of distorting risk a great deal particularly at the tails.

So while my understanding is not as sophisticated as perhaps others, I don't think it's a very difficult or complicated issue. So I would encourage the committee to basically put in the elegant discussion that Dale has given us.

DR. ROBERTS: Okay. Thank you. Dr. MacDonald.

DR. MACDONALD: Yeah. Since Dr. Durkin commented on my terminology, I'd like to make another comment on terminology. And that's the use of the word "conservative." When we talk -- it's never clear when you use the word conservative in the documentation here whether you're meaning conservatively high or conservatively low. If you want a conservative estimate of exposure, I think you usually

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mean we're overestimating just to protect people.

But in the wording of the question here, you're referred to the conservative estimate at the standard deviation. And I'm just not sure whether you mean overestimate or underestimate. So I guess I'm advocating against such general use of the word conservative.

DR. ROBERTS: Dr. Heeringa.

DR. HEERINGA: I'm trying to go back through my recall on some initial sessions on residential uses. And I think what may have occurred here with the use of the uniform distribution is that we offered an alternative as an SAP to a methodology which was using constant values for many of these parameters. Essentially, the suggestion to use uniform or a triangular was in a sense an attempt to move EPA in this particular simulation off the use of a large number of constant values, often with very little empirical basis if any empirical basis, to introduce the sort of any type of uncertainty into the parameterization of this particular piece of the model.

So I think that the suggestion to introduce some distribution to introduce uncertainty into the estimation. Now, maybe that was a poor recommend. But it was really in contrast at the time to the use of fix values and often values without any empirical basis as the basis for the residential route of exposure.

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DR. ROBERTS: Okay. Thank you. Any other discussion among Panel members might help sharpen our recommendation? Dr. Adgate.

DR. ADGATE: Just to say that Steve's right. I think that's historically accurate.

DR. ROBERTS: Okay. Then it seems to be, as I pointed out a little earlier, the consensus that it would be good maybe to move beyond the uniform distribution. We have lots of suggestions for how you might do that. Hopefully. Those might be useful. Do you have any questions, clarifications back to the Panel about our comments and recommendations?

MR. EVANS: No, I don't.

DR. ROBERTS: In that case, let's go ahead and take a break now. I'll reconvene in 15 minutes, and we'll take the second question.

[Break.]

DR. ROBERTS: Let's go ahead and begin. Before we tackle Question 2, I believe Ms. Mulkey wanted to make a comment.

MS. MULKEY: Yes. I think it would be a good idea to clarify the regulatory information on DDVP pest strips, as I understand it, perhaps a misimpression we gave you. We wanted to that analysis will, also, have to consider a different scenario.

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But, in fact, the regulatory status of the pest strips is that the registrant -- well, first of all, I should say that DDVP is one of a handful of remaining organophosphates where we have not completed the risk assessment and the risk management process for the chemical. So it is still one where are actively working through the issues specific to the individual chemical.

The registrant of that product has asked us on a voluntary basis to remove from their labeling the authorization or the labeling for use of the pest strip in primary living areas such as bedrooms, living rooms, kitchens, any primary living areas as I understand it. But the product would continue to be marketed even during this period for areas such as closets, basements, attics, garages, perhaps. And I'm speaking without absolute precision. I don't have the labeling with me.

I believe this is consistent with the regulatory status of the product in California. But as of now, the registrant has not voluntarily amended its license to prohibit those uses. They have instead voluntarily changed their marketing, that is, their labeling for that period.

So unless and until we complete our regulatory conclusions about the product, I think, and in light of the limitations or the scope

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of the voluntary actions by the registrant, we should not leave the impression that the DDVP pest strips are quote "canceled."

And I wanted to say that early enough that if that caused you to be more interested, any of you, in talking about that part of the risk assessment, it does not appear to be moot or irrelevant, those parts of the risk assessment.

DR. ROBERTS: Thank you for that clarification.

Let's go ahead and take Question 2. Could you pose that one to the Panel. You did, by the way, a great job on the first one.

MR. EVANS: The use of calendar based models also allows exposure accessors to consider exposure from a variety of sources from the same or from different chemicals. Longitudinal survey data such as the national Human Activity Pattern Survey (NHAPS) are available for consideration by HED for use in future assessments. In addition, from a practical standpoint, the use of such survey data ensures combinations of exposure do not come from unrealistic random combinations that current models may produce (e.g., activities adding up more than 24 hours in a day).

The use of calendar-based models provides an opportunity to explore the potential for the co-occurrence of multiple sources of exposures from residential pathways. In the cumulative assessment,

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OPP used summary statistics from sources such as the Exposure Factors Handbook (EFH) regarding the time spent indoors, time spent on lawns, and time spent at other outdoor locations. In the preliminary assessment, we assumed these activities were stochastically independent.

OPP is currently evaluating data in the EFH such as data from the NHAPS to determine if it can directly incorporate (i.e., empirically) information on an individual's activity patterns over a full day from this database to account for the likelihood and duration that an individual might be exposed to a pesticide through various activities over the course of a day.

Please comment on whether and how OPP might directly incorporate NHAPS or similar time use data into the software to better account for variation in activities across individuals?

DR. ROBERTS: Thank you. Dr. Freeman, any suggestions in that regard?

DR. FREEMAN: Basically, I was trying to think about that. And what I said was, Gee, what you really need is a statistician. But, in fact, I think incorporating NHAPS might be done similarly to the way the dietary data was incorporated for that model.

I love NHAPS. I think it's a great data set, but there are

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problems. One of them is that while it is a very rich data set, it is about half the size of the CSFII. It only has about 10,000 cases for the United States. And if you are then breaking it down in terms of children of different age groups, you're beginning to get into small numbers again. Small is relative. We're talking hundreds across the United States.

There is, also, the problem that there are several versions of the NHAPS questionnaire that were used. And trying to integrate results of them, I'm not sure how you do it. That's going to take somebody who really knows how to work with those data sets.

One of things that's really great about NHAPS, which would be very useful for you, is that if you look at the data as a whole, you can see both regional and seasonal differences in activities. Everything from ventilation, whether you have your windows open or not. In the winter, it's very different in Minnesota than it is in Florida. This is very useful in you're looking at infiltration from outdoors or things like that.

If you go back to the children, if you then break it down either by region or season, you're getting into small numbers. And if you break it down by both, then you're really into small numbers. You're getting to where we are with the hand-to-mouth stuff, you know, 10 to

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30 in a group. And that's very, very frustrating.

But at the same time, there may be differences that you want to pick up when you're doing this regional analysis. And I'm not sure how you're going to want to play the game. Whether you're going to want to use, for instance, all children between the ages of 12 and 35 months for the nation as representative of kids all over the place so you can look at seasonal differences or whether you want to break it down by regions or forget the seasons. It's going to be a little bit of a challenge there.

One of the other things that you talk about, ask questions about, is whether or not activities are independent. Many activities that people engage in, not only activities but where they engage in them, are not independent either within a day or across days.

For school age children, children of people who work, and for adults who work, both daily and weekly activities time allocated to them when they are done and where they are done are driven by the occupation or for the school-age children by being a school-age child.

You have to keep that in mind when you're going to be drawing from this wonderful rich data set that some of the things for individuals are not independent.

I guess that's all I have to say.

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DR. ROBERTS: Okay. Thank you, Dr. Freeman. Dr. Adgate, would you like to add something.

DR. ADGATE: I don't have a whole lot to add to that. I think I said pretty much what I was going to say in response to the first question.

The one additional thought that I have is that -- and I'm not a statistician and they probably ought to be consulted on this -- there are techniques that exist for estimating longitudinal patterns and distributions from what is essentially cross-sectional data. And I think that's a general problem that you have with a number of your analyses. And it might behoove you to put some resources into that general problem in seeing how you can apply it where you need to as a tool in this analysis.

DR. ROBERTS: Thank you, Dr. Adgate. Dr. Hattis.

DR. HATTIS: Yeah. I think, generally, the idea of incorporating the activity pattern data over sequence days is a good idea. And the likelihood is that these things are going to be associated with weights that you can use to adjust your population weights of each individual that was studied in the survey.

I would say that, as we go forward, in general, the approach here should not be a rolling average but a very simple compartmental

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model in which the cholinesterase inhibition tends to decay at some rate that can be inferred from one model of the approach to steady state observable in the animal experiments.

And, two, a human-animal adjustment factor to take into account that we big animals tend to metabolize and eliminate things at a slower rate. And the center of that distribution is usually approximately given by a animal body weight to human body weight to the one-quarter power-type formula as Lorenz can testify to.

I basically got -- as to the uncertainty of that translation, I've got some recent work that sort of gives the observed spread of animal-human conversion factors, in this case rat-human conversion factors, based upon the old Frederick data sets and several other sets that have been compiled by Paul Price.

To make a long story short, for the 18 rat-human projections that were available, sort of the geometric mean departure of the human potency from the observed animal toxic potency for these anticancer agents was about .89 with 95th percentile of about, you know, 4.3.

Anyhow, there's some real data that can be used to get the uncertainty and what, at least, a starting animal-human projection factor for the reduced metabolism rate is that can be used for that kind of modeling. And I cite a reference here.

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But basically the 7-day window or a 21-day window is possible. It's almost as easy to model the co-expected brain cholinesterase inhibition itself with the adjustment that you should expect the humans to eliminate the inhibition at a lesser rate than the rats do.

Whether that's something that you want to attempt for June or on some longer-term basis, it's up to you.

DR. ROBERTS: Dr. Reed.

DR. REED: I don't have a whole lot to add into what's been said.

I'm really excited about data becoming available. I'm curious about and I'm not a statistician and I'm not ready to make some recommendation or anything. But I'm curious about how the different data bases could be used together in separate sets or how that choice would be. I'm hoping that someone might be able to make some comment about this issue. I think it's very important.

The other one is sort of not directly about this question, but I think it's an important point. It might be a good place to bring it up. It's that the importance of doing a mass balance whether it's been time or location or anything. I think in one of the previous meetings we brought up an issue or the concern about such a situation where, if a certain proportion of the ratio has been taken up from the same

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location area or contact surface, then it should be that it's no longer available for the next time series exposure.

So that I would like to see a more clear coverage on that issue.

DR. ROBERTS: Dr. Durkin.

DR. DURKIN: Since I'm kind of at the anchor position here for exposure assessment, I do want encourage, of course, the use of calendar-based models in response to the question that you proposed to us to the extent that we can demonstrate that they lead to plausible results. But there are a few other odds and ends with the exposure assessment that I would like to bring up briefly.

Two of those relates to comments that we heard from the public; one being the transparency, the ability to drill down by chemical. I was thrilled to see the graphics from the drinking water folks who were showing us over time the different individual chemicals. I haven't seen that in food. I think that sort of thing is very important, and I want to encourage that kind of transparency.

The other minor footnote that I will pass on is that, on the issue of inhalation exposures, I think you have addressed extremely well, perhaps not in the document that we are dealing with here but in a document that you referenced. I went and got ahold of it; it's your document on I think it's called "Residential Exposures," rather large

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and it's on your web site. And in general, except for things like DDVP, the inhalation exposure, I think, it's relatively well known and documented is going to be extraordinarily small compared to the dermal and oral exposures.

Two other points. One is I am a little concerned that my lap top always goes to sleep when I look at it. Okay, there we go.

The one sort of serious concern that I have about your exposure assessment is the failure to address populations that live adjacent to sites where there might be a lot of agricultural use. To me, conceptually, this is something like the sorts of exposures that you did address with sprays for public health which I think was very appropriate.

But there is a subpopulation, and I don't know how big it is. But they do live adjacent, right up next to things like cotton fields, tobacco fields where there are a lot of chemicals put out over the course of a growing season. And these people do have gardens. They have lawns. The extent to which you want to look upon them as maybe a typical subgroup; I can't really answer that. I don't know. But I just bring it to you for your consideration.

The last point that I'll address again, just briefly, relates to how you do your exposure assessment and then start to segue into risk

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characterization. And this is really a follow-up from a question that Dick Bull had.

What you have always done with the pesticides has been to combines different routes of exposure by taking the let's call it a "point of departure" for the route-specific points of departure. So you take an oral study, an inhalation study, and a dermal study; and then you take ratios to the exposures by the same routes. So you're not really doing route-to-route extrapolation; and that's fine.

I'm not critical of it. But I do think the document might benefit from at least addressing why you don't take the other approach, that I think Dick is comfortable with and I am as well, and, in fact, it is one that I tend to use, where you take the multi-route exposures and do your best to convert it to an equivalent oral dose and then you use the oral tox data as your point of departure. The nice thing I can say about that approach, and you ran into this with your analysis, is that, in general, the oral studies are more abundant and they tend to be better. A lot of the dermal and inhalation studies, first of all, there's fewer of those and they often do not have the same quality. And this is particularly true had you look at the longer term effects.

So I'm not trying to proselytize here to get you guys to convert in any way. But I do think it is something worth talking about in the

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document because I do think it makes a difference in your ability to characterize risk.

And I would, also, note that taking that route-conversion approach is going to end up very consistent with where I see you going, and we'll talk about this at the very end of the day or tomorrow, where I see you going with PPBK models as you have discussed in your future dates.

So that's all I have. Thank you.

DR. ROBERTS: Thank you. As Chair, I appreciate the interest in panel members in getting in comments before we move away from exposure into risk characterization, that it may be not exactly to the questions being posed.

Let me ask the Panel members, though, as we go through the questions, let's go ahead and focus our comments and feedback on the specific questions. And if we will sort of maintain our discipline in that regard, I will promise the Panel the opportunity this afternoon or at the end of the session to offer whatever comments they might have had that just didn't fit in with the questions or they didn't get the opportunity to raise earlier. And that would apply to any of the aspects of the cumulative risk assessment, hazard and dose response exposure, risk characterization and so forth.

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With having said that, are there any comments from other members of the Panel as it specifically relates to the question posed to us here by the Agency?

Let me ask the Agency, would you like some clarification on our response to this question, or is it pretty clear?

MR. EVANS: It's pretty clear.

DR. ROBERTS: Okay. Great. Then if they're no other comments on this question. Let us proceed to risk characterization.

If the Panel will note, and the audience as well, that we are well ahead of schedule. I believe that it is possible for us to complete our discussion of these questions this afternoon. Having said that, I want to assure the members of the Panel that they will have every opportunity discuss the remaining issues as fully as necessary as well as having the opportunity to make these other comments as I indicated just a moment ago.

To alert the audience, I think we're going to finish the program today. We'll stay as long as we need to do that, so we might run a little bit long today. Barring some disaster, and if that takes place, I'll ask the Panel to meet tomorrow morning. The session will be closed today. Meet tomorrow morning at 8:30 to discuss report writing and coordination.

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DR. ROBERTS: Dr. Doyle, welcome.

DR. DOYLE: Thank you very much. Dr. Miller is kicking off the presentation. He's coming in just now.

DR. ROBERTS: Okay. Here he comes now.

DR. ROBERTS: Mr. Miller, are you ready to go with risk characterization?

MR. MILLER: Yes.

DR. ROBERTS: Great.

MR. MILLER: If I can just have the first slide and then the next one.

Okay. What I'll do first is just kind of go through the outline of the presentation. Before I go through the outline, I'll just kind of quickly go through kind of what you've before in the sessions here.

On Tuesday you heard from Anna Lowit and Woody Setzer a little bit about BMD10s, that those were 21-day steady state equilibrium cholinesterase inhibitions based on that time period.

Yesterday, we discussed with you some of the mechanics of the analysis options within DEEM and Calendex. Two options were single consecutive day, and the second option was the rolling time frame.

Today this session is concerned with comparing the time frames of exposure, for example, 1, 7, 14, 21 or 28 days which are available

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within DEEM Calendex with a time frame of toxicity 21-day BMD10 talked to you before on Tuesday by Anna and Woody.

Just in this outline here, this slide here, we're going to be talking first just a summary of preliminary results and findings. A single slide on that. Then we'll be talking about introduction to key principles for conducting risk characterization. I'll talk a little bit about the hazard and exposure aspects.

I'll talk about what we did in the preliminary cumulative risk characterization assessment. I'll remind you about the time frame considerations and some of the specific comparisons that need to be done between toxicity and exposure.

After that, what we'll do is some example exposure scenarios, and Beth Doyle will be discussing this kind of in a more interactive session with you with overheads. And then finally we go through the questions for the SAP.

Just as kind of a summary of the preliminary results and findings. In general, we found consistent exposure at risk patterns across regions. The major contributors to risk for indoor residential exposures are uses of DDVP. Exposure through food is considered to be national and does not vary by region. We're performing additional analyses on these results, and Bill Smith went through these with you

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yesterday.

And then, finally, drinking water and outdoor lawn and garden uses do not appear to be significant contributors to risk.

Some key risk principles for conducting a cumulative risk assessment. One key consideration is the time frame of toxic effect. For example, what is the time to the peak effect and what is the time to recovery.

With respect to time frame of exposure, some key considerations include how often does exposure occur, at what levels do exposure occur, and then what is the exposure duration. And then, finally, what some consider to be the crux of the issue would be how are exposure and toxicity compared; to what degree to the time frames need to match between exposure and toxicity.

In the September 2001 SAP meeting this was considered of how to compare the time component of toxicity endpoints with the time component of exposure. You said the cumulative risk assessment should ideally compare toxicity endpoints and exposure durations of the same time frame and, also, that, to the extent possible, comparison should take into account the pattern of human exposure.

With respect to -- I'll give you a reminder of some of the hazard aspects that you'd heard about from Drs. Lowit and Setzer. The

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BMD10 is based on steady state or equilibrium cholinesterase data. That's the point at which continued exposure at the same dose level does not result in further reduction in cholinesterase activity.

The RPFs and PODs are based on studies of 21 days or longer of continued dosing of naive animals, that is, animals not exposed to OPs before the initial dosing period. This represents 21-day steady state or equilibrium conditions for cholinesterase inhibition and believes to be a more stable measure of relative potency factors and points of departure.

And then finally following the insult, recovery of cholinesterase inhibition that may requires days to weeks.

With respect to the exposure aspects, human exposure patterns to multiple OP pesticides may be single day, for example, spike or short-term exposures through food, drinking water, and residential uses, superimposed imposed upon more or less continuous exposures through food. By monitoring data from NHANES, for example, suggests that a sizeable portion of the population have OP metabolites in their urine.

It should be remembered, also, that most animal data available to OPP are developed using laboratory animals that were naive in their exposures to OP; that is, again, they were not exposed previously to

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OP pesticides.

Continuous exposures through food might resemble the multi-day dosing used in determining the BMD10.

The preliminary cumulative risk assessment used the BMD10 which reflects continual dosing for a sufficient period to produce equilibrium response. More specifically, the BMD10 used in the preliminary cumulative risk assessment is based on a multi-day animal studies, dosing studies, and reflects that multi-day dose required to achieve a steady state 10-percent inhibition of cholinesterase.

In the PCRA, OPP developed a distribution of single consecutive day exposures, again, not rolling time frame, and compared this to a steady state or equilibrium multi-day BMD10. What we indicated we would do would be consider the patterns of exposures, looking for periods of sustained elevated exposure over a period of time. And we indicated to you, again, yesterday that we recognize that such sustained elevated exposures at high percentiles are unlikely to reflect the same single individual.

DEEM(FCID)/Calendex also permits the rolling time frame approach. This measure exposure to the same individual. They are tracked. The same individual is tracked over the time frame of interest and averaged for that individual over that time frame. The SAP

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considered this issue in yesterday's session of this meeting.

While this rolling time frame approach may allow for a better match between selected exposure time frames, for example, seven days or longer and the hazard endpoint, BMD10, OPP is concerned that this may not adequately permit estimates of risk associated with shorter duration exposures, for example, a single day spike or short-term exposures.

While an advantage of the rolling time frame approach is that it better simulates continual non-naive exposures and allows us to better match the time frame associated with the toxicological data, results of this averaging process may obscure one-day spike or elevated time frame short-term exposures.

BMD10 associated with a 21-day steady state response is appropriate for 21 days or more. If an acute, for example, a one-day or short-term, less than 21 day, exposures, if those are of concern, how might OPP evaluate or compare such exposures with toxicity data that is based on a multi-day BMD10. In other words, how does one estimate the effect of different exposure patterns on risk given those two pieces of information?

Some information is available with respect to how multi-day BMD10s compare to one day NOAEL, no observed adverse effects

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levels. This information was provided to the Panel in a supplemental submission in January 25, I believe. A rough comparison of the BMD10s with a no observed adverse effect levels based on the cholinesterase estimates data from single-dose studies reveals a good similarity of values based. Keep in mind, though, that it's based on a limited data set and there are some exceptions to that.

This next session it would be by Beth Doyle, in terms it would be an interactive session with transparency acetates. I don't know if you'd like to ask clarifying questions or hold off until after lunch.

DR. ROBERTS: Let me go ahead and ask the Panel if they've got any clarifying questions on what you've presented so far. I don't see any. So let's go ahead then.

DR. DOYLE: As we discussed before, is it better to do this right before the question or after lunch? What would be your preference, Dr. Roberts?

DR. ROBERTS: Now. I'm seeing some people say they want to go ahead and talk about it now.

DR. DOYLE: One of our concerns is that we have a very thorough discussion of the matching of the time frame for the exposure with the appropriate hazard endpoint. And we have tried to frame here for you, in a very loose way, a number of things that we have

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considered as issues. We wanted to impress upon you the variety of types of issues that we have to deal with in this assessment and some of the complexities that we see. And we'd like to hear other complexities you think we've misses and also suggestions for how we might best deal with this.

So I'd like to graph out for you some of the issues to frame-up the discussion. One of the concerns we have is that we have a variety of different potential exposure patterns. If you bear with me, let me draw the first. Unfortunately, our markers are dead.

But the first exposure pattern with which we have concern is one in which there is a very low background and there is a spike above a very low background.

This is about a 40, roughly 42-, 45-day time frame. We have a potential that we have an exposure that looks something like this. Okay. In this case you have a very low background exposure, essentially, no exposure at all. And that will run along for a series of days and then very abruptly a peak of exposure occurs, followed by a rapid decline and then another very low exposure.

Now, you might argue in a case like, if this is our 21-day BMD10, that is not an appropriate endpoint for consideration there because, in fact, you have essentially a true acute exposure. It might

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be argued that this would be more appropriately reflected by an acute NOAEL of some sort.

However, if the acute NOAEL is up here, you can see it makes quite a difference. Now, that depends to some extent, though, on how you express your exposure because there's been a discussion of rolling time frame. So we're further faced with the issue that if we do a 7-day rolling time frame, we get something like this. And that sort of shifts our type of concern that we're dealing with quite a bit because you maximum exposure has fallen tremendously. But you have a very wide period of exposure to consider.

So by looking at the manner in which we do the calculation of exposure, we have changed the question, and perhaps artificially; but we certainly have changed the nature of the question. And you could continue to widen and lower that peak based by using a longer averaging time.

Now, we have an alternative possibility which we may be dealing with. We don't know. It looks something like this. This is a higher background level. If you recall, we had a BMD10 that looks something like this. And in this case, your background -- okay. In this case we have a BMD10, which is very close to our background level, so we're running at an exposed individual, they're already

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inhibited. Suddenly they incur this peak exposure.

Now this is a little bit of a different situation that you have with our tox data for our acute exposure assessments. You don't have a naive, if you will, person being expose to a sudden pulse. You have a person who already has a substantial potential degree of inhibition. It's not unsafe yet at background. But when you hit this peak, you're rising not from zero anymore but from previous exposure.

So, again, then it becomes a little more problematic about what would be the appropriate toxicity scenario to use for comparison. And if we do a rolling 7 day, then you get a different picture much like before. Looks something like this. And, again, I'm sorry for the drawing. I'm very poor at this. You get something like this, which spreads out the exposure. Well, it comes down. But it does spread out the exposure and, again, widen that peak substantially.

Again, the question, I think, is different now, what the appropriate toxicity comparison is, because you're not starting at zero. You have a substantially exposed population that's now receiving an insult. So that's a different sort of issue.

And then we come into the situation where we have a series of spikes. And regardless of what your background is, it raises another question for us. and we have to deal with this one as well. And, say,

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for instance, it's going like this and you have a spike; and then maybe a week later or a few days later you get another spike and so forth.

Now, this is a daily series. And, again, here's our BMD10; and here's our acute. Well, certainly there would be a certain simplicity in being able to say these are three acute values. And that would be very easy to do.

Except that if you look at a rolling average, you get something that starts to ooze together. You start to get something that sort of like this. And then it goes down after. But, in fact, your exposure with decline included, may never truly go back down to even your background. You may have a sustained elevation. And it's a little less apparent.

Again, these are certainly three independent exposures now because they're too close together. And we haven't even gotten into discussing recovery at this point. We're just looking at exposure.

And last but not least is what we're afraid we probably have, and some of our scenarios suggest that we do have, is a mixed situation where you're going along at background and all of a sudden you have an elevation of some sort. Maybe you've been working in your lawn that day. And then after a while it goes back. And all of a sudden you get a peak from some other use and another peak and so

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forth.

Well, you can argue very effectively, I think, that for this portion in here, that BMD10 is probably appropriate for this section if, in fact, this is an individual exposure and you're seeing the sustained elevation. That certainly is a subchronic exposure and that would make sense.

But if you go to each separate peak, it's less clear that those are actually acute exposures because depending on how you look at your averaging time for presentation, you're actually doing something akin to this. And then it goes back up here a little more. I'm sorry.

At any rate, you have something then that remains elevated for a substantial period of time. And I think that we have these issues with regard to exposure scenarios. But we have, also, issues with regard to, as I said before, recovery of cholinesterase inhibition. Dave mention that in his presentation. You could argue a person never recovers in this scenario between exposures.

The same is true here. And then you have to allow for the distinction of what your starting point is. What is your baseline condition of your exposed individual? Are they truly what we're referring to as naive, that is, never previously exposed. Or are they previously exposed that are now incurring a separate additional insult.

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So we just wanted to frame this up a little that these are the variety of types of issues that we'd like to see you think about. We have no single answer, necessarily, that's the right one that we're looking for. We would be happy to see a variety. We are open to any suggestions. And I'd like to thank you for your comments in advance.

DR. ROBERTS: Thank you, Dr. Doyle. Are there any other aspects of the presentation? Let me, then, open it to the panel for questions of clarification. Let's try and avoid getting into the comments, but certainly clarifications on these issues are fair game. Dr. Bull and then Dr. Conolly.

DR. BULL: Mine was part of the comments.

DR. ROBERTS: Okay. Dr. Conolly.

DR. CONOLLY: Yeah. I just wanted to be absolutely clear. I think it was pretty clear that the graphs you were drawing were graphs of exposure. And so really the question you're asking is what's the linkage, what's the appropriate linkage, between the exposure and cholinesterase level.

DR. DOYLE: That's correct. And, again, the averaging time for the exposure will affect that. All of those things combine to give us a very complex question.

DR. CONOLLY: Right. Thank you.

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DR. ROBERTS: Any other questions from members of the Panel? If not, I believe we have some public commentors that are interested in making a presentation. Mr. Jack Zabik from Dow AgroSciences. Is Mr. Zabik here?

MR. MCCALLISTER: Jack Zabik's not here. I'm taking his place.

DR. ROBERTS: Okay. Welcome. And could you introduce yourself for the Panel, please.

MR. MCCALLISTER: My name is Ray McCallister. I'm with the Croplife America here representing the FQPA Implementation Working Group.

Comments are fairly limited, and they're not going to address all the issues that EPA has just raised. But I wanted to say that the IWG strongly supports the multi-day rolling exposure calculation to match the toxic endpoints which is also based on a 21-day or longer exposure test animals. In the risk assessment the exposure and toxicology scenarios must match as the panel has previously advised the panel and repeated during these sessions.

The Agency has raised questions in sessions yesterday about the use of the available food consumption data to approximate a moving dietary exposure average. Some of those questions raised would tend

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to make the risk calculation more conservative; some less conservative. And Panel members raised additional issues that need to be taken into account.

For example, I feel that the list of foods and commodities that would influence the leftover issue, that is, what foods might be more likely to be consumed on subsequent days, is probably fairly limited and can be fairly easily defined.

EPA has in hand now data from industry and from USDA that directly address the homogeneity or variability of residues within a bag of apples or oranges or potatoes to determine how variable those residues would be, how likely the residues of fruit consumed from that bag tomorrow are going to be similar to those consumed today.

The EPA can and should call on the expertise of USDA's Food Surveys Research Group in addressing these issues of estimating longitudinal dietary consumption. These are the folks that conduct the CSFII study. They may not have solved all the problems that were raised by EPA and by the Panel members, but they have considered them analytically for years and will have valuable insights to offer.

The CARES software model is designed to specifically address some of the issues raised by Panel members. For example, it assembles a pool of demographically similar individuals for use in approximating

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a rolling average of dietary consumption.

The issue of the spikes and exposure rates today must be addressed by combining consideration acute tox values as well as the chronic tox values.

Finally, the IWG has benefited considerably by the EPA's presentations and the SAP discussions of the cumulative risk assessment issues. We will be providing detailed comments to the Agency during the public comment period on the new issues that have been raised by during these sessions.

DR. ROBERTS: Thank you. Are there any questions? Clarification? Thank you very much for your comments.

Let me see. We one other individual that has indicated an interest in addressing the Panel. Dr. Christine Chasen if I pronounced that correctly.

Okay. Could you please identify yourself for the record.

DR. CHASEN: You were close. It's Chris Chasen, and I'm with the Lifeline group. And we've had the pleasure of presenting Lifeline to this Panel before. We will be presenting some written comments to you. But I just wanted to point out a couple of issues for your consideration.

There's been intermittently discussion about the dilemma that

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we always face when we're trying to fit cross-sectional data into what basically are longitudinal questions. And there are two components to that. I just wanted to point this out.

One, of course, is that we've all saluted the problem that there are not adequate longitudinal data sets that are in any of these and so about it. So we have to do the best we can with the cross-sectional for the moment. I was very pleased to hear the Panel endorse the idea that you can, however, use cross-sectional data if you take a look at some of the relationships that are referred from other data bases. And so there is still a lot of improvement that we can all make in how we use the cross-sectional.

However, I didn't hear very much conversation about how the models use the cross-sectional data. And this is really important. Because even with completely cross-sectional information, how the models handle it is really going to be important. I'll give you just one of this; but there are many, many, many places in these models where this becomes important.

One example would be that you got to keep the individual in the same house from Day 1 to Day 2 to Day 3 to Day 4 until they move. And that has to be an abrupt difference. So when you talk about modeling a person across some X amount of time, it's not -- the model,

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in fact, can take the concept data that we have about mobility characteristics in the United States and whatever, and at least hold that person in a house that is consistent from day to day.

The same would be true. There are socioeconomics. You can't get rich one and go poor the next one, although that seems to be happening. We have to adjust the model accordingly. And, also, hold these people in an urban or rural setting so they don't bounce back from Iowa to New York City. There is, in fact, a significant use of pesticides in urban situations, and we're considering residential treatments here.

A second. I'm just going to go briefly through a couple of these points but we'll be elaborating on that.

Another one is I think we need to take a look at seasonality just a bit more because I think we may be overlooking one important thing. I will concur that in the United States there is not much difference in the intake of foods from one season to another. That seems to be even true with water. And that may be a function of air conditioning or something. But we do have -- now there are exceptions to that, of course, in our food supply. And I think most those are obvious, and we would know that.

However, there is a difference seasonally from residues, on the

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residues on the foods. So I don't care whether it's an apple or an orange or orange juice, whatever, the source of that food changes in the United States seasonally. And even though it's nationally distributed, the source of the national distribution changes radically.

And obviously, if you're changing the source, you're changing the pest pressures; and obviously, then, you're changing the patterns of usage. So it's not surprising that if you superimpose on the model one usage profile in the calendar base, you're going to end up with an answer that says there's not much difference from season to season. But, in fact, you need to be able to take a look at the source.

If you don't take a look at the source, you also can't account for import versus export situations. Now we may know an awful lot about usage profiles in the United States. But how much do you now about the other usage profiles from where our increasing percentage of foods are coming.

I know that the PDP data set does look at imports, but there are other ways where we can account for the what we don't know of pesticide usage from the food imports. And that wasn't discussed.

Another thing that was not discussed was how the models use the water intakes, the consumptions of water, particularly for kids. We're going to put in just some basic information if you want about

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the water intake distributions in CSFII '94, '96, '98 for the Panel from kids in different age groups, including infants. When we were working with Lifeline, we went through exactly these issues. And we'll share the background information that we have on that and the subsets of information out of those data sets.

Lastly, as you heard, Lifeline will be running this. I just wanted to emphasize that the results of that effort will yield three things. We will certainly have a final report with new manuals. Secondly, we will have a disk with the inputs and the results from the analysis. And thirdly, a free copy to anyone who wants it of the complete version of Lifeline that was used to run those risk assessments. So you'll be able to put the data in, play with it however you want, take a look at the drivers or whatever else is of interest.

As part of this, you know that Lifeline has shown you those situations where it likes like there's less exposure to certain age groups when in fact -- but what we have suggested -- I can't proof this. But what we've suggested is what we're really seeing is there are places in the model where we have the least information about activity levels or the model's most vulnerable, if you will, to underestimating exposure.

There are ways that we can look at and can play with some

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sensitivity analysis to know whether or not what you're suffering is a lack of data or whether or not you can compensation for it by things such as increasing the time of the day that you're spent on another field. That does not solve, however, the issue how much time as part of your life are the exposure opportunities changing.

As part of this whole thing, I think that the EPA certainly has done a wonderful job in incorporating a lot of these. And I'm very pleased to hear the comments from the Panel because you zeroed in on many of the issues.

My last comment about Beth's presentation, and I'll make a suggestion for how you can deal with some of the points she brought up. If you take an assessment of all of the -- what she showed you was a situation for a person. Let's say you have a thousand people across your simulated population. Each of those thousand people have a different scenario. Some will be naive with one peak; some will be naive with two, three, six peaks; some not be not native with no peaks. Same situation.

Well, you can't, I presume, regulate person by person in the United States. You're going to go and look at across population. And there are methods for doing that presently available.

What you can do is take and look at the peak values, the

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maximum values, across all the people in the population. And then, also, take the averages, you can do that even one day at a time or across rolling windows whatever, and the difference between those two distributions gives you an indication of the frequency in which peaks happen.

If you have 90 days for example, if you have 80 of those days with peaks, the average of that scenario in the population is going to look a lot more like the peak, the maximum of the peaks. As these two things converge, what you have is a frequency of events within that time period. The farther apart they are, it insinuates that you have very rare events, rare peaks happening in the group.

Now, that just gives some guidance, I think, to the regulator as to whether or not you really should be looking at applications of acute metrics or applications that may be long-term exposure scenarios. You can do this across -- and we've done this frequently -- 1 day, 7 day -- this is rolling window -- 30 days, 90 days, and 365 days; and then just compare just for the exposures. Be dammed the toxicology now.

Just for the exposure to see how similar these numbers are because that gives you an indication of whether you're looking at peaks across frequencies that are daily events, weekly events, monthly

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events, seasonal situations, or annual situations. And the differences between these distributions at least opens up an idea as to whether you're dealing frequently occurring scenarios for exposure or not.

And I would recommend that that approach be taken at least to take a look at to give you some confidence that you're using the correct toxicology metrics. There are techniques such as this that are available, and I think they will be hopefully a point of discussion in the future.

So we'll put this down in writing very, very quickly and try to get it to you. Maybe it will be helpful. Thank you.

DR. ROBERTS: Thanks, Dr. Chasen. Could you give us an idea on the time frame for completion of your Lifeline analysis? You mentioned that you will have that available.

DR. CHASEN: Well, we're just going sort of going to go as fast as we can. But it certainly will be available between now and June.

DR. ROBERTS: All right. Thank you. Other questions? Dr. McConnell.

DR. MCCONNELL: Yeah, I have a question. I was intrigued by your last comment where you said you'd have some data for one day, seven. What sort of magnitude difference was there in those values for exposure if you look at a 365 day versus a 7 day? Were

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they significantly different?

DR. CHASEN: Are you talking about for the OPs?

DR. MCCONNELL: Yeah.

DR. CHASEN: I haven't done it for the OPs yet.

DR. MCCONNELL: Well, whatever.

DR. CHASEN: I didn't get that far.

DR. MCCONNELL: Well, whatever chemical.

DR. CHASEN: Well, it depends on the use scenario and the chemical you're talking about.

In cases where you have a pattern that is seasonally or dependent upon seasonal activities, you're going to suddenly see a break in the 1 year and one day won't look like the 90 day. And maybe the 30 daily will look like the 1 day. And then all of a sudden there'll be a big difference between the distribution of the peak values between the distribution described by a 30-day rolling window versus a 90-day rolling window.

Now, there is no such thing as frequency data, per se. But this infers frequency. I get nervous with all these statisticians sitting, and I say things like that. It's only meant as a tool to give you an idea of whether or not you're looking at frequently occurring scenarios where you have a lot of people seeing frequent peaks or a few people seeing

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frequent peaks or a lot of people seeing some kind of seasonal peaks or something like that.

So the models can give you more than just a risk assessment. What they can do is provide ways to play with profiling. Okay. And then from there maybe you go back and take a look at the toxicology metrics that may be most appropriate to deal with this. And you can look at that across populations or subpopulations.

And I will, also, point out to you that here's another dilemma. Those relationships change with age. That shouldn't be a surprise. Think about how the time you spend in your day, change your exposure opportunities, and if you're a 6-year-old, that's going to look very different than if you're 35 or if you're 56. And so those relationships -- I don't know what -- I mean I think this -- I don't want to confound this too much, but I do think it's important to look at these things at different time and groups to see, in fact, where are we seeing those kinds of shifts.

DR. MCCONNELL: Thank you.

DR. ROBERTS: Any other questions for Dr. Chasen? If not, thanks very much for your comments.

DR. CHASEN: Thank you.

DR. ROBERTS: Is there anyone else in the audience that would

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like to address the Panel on this subject. Oh, I see someone in the back.

Welcome. Could you please identify yourself for the Panel.

MR. GRAY: Sure. My name is Ed Gray. I work at McDermott, Will & Emery. I'm really not here on behalf of anyone else, although I do a lot of work with the IWG.

I just wanted to raise one question that just occurred to me as this thing came up. And that is it seems like in almost every hazard or risk assessment that anyone does they have a series of different kinds of assessment the do. They do an acute. The do a subchronic. They do a chronic. And they do that because there recognize there are differences in the exposures as well as the toxicity endpoints. But here we seem to be trying to make different things into one thing. And I can't figure out why we can't just do two.

That's my question. I don't have any profound back up on that, but it seems to be a question that ought to be raised. Thanks.

DR. ROBERTS: Dr. McConnell wants to know what are the two?

DR. MCCONNELL: Yeah. Are you talking acute and chronic when you're say two?

MR. GREY: Yes.

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DR. ROBERTS: Any other comments or responses to that from the Panel? All right. Anyone else in the audience? The last opportunity for public comment.

Dr. Sass, could you identify yourself for the record, please.

DR. SASS: Jennifer Sass with the National Resources Defense Council.

This is an idea not a comment. It appears to me that possibly one thing that might be on the table for consideration in looking at the rolling windows -- and I'm calling them in my notes the rolling window averages -- is that it might go to tackle some of the problems including possibly seasonality which I think we all recognize is a serious omission is to do a rolling window.

And I like Chris's idea of doing different time periods as a first trial, time permitting and energy permitting. But, also, keeping the having the diets the way they are which is two diets alternating throughout the year but keeping the tolerances constant for that rolling window period. So if you chose a seven-day rolling window period, you'd have the diet as is already -- sorry -- residues -- hold the residues constant for the period of seven days so that it would tackle the problem of the leftover food in the fridge; or the realistic scenario where people buy their groceries once a week or four days if you want

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to do that kind of window; and then eat whatever's in that market basket so to speak in your refrigerator for those four days so that whatever the residues are in those grapes or those apples that's what you're getting for X number of days.

So holding those residues constant. It would also tackle in some way possibly the seasonality if you use that approach to try and get at the fact that you eat a lot of peaches for a long time when peach season is here and not so much at other times, and you might be able to extend that.

I think it might, also, tackle some of the Beth's diagrams, which I thought were excellent and really clear, in the sense that those peaks would be muted out; but they would, also, be extended and they might be more easier to detect. So that when we look over a period of a year and see what looks to me like something you might get off a radial, like this, then, actually, some of those larger peaks would be extended for a period of seven days rather than one which might be a more realistic -- well, I think it is a more realistic scenario at least in some eating patterns. And certainly I think we recognize in children who don't have a varied diet but a pretty constant diet often high in fruits. Fruits anyway; I don't know about vegetables. And so those peaks might be extended and more recognizable and in a way more realistic

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and capture that.

DR. ROBERTS: Okay. Any responses or comments from the Panel? I think we have another public commentor. Dr. Schreiber.

DR. SCHREIBER: Dr. Schreiber, from the Attorney General's Office.

I didn't realize this was our last opportunity to comment today. So I just wanted to raise a couple of issues I didn't actually hear discussed, but I wanted to just be on the record of bring them up. And, again, we will be providing more formal comments.

I didn't hear any discussion of how endocrine disruption effects are included or addressed in the OP cumulative risk assessment other than I know, in some of the materials I've read, it will be taken up at some point. Can you give us an idea of when it will be taken up and how we will know about it before the final cumulative risk assessment is completed? That's one question.

Along the same lines, at what point is the FQPA Safety Factor considered in this assessment? I haven't heard anything about the FQPA features of this assessment.

And then, finally, and perhaps most importantly, what does EPA and the Science Advisory Panel consider an appropriate MOE for OPs for the cumulative risk assessment? I think that's the million-dollar

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question here. We see these, you know, graphics that show that the cumulative risks, at least on a few of those slides that I can recall, are somewhere in the range to 10 to 100 for the cumulative chronic risks. That seems to be over EPA's goal of 100 as a minimum MOE and that's without even considering this FQPA Safety Factor and endocrine disruption risks.

So I guess my question is a combination of when will the endocrine disruption risks be considered, when with the FQPA Safety Factor be considered, and what is an appropriate margin of exposure in terms of cumulative risks and when will you let us know?

DR. ROBERTS: Okay. Thank you, Dr. Schreiber, for offering those questions.

I don't know if there's any Panel members want to do any follow up or not. If not, we'll certainly take those into consideration as we get into our discussion a little bit later on.

DR. SCHREIBER: Thank you.

DR. ROBERTS: As Dr. Schreiber pointed out, and I would like to point out, that this is the last opportunity for public comment before we move into our discussions. Actually, it is the final opportunity for public comment on this topic. So with that in mind, last call for public commentors. Okay. With that, then we'll close the

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public comment session.

I'm reluctant to go ahead and tackle the first question because it's a meaty one. And I'm not sure. I think if we go into it we might go very late before we get to lunch. So let's take a lunch break now, let everybody ready to go, their thoughts lined up. Let's reconvene at 1:30 fresh and ready to go.

[Lunch recess.]

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CERTIFICATE OF STENOTYPE REPORTER

I, Jane F. Hoffman, Stenotype Reporter, do hereby certify that the foregoing proceedings were reported by me in stenotypy, transcribed under my direction and are a verbatim record of the proceedings had.

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JANE F. HOFFMAN

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JANE F. HOFFMAN

849 S. Irving Street

Arlington, VA 22204

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FIFRA SCIENTIFIC ADVISORY PANEL (SAP)

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FEBRUARY 7, 2002

VOLUME II

Located at: Sheraton Crystal City Hotel
1800 Jefferson Davis Highway
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Reported by: Frances M. Freeman

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DR. ROBERTS: Ms. Olga Odiott, our designated federal official has an announcement.

MS. ODIOTT: We have received several requests for the availability of the agency presentations and the overheads that have been given to the panel.

We are making extra copies right now, and we're putting those copies in the docket. They should be available from the docket by Monday.

In addition, we have the electronic copies of these presentations and the overheads. And they are already with the person who posts all this information to the web site. They should be available tomorrow morning.

So I hope that satisfies the request of many people here that are very interested in having these copies.

DR. ROBERTS: Thank you.

Dr. Doyle, Mr. Miller, would you pose the first question to the panel, please?

DR. MILLER: There are several key principles for conducting a cumulative risk.

One such principle concerns the time frame of both the exposure, what is the exposure duration, and of the toxic effect, what

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are the times to peak effect and the time to recovery.

Both must be adequately characterized prior to performing a cumulative risk assessment so that an individual's exposure is matched with relevant toxicological values in terms of duration. There are several important considerations with respect to the temporal characteristics of the exposures and of the cholinesterase inhibitory effects of organophosphorus pesticides in estimating their cumulative risk.

There may be single day spike or short term exposures to organophosphorus pesticides via food, nonoccupational residential uses and drinking water as well as more or less continuous exposure via the diet, food.

In the preliminary OP cumulative risk assessment, OPP used relative potency factors and points of departure developed from cholinesterase inhibition in rats exposed to pesticides for 21 days or more.

This practice was adopted to reflect cholinesterase inhibition at a point in the treatment schedule at which a steady state had been achieved.

OPP elected to use data reflecting a steady state in the interest of producing relative potency factors, RPFs, that are reproducible and

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reflect less uncertainty due to rapidly changing time sensitive measures of cholinesterase.

In addition, when the compounds are at steady state, the differences in toxicokinetics among the OPs are less likely to impact the assessment.

OPP has information that indicates that the American population in general has some continuous level of exposure to OPs. Biomonitoring data from NHANES suggests that more than 80 percent of the American public have urinary metabolites indicating possible exposure to OPs.

Most animal data available to OPP are developed using laboratory animals that were not previously exposed to OPs. In other words, the laboratory animals used in the toxicology studies were naive in their exposure to OPs.

These studies show that OPs can produce cholinesterase inhibition after a single exposure. A rough comparison of the BMD10s derived from female brain rat cholinesterase data from 21 days or longer duration with no observed adverse effect levels based on cholinesterase data from single dose studies reveals good similarity of values with differences rarely exceeding two to threefold.

Also, animal data suggests that recovery from a single exposure

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may take days to weeks.

In light of all these factors, OPP wants to evaluate exposure across the most appropriate time frames.

In the preliminary OP cumulative risk assessment, OPP developed a distribution of single consecutive day exposures considering the pattern of margins of exposures occurring at a particular percentile of exposure across the calendar year.

This approach focuses on exposure to the population of interest as a whole rather than attempting to track the variation in an individual's exposure from various sources of pesticide exposure.

As an example at the 95th percentile of exposure, each day of the year will reflect a 95th percentile exposure for the entire population and not reflect what may be lower multiday average exposures for any given individual.

Calendex allows calculation of multi-day, rolling averages of exposure estimates for the individuals within the population. While this may allow for a match between selected exposure time frames, for example, seven days or longer, and the hazard endpoint, OPP is concerned that this may not adequately permit estimates of risk associated with shorter duration exposures.

The question to the panel is, please comment on how best to

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evaluate risk taking into account the temporal characteristics of the hazard endpoint, that is, cholinesterase inhibition, and the temporal characteristics of the exposure patterns for the food, drinking water, and residential/nonoccupational pathways, with specific reference to: The pros and cons of various approaches of combining the exposure and hazard time frames to estimate cumulative risk, and methods to estimate the biases in each approach.

DR. ROBERTS: Thank you. A challenging issue.

Before we get to the responses, again, let me please ask the panel members to focus their comments on the response to this particular issue, and then we'll have opportunity for other comments on other even perhaps related issues later on.

Dr. Rhomberg is scheduled to lead off our discussion on this. Please do so.

DR. RHOMBERG: Thank you.

Well, first of all, I would like to thank the OPP for a very clear explanation both yesterday and today of the nature of these issues. And I think that that is going to help a lot in our discussion. It was very well laid out.

I think it was helpful the talk this morning about the nature of the problems that was maybe expanded maybe even a little beyond

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what was in the document. And I think that some of the problems that the agency sees are little bit clearer after this morning's explanation, at least they are to me. And I think that they have noted some real issues.

If I may, I'm going to have a little bit of a long answer, because I think that the issue here is being confused by two separate things being muddled together.

And I think that spending some time structuring the issue is probably worthwhile for the benefit of the discussion of all of us. So I'm going to go on for a little while, but I don't mean to be dominating. But I think it might be helpful if I'm sort of able to work through my answer first.

And I would like to also just as a preface say that it is really important here to distinguish between the ideal and the possible.

And I think it is worthwhile discussing both of those. We discussed the ideal not because you didn't do it and it is not right until you did, but rather you have to really know where you are trying to head with this in order to decide how far you actually have gotten already and are able to get with practical measures.

So I think it is worthwhile talking about both of those issues. But I am really going to try to be practical.

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Obviously, the practical constraints are data. When you start thinking about sophisticated things, they usually require data. Time, in that you have a quick schedule and you have been working on this for a while and you would like to get finished and I think people would like to see it done.

And frankly, also, there is an issue of familiarity and policy issues. When you try to do different things, it takes a while for everyone to be comfortable with the fact that, yes, this really means what it appears to mean and it accomplishes what we want it to accomplish and we're not fooling ourselves.

And frankly, I think that that might be something that might become limiting here just because there are some more things to consider here that haven't quite been touched on.

What we're faced with here now is the longitudinal exposure profiles that you can get for individuals from the Calendex process as described before.

If this is an ideal thing, if we say this is really done well, then it reflects people's patterns of exposure over consecutive days in a way that we can rely on.

I think it is probably worthwhile separating the issue of have the existing profiles that you have been able to calculate so far with the

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methods you have on board achieved that.

In other words, do we have good profiles that we can rely on from the question of given good profiles how would we use them and how would we interpret them.

And we spend a lot of time -- in fact, one of the questions yesterday was really about how good are the profiles in the ways of getting for them for longitudinal exposures characterization.

I think it is fair to say that there was sort of a mixed reaction on the panel to how sort of, well, we think that has been achievable so far.

Some of the comments today, including the public comments, are really about that former question, I think of, you know, are the profiles any good.

We can reopen that if we think we need to, but frankly, what I'm going to do in my comments is assume we have profiles that we think are good or good enough to use and focus on the question of how do we use them and how do we interpret them.

Well, certainly, when you can do this you've got several advantages that handles the issue of multi-day exposure patterns and the possible positive correlation, the leftover effects and things like that.

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It allows for ongoing effects like the gradual attenuation of exposures that come from a residential exposure or something like that as we heard about earlier.

And nonetheless, most exposures are not going to be of the sustained type. And it will allow for the fact that when you average in some high peaks and some lower things, things like that, the averages are lower. And that's important to understand as well.

So the question is if we have these, how do we use them.

Well, since -- as I say, I am going to go on for a little while. I think I will quickly sort of state the main idea, which is, I think that there are two issues that you would want to talk about with some sort of averaging kind of process.

And that a lot of the difficulty that you are having with it stems from not really distinguishing those and recognizing them as two separate things that maybe even need sort of two separate averaging exercises.

The two things are, basically, pharmacokinetics and pharmacodynamics. On the one hand, the relationship with exposures and the history of exposures to the changing pattern of cholinesterase's inhibition day by day that will change as a function of current exposure and exposures in at least somewhat recent past.

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That's on the one hand.

Clearly, that involves some longitudinal issues of exposure there.

And then the other one is a toxicological issue of given that you have a profile like this of changing cholinesterase inhibition, how long can you tolerate various degrees of cholinesterase inhibition without having a toxic effect.

Maybe you can tolerate a very severe inhibition for a short time and not as -- maybe a lesser inhibition if prolonged for a long time would also cause some concern.

And obviously, both of those issues are on the table. And as I say, I think the part of the problem is trying to address both of them with one rolling average approach when in fact there are two things.

So let's look at that first issue, the one I have called pharmacokinetics.

I'm going to start by just sort of considering the way toxicological testing is done and the way doses are expressed and how those would relate to cholinesterase inhibition.

First of all, consider an isolated single dose experiment. When I say isolated, I mean in a naive animal. You give them a single dose as quickly as you can and see if it's enough to cause acute toxicity.

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If you give larger and larger and larger doses, you will get higher and higher peak levels of cholinesterase inhibition.

And in that situation where there is no previous exposure and failing to have some sort of pharmacokinetic difficulties like saturation or metabolism or whatever like that that for the time being let's set aside, assuming the pharmacokinetics are straightforward, the dose level that you give in that single dose is really a surrogate for the peak concentration that you get. And they will be linear related and you will double the dose and you will pretty much about double the peak concentration that you achieve. And so you can use one as a surrogate for the other.

But, of course, we don't have that because we have ongoing other exposures that will have occurred before the peak. And so we want to say, how do we deal with that when we don't have that.

Let's think of the other kind of testing. Chronic toxicity testing where you've given exposure for at least -- it doesn't have to strictly be chronic in the strict sense of the word, but at least ongoing exposures of the kinds that were used in the relative potency factor exercise.

Here you have, again, starting from zero, but you have a dose rate now that has continued on for a period of time until you achieve

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steady state.

Here again, the dose rate, the number of milligrams per kilogram per day that you use eventually has a one to one correspondence in its linear relationship with a steady state concentration of or steady state level of cholinesterase inhibition that you achieve.

So again, in the strict sort of paradigm toxicity testing where the things are kept simple because of experimental reasons, you have this nice correspondence. And the dose rate is a surrogate for the cholinesterase inhibition level that you achieve.

But we don't have that either in this situation. We do have ongoing exposures, but they are not constant, and so they won't come to a steady state. They will pop up and down. They will go up and down depending on the changes in the dose rate from time to time. And so we have to figure out how to deal with that.

Now, traditionally, in risk assessment what we have done is hope that these two alternatives that we have that we do by different kinds of testing and that we evaluate different kinds of exposure scenarios by, when we do a risk assessment, sort of more or less correspond.

We say, well, if typically speaking background exposures are so

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low that the spike that we get from an acute exposure is essentially like somebody was naive, then the testing in the naive animals is directly relevant.

Similarly speaking we say on chronic exposures if it's sort of more or less an ongoing exposure of the same kind of level, then that will tie in humans to a sort of steady state level of whatever the thing is being caused, the concentration of the compound or the effect it may have or, in this case, cholinesterase inhibition. And again, the animal experiences directly relevant setting aside all of the problems that we always have with cross pieces extrapolation and so on. But it is sort of qualitatively relevant the kind of thing.

So then the question is what do we do when we don't have that. We have this fluctuating thing. Let's go back to the acute case again, this single spike exposure. But now say, okay, this happens in the context as Dr. Doyle was showing some ongoing exposure that you had before and not in a naive animal or naive person.

Well, the one day exposure you have, you really can't just take that one day exposure and compare it to an acute level because you are starting off, as was explained this morning, from some background level of cholinesterase inhibition that comes from your previous day's exposure.

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So if I see how high I can jump off the floor here, I can jump a certain height. But if I stand on the chair and jump, I will reach higher. And it is not me who is jumping better. It is that I'm starting from a different level.

So what is the chair here? What is the chair? The chair comes from previous exposures on previous days.

So when you think about this now from the point of view of the rolling average, clearly a rolling average that is centered the around the day can't be doing it. Because how can exposures that you are going to have, now for an acute toxicity issue we're talking about, how can exposures you are going to have tomorrow or the day after or something like that affect your level of peak cholinesterase inhibition that you have today.

I will gladly expose you Tuesday for a toxic effect today. It doesn't make sense.

So at the very least, for an acute exposure or for this sort of pharmacokinetics issue, you have to go backwards in time and not the other way, not forwards, when you are doing a rolling average.

But beyond that -- then the question is how far back do you go. Well, beyond that, it is clear that if you go back far enough, the exposures that you got a month ago, two months ago, those are no

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longer affecting your background level of cholinesterase inhibition today.

What happens in an execute exposure is you get a peak of inhibition and then you get a gradual decline in that as you recover from it. That decline can be rather slow.

But it happens at a nice exponential rate at least in simple kinetics.

So what you can really say is that the cholinesterase inhibition level that you have today from today's exposure is a product of today's exposure, plus some fraction of yesterday's exposure that is sort of hanging over and causing some residual uncorrected, unrecovered inhibition that happened yesterday.

Plus, some smaller fraction of the day before that, and some maybe smaller fraction still of the day before that and so on.

So what you really have is instead of -- first of all, the weighted average has to go backwards in time. Secondly, it shouldn't weight every day equally. It should weight the current, the most recent days more than the more distant days.

How specifically could you do that. Well, you could really do that with sort of an exponential decay type of thing where you say, why is there this kind of exponential -- why is there an exponential

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return from a peak level of inhibition back to normal.

Well, you, I don't know, clear the compound out and/or you repair the cholinesterase that has been affected and/or you synthesize new cholinesterase. So all those processes are going on. You eventually recover.

So I think if you see it this way, you realize that at least one reason for the rolling average thing is to try to be a, sort of, account for this pharmacokinetic kind of process. Because that's what this is. It is pharmacokinetics. Older exposures have less effect on your current level, but they all back to sort of several half lives and in the past have some effect.

And how would you then handle this other than by a rolling average. Well, certainly, as I say, it should go backwards. It should sort of diminish the further out it goes.

One possibility, which Dale Hattis basically, accidentally, adumbrated my remarks with, was to do a simple pharmacokinetic model of the kind that Woody Setzer did in the relative potency factor curve fitting exercise. It showed the power of a simple model like that.

And basically, this one would have to be maybe even a little simpler than that. And you could find a way, then, of tying an amount

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of exposure with the cholinesterase inhibition causes today and the next day and the next day and the next day and so on as a way of doing this kind of averaging.

Or even simpler than that, a suggestion that I actually made a number of years ago, and, frankly, most of my comments today are going to be trying to remember what I wrote on this issue about three or four years ago at the Vermont Elsey (ph) Aggregate Risk Assessment Meeting, where this issue at least -- well, that was sort of the beginning, if I may, sort of, crow for a second, it was at the beginning of the consideration of models like the life line model where you were starting to actually look at calendar-based approaches.

And I, at least, recognized then that some day we are going to be at exactly the point we are at today where we have to decide how to interpret toxicologically these results, and what would you do once you got there.

This is before we could do those things. I said, one of these days we are going to succeed. I was convinced we were. And now, we have. What would you do with those results.

I wrote a little essay about how you would do it. Basically, I'm repeating that now.

What did I propose, then? To use basically a half life of

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recovery from the sort of peak of cholinesterase inhibition as a way to decide how that exponential weighting should go off into the past.

So for instance, I'm going to make it simple and say let's say a half life is a day. And I know that's too short for real. But let's just say that it's a day.

That means that you would count today's exposure fully, half of yesterday's exposure, plus a fourth of the day before's, plus an eighth of the day before that.

And pretty soon it goes away to zero. So you really only have to go out five or six days. The longer the half life is, the longer back you would have to go.

Please note this is not averaging those. It's actually summing them up. Because that four days ago exposure still is affecting your sort of, you know, the chair that you are standing on to some degree, although in a diminished way the farther away you get from it in time.

That would be very simple to do. You just sort of apply this sort of running sum, exponentially weighted running sum and then go through. Instead of a moving average. It is in simple enough calculation that I did it on a spreadsheet there to make a seminar in a half an hour after I thought of it.

So it is not hard to do computationally.

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How do you get that factor, that half life factor? We say, oh, we have to go find this in the literature and so on.

I think you actually have gone a long ways towards that already in the analysis that you did of the steady state data, how long do you have to go to get the steady state. Because the time it takes to get to steady state is also directly related to this half life.

It is sort of delimiting half life. It's the half life that sort of limits -- of the process that limits the recovery rate. And as I say, that might be resynthesis of enzyme. It might be recovery of enzyme. It might be clearance of the compound depending on the thing. It could even be different for different compounds in a way that would be interesting to take into account.

Basically, how long does it take to get to steady state with a repeated dosing thing. About four half lifes. Four or five. Depends on how clearly you think you've -- you know, the exact point of where you think you have got steady state. Obvious -- mathematically, it is infinite time because it's an asymptote. But you get very close within four half lifes essentially at steady state.

So you could say, okay, 21 days. So a fourth of 21 days. That's about five days is a half life for these. Obviously, it is shorter for some and longer for other compounds.

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Frankly, I think the difference between compounds won't be such a big deal here compared to -- the bigger factor would be just what do you choose for the sort of central estimate of all this. You could probably do it with one half life. Or if you think you have the data for it with several compound specific half lives.

Now, this is all practical. Obviously, the ideal thing to do would be a real pharmacokinetic model. Before Rory says it, I will say it. A real pharmacokinetic model where you can look at the metabolic activation and the clearance and any kind of interactions and saturations of processes that go on there and so on and so forth.

That kind of modeling is probably accessible, but not quite in the time frame that you have here.

On the other hand, this simple thing or probably the pharmacokinetic model as Dale was and probably will again suggest, is probably something you can do in your time frame.

I would also say something you should do from this point of view. It is not really addressed in the document what kind of level of cholinesterase inhibition you would expect in humans given dose rate and milligrams per kilogram per day vis-a-vis what you saw in the rats.

I think it is sort of implicitly assumed that it should be the same. But it is almost surely not so, because half lives tend to be

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longer in humans for various reasons. We have slower physiological processes. It takes us longer to pass all of our volume of distribution through the expletory organs. Metabolic rates are slower. And things like synthesis of protein also tend to be slower too.

How much slower? A good guess would be based on allometric scaling by the one fourth power of body weight ratio that, again, Dale Hattis mentioned. This is sort of physiological time scaling. Roughly speaking, human bodies run sort of four times slower than rat bodies.

And so you would say maybe four times longer. That would make a 20 day half life in humans.

You really have to somehow somewhere take that into account. Because if you don't, you are not allowing for the fact that five days ago exposure in a rat they have had more time in terms of clearance activity to get rid of it than a human would, because a human clears it away more slowly.

For every other kind of compound with this kind of slower clearance in humans, the result that is for a given milligram per kilogram per day rate the concentration at steady state goes higher or in this case the amount of enzyme inhibition would be higher.

Again, by about that factor four. So if you don't take that into account, I think you are missing something important.

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If you did the kind of calculation I was talking about, it would automatically take this into account, because you would need to use the half life, obviously not of rats, but of humans in doing this kind of, what I was calling it, exponentially weighted sliding or progressive sum or something like that, I can think of an another name for it, that would automatically take into account.

Parenthetically, if you did this with different half lifes for the different compounds, you could do that. And if they're radically different, it could make a big difference.

This, frankly, is an automated answer to a question. If you don't see it looming on your horizon, you probably should. Carbamoates (ph) and OPs. Carbamoates have much shorter half lifes. There is the famous phenomenon of the carbamoate comes first, then the OP comes second. And then you just switch the order, but with the same doses, and toxicity is completely different.

Why is that? It is because one of them lasts longer in the body. It just raised the chair for the other one more, so to speak.

That would be automatically taken into account by this half life issue.

It would be, I think, a good way of handling that issue. In fact, the only way of handling that issue.

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It also emphasizes that in this whole process what we're really doing is we're making an assessment of carboxy -- sorry of cholinesterase inhibition.

This is an interesting thing about the whole cumulative risk problem, which is, in a way, a little bit of a tangent here that I didn't want to get off to.

But when you do a common mechanism of action based assessment, you are really making the assessment of the mechanism of action in the various ways of sort of affecting it.

And the class of compounds that all do that is in a way almost sort of an arbitrary thing. So we're really making an assessment here of cholinesterase inhibition as affected by a whole set of compounds.

Putting all this stuff in terms of cholinesterase inhibition then makes it into the common currency that's really sort of implicit in your whole approach to the thing, or inherent in the whole approach to the thing.

So what would happen if you did that kind of weighting that I was talking about. First of all, you have to realize it's a different kind of exposure measure because it is not sort of a daily exposure and it is not an average daily exposure. It's this sort of summed up thing.

So the numbers will get big because you are adding exposures

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from previous days, although fractions of exposures from previous days.

You have to tie that to the cholinesterase inhibition that would result from it.

And the way you do that is by doing the same kind of exponential process on the rat data that you use for the steady date and say, this kind of steady state, exponentially weight exposure thing leads to 10 percent. It is just a matter of rescaling the dose scale, and that will all take care of it. So that should not be a concern there.

What does that all mean for all of this? That, clearly, one of the reasons for doing this kind of moving average is really sort of a poor man's pharmacokinetics. And it doesn't work for that.

On the other hand, a small modification of it would work pretty well.

What I just described probably gets 80 percent of what full pharmacokinetics would get you, I would say. Rory is not quite so sure.

I don't think that in the long run -- I think in the long run you want to try to do the full blown pharmacokinetics. But I sort of predict -- I know that in the short run you won't be able to do that. And I predict that in the long run when you do the answer you get

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from this will be quite close to that.

So that means you have to do, even for acute exposure, just for the peak, you still have to do this kind -- some kind of rolling average but modify the way I have discussed in order to really get the right answers.

Now, what about the other issue? That other issue still exists. That other issue of, well, okay, so for acute exposures, the issue is peak inhibition rate -- or for acute toxicity, I should say. It really should say, for acute toxicity, the issue is the peak that you achieve.

You could assess that easily in these profiles by doing the kind of thing I get. I basically would recommend translating all this into an estimate of the degree of cholinesterase inhibition you get. This common currency that it's really all based on rather than leaving it in milligrams per kilogram per day and having the MOE in that same unit, sorry, the BMD in that same unit and judging the MOE in terms of cholinesterase inhibition.

And you could run through your profiles and see if there is ever a case where exposures sort of build up in their pattern in a way that will ever throw you up over the top.

The image that you could have is these little VU meters that you get on stereos that bounce up and down with the music.

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And then the question is, does, in the course of a whole song, does it ever get over into the yellow or the red zone or whatever. That's for acute.

But you say, okay, it is also conceivable that a prolonged exposure to inhibited cholinesterase at some lesser level than this peak that would cause toxicity nonetheless could have toxic effects. Maybe 20 percent inhibition for a week could have -- I'm just pulling that out of the air, I don't really know this from any data, could cause an affect.

Or maybe it is 15 percent inhibition for a year or whatever.

Basically, other ongoing toxicities would then have to be evaluated in terms of how long you can tolerate how much inhibition. And the difficulty there is that our experiments are always done from this sort of naive animal steady state dosing thing so that we can make that kind of easy connection between the dose rate and the steady state inhibition that sort of allows us to operate in the realm of -- the familiar realm of sort of external exposures rather than internal measures of dose.

When this fluctuating around like that, you can't do that anymore. It doesn't work. And so what you would then have to do is say we have the same profile now operated on by this smoothing and

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integrating process of the exponential thing to get cholinesterase inhibition.

And you could now again do a second run through it. This time really doing weighting average, running weighted average. And say, okay, if you have going through on a seven day scale, if you ever get above a certain level on the seven day weighted average thing, then you run the risk of toxic effects that happen when you are over that level for that amount of time.

And if you do with it a 14-day weighted average, you run the risks of things that would happen if you stay above that level for that amount of time.

The challenge, then, is a toxicological one of turning our studies of toxicology in a way we express doses in them into the kinds of things that could say this sort amount of time spent above level X is what is actually causing the toxicity and things that don't make it that high or for long enough don't keep the inhibition high enough for long enough would not have those effects.

That's a challenge to figure out how to express the toxicity that way. But in a way, you are sort of stuck with it. You have to sort of figure out what to do.

Again, to make it practical, though, what you could do is you

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could do lots of different averaging times. And you will probably discover and the way the data looked to me, you will probably discover that averaging times over a certain amount of time, running averages, once you do it on this inhibition -- translated into inhibition levels data will probably be, you know, have acceptable margins of exposure.

And if it is acceptable for a certain averaging time, it will be acceptable for all longer times than that.

Because, for instance, the way you seem to be interpreting the data on the 10 percent inhibition in the rats is, okay, it takes 21 days to get to steady state, but the implication is that longer and longer times the inhibition doesn't get any worse and neither does it cause any toxicities, that you could tolerate 10 percent inhibition indefinitely.

So that means that any averaging time that keeps it so that you never have 10 percent inhibition, anything longer than that is going to be even less of a concern. And you can sort of see how long the time has to be in order to get yourself into that ballpark and see what -- does that make sense that you are avoiding those toxic effects from what you know from the toxicology.

So that's a long-winded way of saying that I think there are two issues. One is a pharmacokinetic one, which you could solve

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perfectly with pharmacokinetics, but you can solve probably very close approximately with a modified kind of weighted average of the kind that I was talking about allowing for cross pieces extrapolation of the half time issue.

And then there is a second issue which is the toxicological consequences of the profile of day-by-day cholinesterase inhibition that you got out of the first step, and go through that again with a bunch of different weighted averages and see sort of how long you have to stay over what in order to, you know, sort of get something that looks high compared to what you see in toxicological studies and the kinds of internal exposures of enzyme inhibition -- of a cholinesterase inhibition that led to toxicity in those experiments.

I think that if you do that, again, this is all predicated on the notion that these profiles of the exposures you get are good enough to handle all of this, you really sort of bracket things. On the one hand, you have the acute effects. On the other hand you have sort of, say, chronic and anything longer than this is also okay.

I think that you can probably with the data you have, but just a little different way of treating it and analyzing it at the end, come up with a fairly good characterization of what is going on.

But it comes by separating those two issues and realizing that

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you can't do them both with one averaging, one rolling average. You have to do it twice. One for pharmacokinetics in the special way that I mentioned and then the other for toxicity.

That was long enough. That's about it. I guess I will let everybody else comment on this and their perspectives as well.

DR. ROBERTS: Thank you, Dr. Rhomberg.

Actually, you posed some interesting ideas. Before we get to the next comment, I wanted to check with the agency. Do you want any clarification on his comments before we move on, or would you want to sort of hold those until you hear from other members of the panel?

DR. DOYLE: I think for our purposes, and if you disagree, tell me, but I think it would be nice to hear a range of comments and then have a discussion if that would be all right?

DR. ROBERTS: That's absolutely fine. Let's go, then, to Dr. Brimijoin.

DR. BRIMIJOIN: In comparison to Dr. Rhomberg, I'm just a simple pharmacologist. I feel like something like a guy who spent most of his life trying to predict the weather from cloud formations, humidity, temperature, dew point, and now we're entering the era for four dimensional climate modeling on a super computer. So I'm not

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going to attempt to fly the super computer.

So I agree totally with Dr. Rhomberg's approach in general as an ideal to the extent that I understand it.

So I'm going to raise -- I think we have heard about a way which -- I think you have done a nice job of pointing out something short of the ultimate ideal of a perfect physiologically-based pharmacokinetic model, which would nonetheless capture a great deal more of the actual variation that is going to be out there and the toxilogical consequences of that. And I think that's commendable.

I'm somewhat uncertain about whether in the time frame that we're talking about now whether -- how well EPA will be able to rise even to that next level. I guess I would see that as possibly the next step that something we should in fact really point our guns at i so soon as we have decided what to do in the immediate case.

So I just want to raise an issue that has stuck in my mind as I listened to the deliberations the past several days. And one that I believe would be captured if we were able to move to this semi-ideal exponentially-based averaging method that is looking at half lifes of effects, summing them appropriately and with appropriate rolling averages over the calendar year.

A much simpler grosser look at this issue would be, however, to

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ask whether -- well -- come back to what I still think is central to the EPA's planned approach now and may still be the way we would proceed if we could get to you at the next level with this sort of, how should we say, exponentially weighted rolling sum.

And that is the issue of -- if I do understand the agency's position correctly, we're going to use a lot of science to turn the multiplicity of OPs out there into a single OP. So we're going to use relative potency factors.

And so almost everything else we do the effects of that are going to be a condition on how we make the choice of generating these equivalents, relative potency factors to generating what you might call equivalent exposure levels.

And I see a potential, anyway, I believe, in fact, maybe some actual danger in trying to lump everything together in this way, however elegant it may be mathematically and however essential it may be to get a proper manageable algorithm depending on just how much difference there is in the, say, biological half lifes of these -- effect of biological half lifes of these agents.

So come back to the issue of determining relative potency factors based -- in comparison to methamodophos (ph) based on steady state effects. So dosing paradigms bring us to steady state.

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I think the evidence is pretty good that you do get there at least in animal treatment models, exposure of about 21 days or so. And that sounds right to me.

It may not be actually that much different in humans. There are some of these parameters that differ maybe quite a lot. But I happen to know something about the turnover times of cholinesterases in humans. And they may be different. But I don't think they are scaled by a factor of four.

But anyway, let's grant that we have got a, for the sake of argument, we have a way to dose animals and determine with -- be confident that we are at steady state. And that's a comfortable position to be.

So then we can generate based on the tightest available data which we have learned is inhibition in the female rat brain. We can generate some relative potency factors that we have a lot of confidence in. We can use those to convert things back so we can decide that one milligram of chlorpyrifos, which is not relevant anymore, but is equal to 10 or 0.1 milligrams of methamodophos, fine. So we can start adding these things up.

I think that from the admittedly simple minded viewpoint that I have, that would probably be a fairly good way of summing up effects,

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and then cumulating effects, I guess that's our business right now, accumulating the effects from exposures to multiple OPs that were coming in in a dosing pattern, thinking of Dr. Doyle's high tech, graphic, but actually very lucid explanation of our problem here, dosing patterns that are either -- they are continuous enough or repetitive enough that they tend to generate, let's say, lumpy looking exposures rather than spiky ones.

And again, in a very simple-minded way, I imagine that is the way we get exposed to agents in food, in water and air for the most part because we happen to live right down stream from the methamodophos factory.

And I think probably a lot of this background exposure that results in 80 percent of the population having detectable metabolites in their urine comes in this way. I feel pretty comfortable about that.

What I don't feel comfortable about, I don't feel authoritative enough to say I feel uncomfortable, therefore, there is something radically wrong, is whether this approach, single method for calculating RPFs based in this way is going to serve as also or equally well with the sporadic exposures that I expect are coming from residential lawn pesticide, orchard -- acute exposure scenarios where I think the Orkin man visits, the house is bombed or the cracks are

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coated.

I imagine that does lead to a spiky irregular dosing pattern.

And so that would be just fine if there isn't very much difference in the relative potency factors estimated not at steady state but after an acute dosage.

So if they are really the same or almost the same, I think that's just fine.

And the document we have here indicates without going into specifics that it isn't too far off that maybe two to threefold.

But at least I want to raise for consideration the idea that when we're folding in these different individual compounds into a cumulative assessment, a cumulative assessment where we are actually cumulating exposures based on these equivalent doses, that we need to take a close look at what the relative potency factors would be or are after an acute exposure.

And I would submit that if they are noticeably different, we should think about actually somehow splitting up the algorithm to take -- to decide that for the compounds that are, the very limited number that are still approved for residential exposure, give consideration to either substituting the relative potency factors based on the acute data for the chronic ones or somehow weighting things so that when we are

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specifically dealing with the kinds of applications or the kind of exposure scenarios, residential exposure scenarios, that in those scenarios we use a relative potency factors that are derived from a time frame that is consistent with the likely pattern of -- the likely temporal pattern of the exposures.

That's really my only comment.

DR. ROBERTS: Thank you, Dr. Brimijoin.

Dr. Richards?

DR. RICHARDS: Thank you.

I find myself sitting here thinking that I'm sort of the panelist equivalent of the naive rat that has had relatively little exposure to organophosphorus toxicity arguments and so forth.

So I'm starting from the bottom. Not on that chair. And maybe that means that my brain won't be quite as inhibited and I would be looking at things in a slightly different way than the rest of you. I don't want to take that analogy too far.

But my experience with OPs is mostly through what we see in monitoring water sources. So I'm not really that familiar. And a lot of this toxicokinetic modeling stuff is new to me. I'm just happy I can even say it.

But from that perspective, I would say that I had some real -- I

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really have found the exposure side of things very interesting, very innovative, very imaginative and quite reasonable. And I have had a real hard time getting my mind around the toxic side of things, the toxicity side of things.

It's basically -- the problem as far as I can discern is that I'm having a hard time deciding what is the toxic effect you are talking about.

Is it cholinesterase inhibition itself? Is that just a measurement endpoint that is used as a surrogate for some other toxic effect?

If it is a measurement endpoint but not an effects endpoint, then what are the health effects that we're concerned about?

It seems to me this is a much more subtle and obscure issue than would be the case if we were talking about a known and established carcinogen or mutagen or something like that.

Then we know what we're trying to protect ourselves against. It is not the cholinesterase. It's the cancer that it causes in that hypothetical example.

In this uncertain context about what the effect we're trying to protect against is, there is one point it asks the question about how long does it take for recovery. Well, the question is what is recovery.

And at least for me, the lack of clarity of my understanding on

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these questions makes it extremely difficult for me to begin to think about what is an appropriate interval for exposure assessment or how you match that up with some kind of a response effect.

I think in a sense a lot of the comments I'm going to make kind of echo what has already been said but perhaps in a more general and less specifically toxicologically oriented fashion.

At one point there is a statement something along the lines of, OPP is concerned that Calendex may not adequately permit estimates of risk associated with shorter duration exposures.

I must say that the presentations this morning really helped me a lot to understand even what this question was all about. Because I think a lot of the basic information that was laid out this morning was sort of missing from the question. And that probably reflects somewhat what I have developed as an answer.

But it struck me that that question about, you know, is it adequate to permit estimates of risk associated with shorter duration exposures, it is in itself a rather vague statement.

Again, what kind of risk is associated with shorter duration exposures. Is that qualitatively different from longer term exposures. Was it just a question of how you average things. How high do concentrations have to be in the short term for them to have some

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effect that we're concerned about here.

One of the things that strikes me is, unless people talk about acute and chronic issues, is that they seem to be defined in terms of duration and intensity to exposure rather than in terms of effects.

In a lot of other cases that I'm familiar with, you may very well have a different acute endpoint than you do -- an acute endpoint may be skin lesions and the chronic endpoint may be cancer or something like that.

So it gets confusing for me to even figure out how you separate acute from chronic if you are only doing it by the dosing pattern. And then you have to go through this process of somehow averaging or aggregating it over time. The two concepts sort of lose their separate meaning for me.

So I suppose really the gist of all of that is aiming at what really is it that we're concerned about that's the toxic effect. I guess I at least could use some clarity on that.

One thing I thought was worth mentioning as a possible analog, and it actually really is quite close to some of the stuff that was presented earlier, but simpler, is a model that has been used in some herbicide studies involved with ecological risk assessment of herbicides in which basically the herbicide is acting as an inhibitor of

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photosynthesis. It is not directly lethal to the plant. Toxicity occurs in effect by starvation.

So you inhibit the photosynthesis. And if the inhibition goes on long enough, the plant dies.

If the inhibition is removed, the plant says, oh, hey, let's make some more sugars and it takes right off again and continues.

And really, all that has been lost in a sense is some time for development of bio mass or whatever.

Now, whether that is important or not is an ecological question. And I'm not really interested in defending this model, but it seems to me that other than the fact that you don't have to do -- in a sense, it is an on/off switch rather than a five-day cumulation or something like that.

But it's very similar. And what you kind up doing is saying, okay, if we can identify the endpoints -- I'm sorry the thresholds for inhibition, then we can simply take time variant data and say, what is the distribution of episodes of continuous exposure above that threshold and link with that the distribution of episodes of recovery or available recovery time. And that is your basic information that you are interested in looking at.

It has in common certainly the same element of this post

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exposure, post recovery, except in this case there seems to be a considerable lag time before you reach full recovery.

But that serves as an interesting model that has been explored in a different arena. It may help to serve this process along.

I like very much the ideas that were presented and I would like to see it develop in that direction.

Thank you.

DR. ROBERTS: Dr. Reed?

DR. REED: Now I understand what people say when you get five toxicologists together you get six opinions. At least the perspectives is very different, but I think the agency wants to hear, different perspectives.

I am coming from a risk assessor's point of view. And I'm looking at this situation that part of that issues or hardship is really not unique to the cumulative risk assessment.

The matching of period of exposure and the toxicological database is really basic in all the risk assessments that we do.

And I think within the cumulated risk assessment framework, one thing that stands out to be different is the relative potency factor. How are we going to come to that and so forth.

Let me go back a little bit to the sort of general issues that we

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deal with in risk assessment. Short of pharmacokinetic models, I think there is always going to be something that we're not as comfortable with in terms of you, you know, period of time and so forth.

What we usually do, I think majority of people do, with different durations of exposure and different patterns of exposure is to do nodical sets of risk evaluation.

Acute, sometimes people define it as after seven days. I would say within three days at the most, usually, single day kind of spike situation. Having done the single spike risk assessment doesn't mean that there is no exposure the next day or day before.

So you do the spike. You do the acute. Then you do a sort of a subchronic or short term. And I think the agency have always done that. Then you do a chronic.

Then if it's related to oncogenicity, then you do a life time.

I think that sort of four measure period of time frame will still work in this situation and should work. Otherwise, we have to go back and rethink the whole risk assessment for even for single chemical.

As I said, short of pharmacokinetic model being able to use and clearly identify the target organ dose and the pattern that goes to the target organ, it is just going to be not quite satisfying.

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And that's okay because we have this mechanism of recapturing all the uncertainties at the very end of the risk assessment in the descriptive part of the risk characterization.

That is just going to make the work of making risk management decision more intelligent in that sense.

So that the risk management decision is not really based on just the numerical thing, the one you seen. So that's okay.

Assuming in looking at the exposure assessment that we have so far, I'm quite confident that it is not a problem to identify a spike in terms of exposure of dose level.

It is not a problem to do the rolling in order to find the highest rolling point within the time frame that you want to match up with toxicity.

So the exposure component seemed to be all there. And it is easy to extract based on what you want.

What I think is -- it is a give and take kind of situation with the time frame and with the different perspective for something in the future is how far we want to go into to figure out what needs to be done, sort of the minimum kind of thing that needs to be done.

One thing is that I think -- I could imagine that the relative potency factor would be different for the acute type of scenario than

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the subchronic or the steady state scenario.

So there is -- at least I would like to see a different set of relative potency factor.

Relating to that, for the acute type of exposure, the spikes, I would like to also to reconsider the selection of endpoints.

It might not be brain cholinesterase. If cholinesterase being the common mechanism is something that we're looking for as an endpoint, it could be some other endpoints. RBC cholinesterase inhibition or plasma. It really depends on how the database look like.

A shortcut to that is that, if one does not have time and sometimes I don't have time, so I make shortcuts, a shortcut of that is that the agency seemed to have already looked at some form of comparison between the acute and the steady state.

And based on the table that we have seen, some of them are fairly similar and some of them very, say, three to fourfold differences. You might be able to get a jump or at least a jump start to make that extrapolation. Not to say that in the future you would not finetune it. And this is about the relative potency factor.

I mentioned that the endpoint could be different. The reason I'm thinking of that is also partly because a lot of acute studies that we derive or we could make use of to make threshold decision comes from

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FOB studies.

And FOB studies -- well, a couple issues with it.

One is for each chemical, there is different time to peak effects. And that's when the cholinesterase is measured.

At least for the plasma in RBC. The brain, I think, usually are measured at the 14 days at the end of that, at the terminal sacrifice.

So because of the different time to peak effect and the measuring of cholinesterase inhibition associated with that, you might find it a little bit fuzzy in terms of comparing the toxicity based on that kind of data because it was measured at a different point.

The way I understood, time to peak effect is not because of the peak cholinesterase inhibition. It is because some endpoints that we decide to use as time to peak effect. And that's why it is going to be a little bit fuzzy.

I would suggest that some time in the future do a pilot study just based on some high contributing chemicals and see what is doable and not doable with the database on that issue.

This morning we sort of got the model of a continuing high background versus low background. What was going through my mind when I look at this question is that with the higher background I could imagine that there is a sensitivity issue in that if an organism human in

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this case have been compromised in terms of having a low percentage of cholinesterase inhibition already as an ongoing.

I would think that the sensitivity of a spike effect would have to take into considerations too in that for clinical science and all that you might see some tolerance with the repeated exposure. But certainly, I have not seen that with cholinesterase inhibition.

So if we're going to use cholinesterase inhibition as an endpoint, then that sensitivity you have to take into consideration if you have high background.

We're arbitrarily using those terms, high and low. We haven't defined what is high and what is low. How low, how high.

In terms of -- when I said that we usually have these four -- when I said that we usually have the four time frame for characterizing the risk, it would look like that from the exposure component if a longer time, sort of a chronic scenario, 30 days, 90 days, a year is going to be a separate set of analysis, then one could imagine that the exposure would always be lower than, say, 21 days or less.

So you might not need to do all these scenarios. You do the scenarios after the steady state, is what I'm saying.

In terms of toxicity for the same thing. If your toxicity reaches

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certain steady state, you don't need to go any further unless the endpoint changes. And that is a possibility.

If you look at the chronic exposure and the endpoint indeed it being not different, that you decided that it is necessary to do a different endpoint, then, of course, you have to go back to the different exposure period again.

I think that's it.

DR. ROBERTS: Thank you, Dr. Reed.

Dr. Hattis?

DR. HATTIS: I just want to apologize to people for jumping the gun on the answer to this question which I, in my confusion, gave the response to the previous question.

And I want to also congratulate Lorenz in giving a much more lucid and (inaudible) explanation of what I was getting at, at least the core of it, than I did.

So basically I want to second what Lorenz said about the modeling of cholinesterase inhibition.

And then in response to Dr. Richards' and Dr. Reed's comments, I want to just expand a little bit on this issue of what I had expected to do for the next question about the long term future of revisiting the issue of what the appropriate endpoints ought to be and how we

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connect them with the adult rat, adult female rat brain inhibition of cholinesterase to a particular -- (inaudible).

I think to do that I want to kind of remember some of the original impetus for the passage of the F Q P A.

And that was the concern expressed in 1993 NIS document that there might well be relatively narrow windows of vulnerability of developing children that could be more sensitive or differently sensitive to neurotoxins in particular than would be the case for adults.

And so I think that what we want to think about is say, okay, look at what is happening during childhood, during early childhood in humans is a process where different neurons are deciding to survive or not survive.

And they are making all kinds of different connections in part by sending signals with each other that are mediated by cholinergic mechanisms.

So that when we have inhibition of brain acetyl cholinesterase in a young child where this process is happening, it is not too far out to suggest that that might have different kinds of effects, give rise to different endpoints, in fact, at different levels of sensitivity than might be found in adult, in an adult brain.

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DR. ROBERTS: Dr. Hattis, if we're going to go into whether or not we have got the right endpoint, I'm not saying that's not a valid point, I think we're going to probably get into that in just a little bit.

DR. HATTIS: We'll get into that next time. Yes. Okay. But just to suggest that the -- as an extension of what Lorenz was saying, we might in the future want to reevaluate how, what our tolerable level of expected brain cholinesterase inhibition might be depending upon the age group. Because both the rates of regeneration might be different in young versus old.

And also the vulnerability to different degrees of inhibition over what time period might be different for young versus old.

And that's such a thing that we can't probably definitively assess today, but seems to me there should be an effort to make that assessment in the future.

And in the meantime, it is not outrageous to suggest that the margin of exposure that might be considered in risk assessment might be different for inhibition, expected inhibition in relatively young age groups than older age groups.

DR. ROBERTS: Thank you, Dr. Hattis.

Dr. Freeman?

DR. FREEMAN: Briefly, to pick up on what Dale was saying,

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given that we're dealing with cholinesterase inhibition and recovery in adult female rats as the endpoint, it may be valuable to know if there are differences in adult or young rats or humans in the degree of inhibition and how long it takes to recover from an inhibition from similar types of doses.

I don't know whether you have much on that yet.

From the other point of view of my table here, understanding the relationship of the temporal characteristics of the hazard endpoint and the temporal characteristics of the exposures from water, diet and residential pathways, requires that the temporal characteristics of the exposure pathways be similar.

In the document we received it says, regional differences in pesticide use are major considerations in appropriately estimating exposures from pesticides in drinking water and residential uses.

I would argue that this is also true for diet and -- my saying that is not simply a matter of wanting consistency in the way the assessments are done across the three pathways, but that it is important to the quality of the assessment to take into account regional and temporal differences in diet and pesticide residues.

To give an example, during the presentation on the water model, a figure of California pesticide use across the year was presented.

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I think that was a powerful example of why it is important to evaluate food pesticide residues in diet by region and season of the year.

There are growing areas in the country. California and Arizona are prime examples that restrict importation of commodities that they grow themselves.

That being the case, the diets of the individuals living in these regions will be influenced by the local foods in their residues more than ones from other areas during the time periods that the local crops dominate the market.

Connected to that is a concern that pesticide treatment of home gardens is only treated as an influence of residential exposure but not on diet.

It is likely that these occur jointly during the same time period as the garden vegetables are treated with pesticides and then consumed.

This will add some complexities to your model. These things are not independent.

But consumption of locally grown fruits and vegetables is common. And in many regions of the country, they are important seasonal additions to diet, and hence to the exposure to the people in

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those areas.

DR. ROBERTS: Thank you.

Dr. Heeringa?

DR. HEERINGA: Just a few brief comments. I have to confess that scientifically I'm probably about as far removed from this subject as anybody here on the panel.

But in some ways, that places me in a position sort of evaluating what I have heard on this particular topic.

One thing that are clear to me in the facts here, the points of departure and the relative potency factors and I think even the effects level that we have seen in these presentations are all based on steady state studies that really in my naive view closely resemble patterns that are more like the chronic exposure pattern and the acute exposure pattern.

I have seen nothing on the scientific discussion in the past two days that suggest that acute events have a different endpoint with regard to cholinesterase except to set the chronic clock running at a fairly high level.

In other words, there is obviously a much more complex mechanism that we don't understand here. But I have seen no discussion of outbreaks or sores or people fainting or people unable to

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function or loss of motor coordination or activity from these acute doses.

Now, some of that must be there and possibly in the studies. But even at the high dose levels, as I understand it when we are looking for steady states that we go for steady state activity at even higher dose levels in the female rat test.

So again, unless there is other evidence that we haven't heard here, I see an absence of evidence. And that doesn't mean effects don't exist for what these acute effects would be on cholinesterase inhibition.

I very much agree with Dr. Rhomberg's model to roughly model bio available levels of OPs on a given day as the sum of the current day's dose and half life depleted doses from the prior days.

That's an excellent suggestion. Because I think it really reflects cumulative processes that are very realistic in normal exposure patterns.

Also, one additional comment that I would have, in the process of averaging, thinking specifically for the chronic exposure path, is the averaging of daily exposures over a window that centers on the current day is actually a form of smoothing.

I think it is much more realistic to create what we would call a

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moving average as opposed to a window average. That is you average over the previous 21 days or the previous 14 days. Because it reflects, again, the realistic pattern of accumulating exposures in the human body.

The other thing that it would allow you to do, and I think this is a piece that I don't understand and I think the toxicologists are going to have to help us inform, is it would allow you to look at the leverage of acute event that comes on top of a period of fairly high exposure.

In other words, if you computed your chronic exposures as an average over previous time, any blip in that chronic exposure curve would probably be the result of an acute event on a particular day.

And again, acute events in the future, while they may be important in the future, they are not really important at this point to exposure levels.

So I think you would have full information of the impact of acute events if you created your moving averages as a function of averages over preceding days, unless there is something that my colleagues see that I'm missing here. I think that even for chronic analysis I would use Dr. Rhomberg's model to get daily sort of available exposure levels and to use moving averages over a

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retrospective period of time.

I don't think anything is lost there I think and I think something may be gained in terms of information.

DR. ROBERTS: Thank you, Dr. Heeringa.

Dr. Durkin?

DR. DURKIN: Under advice of counsel, I'm going to restrict my remarks to the exposure spike issue with the understanding that we'll get other things soon.

The ideas raised by Dr. Rhomberg and endorsed by some of the people around the table are interesting ones to me that the agency could explore. They are contrary to what I will be recommending.

But the only thing that I would want to caution here, and I very much doubt that there would be any disagreement around the table, if you adopt something like that, at least make an attempt to determine if it's consistent with data that you have.

And the reason that I am uncomfortable, not with this suggestion, but I guess I don't have a high optimism that you will validate it well is that the temporal relationships in acetyl cholinesterase that I'm familiar with are God awfully complicated. And they don't seem to follow -- the rats just don't behave. They just don't do first order things all the time.

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And there is some human data out there that have me just totally puzzled. And again, they just don't fit a simple pattern.

Nonetheless, if you do find data to support the approach, I certainly would be the first to endorse it.

My somewhat simplistic recommendation, and I will quote, thus the agency, at this time, goals should be humble, and one of the things that I think that you could look at, I think you have done a Dandy job with steady state, I originally recommended the first time I was down here that we incorporate time as an explanatory variable.

I think that's insane as I have looked at the issue further and come to better appreciate the data that you have.

I am much closer to my fellow risk assessor right across the aisle here taking perhaps a simpler approach if nothing else seems to pan out. Because I think you really have to do to address the spike issue.

But at very least come up with some acute numbers. And I think we have talked about this in the past.

You typically have acute numbers for a lot of the pesticides anyway. You are currently coming up with one day RFDs, or whatever you want to call them, in drinking water has been doing this pretty much forever. So that's not hard.

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I think it is relatively easy. I'm not the least bit surprised for the OPs to see the close correspondence between the longer term and short term. I fully expect that. I fully believe it.

So if Dr. Rhomberg's very elegant idea doesn't appear to be sufficiently implementable quickly or doesn't seem to fit the animal -- and by all means we really have to be ruled here by the animal, they make the decision, and by the available studies, especially that we have on people, and some of those are very good, if that doesn't pan out, I think you really can take a simpler approach.

Now, how you actually implement it, when is a spike going to be considered acute, when is it going to be considered not, you know, that is, I'm afraid judgmental.

And I don't think that we can make up a cookbook recipe here.

But I certainly think you people have the capabilities to make those decisions, make them clearly, articulate them, go out on the limb, and then invite us back so we can saw it off.

DR. ROBERTS: Thank you, Dr. Durkin.

Comments from other members of the panel?

Dr. Bull and then Dr. Conolly.

DR. BULL: I'm going to make some of the same points, but in a slightly different emphasis, I think.

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The issue you got in front of you is a common mechanism. That common mechanism you chose to be cholinesterase inhibition.

Cholinesterase inhibition may not actually account for all the toxicity the member of that class. But that's fine.

You have kind of put part of the issue, not all the issue that Dr. Richards brought, you kind of have to put that to the side.

So you are really only addressing in this process toxicities that arise from cholinesterase inhibition. It is important not to forget that.

Given that focus, then there is no better integrator of toxicity, I mean, your measure here than the cholinesterase inhibition.

And the issue about acute and chronic I think is a trivial issue almost in a way, because acute doses will have certain magnitudes and will give certain rise to certain cholinesterase inhibitions.

And I think you have essentially made some kind of decision. Maybe not as to what the point of departure is absolutely yet, but when you say benchmark dose 10, that's probably not going to be bad for either acute or chronic.

You are talking about things that are in the weeds. As long as you are talking about effects that arise cholinesterase inhibition.

To me, that's best addressed in a pharmacokinetic model similar to what I think a formal model wouldn't be that much more difficult

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and probably be -- than what Lorenz said. But that's fine.

The main variable there, though, is the recovery time. And the recovery time has two, at least two components.

I'm not going to call it a pharmacokinetic model because in my mind that starting to get somewhere else. And you are not talking about kinetics of the parent compound. You're talking about the kinetics of enzyme recovery.

That has at least two components. That's a spontaneous regeneration rate and enzyme resynthesis rate in whatever compartment you are talking about. It doesn't make any difference.

Then that brings it back to the question that Dr. Brimijoin -- the whole weakness of this thing is not trying to use a pharmacokinetic model. The whole weakness is how much confidence you have in those RPFs. Because those RPFs will vary primarily based on differences in the hydrolysis rate of those phosphate esters.

The enzyme synthesis rate will presumably be more or less independent of which agent (ph) caused the inhibition.

So that -- as long as you know that that is what is accounting for differences in RPF, you perhaps can even repair those. And I think there is probably data out there that tells you how stable those are.

This is not my area. But it seems to me that that's a very doable

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and, I don't think, difficult thing to do.

The only thing that I think that I would say, and this gets more to sensitive populations and whether humans are the same as the rats, is you really would need -- you would like to have the big variable here as far as the subject is concerned is in fact those resynthesis rates and how they may vary in different departments and in animals of different -- in humans mostly, humans of different age.

That's the variable that's important here that one, I think, needs to deal with when you start trying to slide from cholinesterase inhibition at some level over into some toxic manifestation you feel arises from that.

That's all I have.

DR. ROBERTS: Thanks, Dr. Bull.

Dr. Conolly?

DR. CONOLLY: Let me just pick up on the point Dick was just talking about.

Dick, I think the RPFs actually would be strongly influenced by pharmacokinetics as well as things like hydrolysis rates. Because a lot of these OPs do require bioactivation.

And bioactivation rates are going to be determined as a potency.

Let me move on to some more prepared comments that I made,

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though, in response to this question.

And this first comment is an effort to hopefully put some of the other comments that have been made by the panel members in a bit of context.

I have some background, some experience in actually developing very ambitious complicated models and then using them in risk assessments.

And what we find, and we're seeing examples of it here today, what we find when we start to develop mechanism based models and participate in the thinking process that accompanies this development is that we're always thinking about the next step you know, about how the model could be refined.

And this actually is in distinction to the more static situation you have with policy based approaches to risk assessment where you just plug a number into a formula and you get an answer out.

But when you do take the more ambitious approach, the mechanistic approach and want to actually complete a risk assessment at some point, it is really necessary to draw a line with respect to the technical development of the various models that are feeding into the assessment, in this case, the cumulative assessment, freeze the model development process at that point, and then go on to complete the

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assessment.

So, of course, refinement of the models and better understanding of the underlined biology can always contribute to future assessments.

It can be discouraging if you are always being told about the things you might do or you could do and you really have a job to get on with an assessment.

So I just want to make the point that sometimes you have to stop and say, okay, we're going to just finish up here. And maybe the next generation of models can contribute to the next assessment. That's one point I wanted to make.

I was told -- actually I read it in the one of the files on the CD that there actually is a PBPK model for three 0Ps. I gather that I think maybe Jerry Blancato (ph) has developed.

So we're not quite as far away from having maybe the most desirable tool for pursuing these kinds of assessments as we might have thought we were.

But it did occur to me when the presentation was being given with the acetates and the questions were being asked about these various alternative exposure scenarios, you know, how to evaluate those, how to think about them, is that you can actually take Jerry's

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model, presumably existing model, and feed those kinds of exposure scenarios into it and see how cholinesterase inhibition varies as a function of exposure scenario.

You actually have a tool for doing that right now. It clearly wouldn't be the same as having a PBPK model for all 29 OPs. It is not what you would like to have. But I think you would find it would provide incites and it might well bound the problem that you are trying to address in some ways.

So I would encourage you to think about exploiting as fully as possible the tools that you do have at hand in trying to answer that question.

Finally, I think I mentioned earlier in the week that I got tasked in January with reading the cancer guidelines. There was a public comment period that finished up late in January.

And so I actually read every page of the cancer guidelines, believe it or not.

And it has been striking sitting through these meetings here over these last few days how many of the issues that arise in the cumulative assessment for OPs are also considered in detail in the draft guidelines for carcinogen risk assessment.

For example, identification of when children are or are not at

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greater risk than adults. Some thoughts on how you evaluate an MOE to decide whether it is big enough or not, whether it suggests that you are okay or whether you might have a health problem.

Thoughts in the guidelines about the benefit of inclusion of some mechanistic data without the development of what they call a full case specific model which in the present context would mean having a full blown PBPK model for all of your compounds.

The other thing Lorenz was talking about, maybe you can include some biological data. You don't have everything you would like. But the cancer guidelines are very clearly supportive of that approach.

If you have some biological thinking that you can bring to bear on the problem, then do it to the extent that you can.

So I would encourage OPP to work with the authors of the cancer guidelines to ensure -- first of all, it would give a more harmonized approach, which for somebody who observes the agency from outside it is always nice to -- it is easier to work with the agency if what is coming out of the agency is harmonized across different groups.

And also, just frankly, to ensure that OPP obtains the full benefit of the thinking that has gone into the development of the

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cancer guidelines. Because so many of the issues in there are relevant, I think, to what you are grappling with here in the cumulative risk assessment for OPs.

I'll leave it at that for now.

DR. ROBERTS: Thank you.

I was going to jump in with my own comments, and then we'll get to Dr. MacDonald. Let me sort of give you my two cents on this.

First of all, I did like the suggestion that Lorenz made. It makes a lot of sense to the extent that I have been able to think about for a half an hour or so now since I first heard about it. I think it is worth exploring.

It may be once you get into it you will hit a wall in terms of the data that you need to do it or that sort of thing. But you won't probably find that out until you try and do it. I think it is worth exploring.

I also like Rory's suggestion about exploring some of the existing models.

Whether or not you can either of those within the time frame of producing your first document, I don't know. You will know better than I do. But I think that those are things that should be looked at in the near future if not by whatever deadline you have to satisfy this

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summer.

In the event that you can't implement those and sort of in the meantime, on the issue of whether to use a one day rolling average, it seems to me by the virtue of the way you have defined your benchmark response as a 10 percent cholinesterase inhibition, there is no time factor in there.

It is not 10 percent on average over certain period of time. It seems to be implicitly sort of an instantaneous endpoint. So soon as you hit that for any given period of time, you are there, which implies that probably the one day or the peak exposures is the most appropriate for the purposes of comparing with the benchmark response that you picked.

And so the only rationale for using a rolling average is that it sort of matches better the way the studies were done to get your benchmark response.

And I think really what you have to say is that the benchmark response developed based on 21 or 28 day exposure is a reasonable he estimate of an acute benchmark response, which is what we really want to work with.

And we don't have the data to do that or do that as well, at least as I understand your presentation of the information. But we have got

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some steady state data. We can get that. To the extent we can compare that with the information we have, it indicates that it is a reasonable estimate of what an acute benchmark dose would be.

Now, the problem, of course, is that you don't have good data to get an acute benchmark response. You don't have a lot of data anyway. And most of the data you have are not the right kind of acute data, because, as you have pointed out, what you are really looking at is an acute pulsar and acute dose on a background of some level of chronic exposure that is going on.

So you really need acute dose response data that are generated under those circumstances ideally. And of course, depending on whether it's a low background or a higher background, you could different responses from the same dose depending on what level of compensatory activity is going on in the body.

I mean, at low doses you might get some sort of hermetic response where it is lower than what happens at a higher dose, higher background. So that's going to be complicated.

Obviously, you are not going to have those data soon, although I think that's ultimately the kind of toxicity data you need to get the benchmark dose that you really want to plug into this analysis.

So in the meantime, I think you are sort of stuck with what you

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have got and making the best argument that you can that it is a reasonable, acute benchmark response.

Again, that would leave me to concentrate mostly on the one day rather than trying to do a rolling average.

On the matter of incorporating time into the response, I think -- there have been a couple comments about the importance of doing that.

I think it is appealing for the toxicologist to think about that it is not just an instantaneous achieving of a certain inhibition of cholinesterase, but it is probably a function of cholinesterase inhibition and time in some way that we don't understand or at least I don't understand. There is people around the table that know much more about cholinesterase toxicology than I do.

But my impression is that we really don't have a good understanding of how exactly that all works to come up with the best way to incorporate both inhibition and time.

And so until you do that, I think you sort of need to acknowledge that that's probably the best dose metric, but we don't have that -- a response metric. But we really don't have that. We're having to sort of deal with just a given level of inhibition instantaneously. And that's what we're going to go with, but realizing

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the imperfections of that.

There were also some comments about the relevancy potency factors. I expressed my reservations about the approach two days ago. And those reservations still stand.

I think that given the way that you have had to estimate the relevant potencies, there is going to be error. There has to be. Because of sort of the fundamental underlying assumption, everyone acknowledges, has been violated.

As a practical measure, I think you are probably going to need to go the way that you have. But I think it is going to be important to acknowledge that there is an error due to that.

I guess the most unsettling thing for me is that I don't think we have a good sense for the magnitude and the direction of the error that we're introducing into this by being forced to do these relative potencies the way we have done them.

So again, I think to the extent that some sense can be derived about the magnitude and the direction of error, that would be useful to incorporate into the analysis. But again, until we get better data or better ways to do this, I don't have a great suggestion for how to fix that problem.

Those are my comments.

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Dr. Durkin and then Dr. MacDonald.

DR. DURKIN: Stephen, I just want really clarification on what I think I may have heard you say.

And if I'm correct, I totally disagree. But I thought I heard you say that in terms of how the EPA should characterize risk, they should take their, let's call it, the steady state ED 10 and compare that to the one day exposures rather than averaging.

And if I misunderstood you, I apologize. If I didn't misunderstand you, I think that is not a good approach, because I think the agency has demonstrated to us both for this session as well as previous ones that the shorter term responses are really quite different.

And they focus on the steady state in order to get some stability in relative potency. That has been my understanding. I may be totally wrong, again.

So I do think that the issue of how to handle spikes in my mind, anyway, is indeed a difficult one as the agency has presented to us. In terms of the steady state ED 10 that you have come up with in whatever final ED you select, it is steady state.

And it would seem to me to make a certain amount of sense to do a time weighted average of some sort rather than to say we are

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going to use this steady state ED 10 to characterize risk from these spikes, these way high spikes that come out of nowhere and don't last for long.

Because I think it is for those things that you might want to consider some sort of shorter term dose response assessment where indeed the relative potencies might be quite different as you have pointed out, I believe.

DR. ROBERTS: I think Dr. Doyle is going to clarify this for us.

DR. DOYLE: No. I'm going to ask a question.

DR. ROBERTS: Okay.

DR. DURKIN: Steve, we are in trouble now.

DR. DOYLE: I think that something is happening today is something that was discussed earlier in the week.

And there is a distinction between BMD 10 used for RPFs and BMD 10 for point of departure. And some of the discussion, I think, is mixing the two. Could you perhaps tease them apart as you have expressed your opinions on the two? Because I think there are different considerations there.

In fact, we only have one BMD 10 that we're using as a point of departure for one chemical whereas we have the whole range of BMD 10s that we are using for the RPF issue.

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So could you clarify in your discussion which is which?

DR. DURKIN: I was specifically looking at point of departure. And as I have said before, that it is at that point of departure that you have to have your relative potency expressed.

So they are kind of synonymous. But I was specifically concerned with points of departure.

DR. ROBERTS: I was too. And I think that that then sort of clarifies the issue.

And then is the benchmark response a certain level of cholinesterase inhibition over a certain period of time or as a result of an exposure over a certain period of time or is it an instantaneous response?

DR. DOYLE: The benchmark doses that were used for the steady state determination are the result of 21 days or more of dosing of rats in all cases.

DR. ROBERTS: That's true.

Again -- it becomes very important at least in my mind how you define the benchmark response.

DR. DOYLE: I agree. That's why I'm asking as you discuss it to that bear that in mind. And then also the application of that value either to estimating a risk or comparing between chemicals.

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DR. ROBERTS: If you want to know what the margin of exposure is relative to a one day exposure that will produce 10 percent inhibition of cholinesterase, I suppose that's one thing as compared to a response over some time or a dose over some time that would produce on average a 10 percent.

So I guess I need some clarification -- it depends on how you approach it. I guess I would need some clarification from the agency in terms of what is the -- are you defining the benchmark response based on the animal study, or are you defining it -- are you using the animal study to try and give you information about a benchmark response that you have in mind?

Is that clear?

DR. DOYLE: Yeah. I think so.

We used the animal studies to provide information to give the shape, the response of the model. So I think it is more the latter. We're trying to use the data from the animal study to develop the benchmark dose.

However, there is a confounder in this question because all of the data that we used were 21 days or greater.

The question is whether that impacts the discussion.

DR. ROBERTS: Dick Bull and then Lorenz.

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DR. BULL: The question is how much more inhibition are you going to allow for single dose.

DR. DOYLE: None.

DR. BULL: That's your point, I think. And if you are not going to allow more than 10 percent as in that situation, well, you have already defined yourself into that corner, and I don't think inappropriately, but that would of course take a larger dose on any given data approach than it would take as a daily dose to approach that over a 21 or 28 day period.

Your external doses will be quite different.

DR. ROBERTS: Dr. Rhomberg?

DR. RHOMBERG: I just wanted to agree with Dick on that.

If you think about it, the steady state experiments didn't have any toxicity in them at all. There weren't any determinations of toxicity. It was just determinations of cholinesterase inhibition.

As I said earlier on in the meeting, I think that the rationale that the agency deployed for why they wanted to look at relative potencies at steady state was sound.

The question of whether the relative potencies will be different for acute things is worth maybe -- because this has come up with several commenters, is worth a second of thought.

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Obviously, if you define relative potency -- you have to think about how you define relative potency. Because in a short term experiment, you won't have any steady states to compare.

You can't say, well, we compare steady states in a short experiment. What would compare.

Presumably, you compare peak levels and say the things -- the relative peaks that are provided or the relative doses it takes to make a certain peak at a certain level is what would define the relative potency.

Now, again, I'm simplifying pharmacokinetics. As long as the pharmacokinetics are linear, which granted they may not be, you will get the same relative potencies out of the steady state issue that you will get for the peak issue.

For linear models, those should be the same. The ratios of those things among chemicals should be the same. And the long term ones should apply to the short term ones.

Now, there is a ways to screw that up with all sorts of funny pharmacokinetics and so on like that. Of course, there is no way around that but to do all of the experiments.

So I think that's worth noting.

DR. ROBERTS: And I agree.

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Dr. MacDonald.

DR. MACDONALD: I trust dealt we have dealt with this topic. I want to get back to the rolling averages. Because I saw the -- the rolling averages on the windows on the model inputs, diets and residues, in particular, in attempt to generate auto correlation in the inputs at the expense of extreme values.

And I think that's a good, simple way of doing it. I don't think doing that -- the fact that you are averaging ahead and backwards in time really matters.

And it is quite a separate issue from taking, computing an accumulated exposure as a weighted average of past exposures. I think you could actually do both on the same model.

DR. ROBERTS: Dr. Conolly?

DR. CONOLLY: This is just a clarification from the chair.

A couple of people have made comments about RPFs in the context of answering this question. I prepared some comments about RPFs thinking I would offer them in response to the second question.

And I just want to know if I should hold off or go ahead with it now.

DR. ROBERTS: Why don't you hold off and then we'll revisit and hopefully come to closure on the RPF issue in the next session.

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Are there any other comments about our sort of relationship between rolling averages and toxicity values?

We have had a good discussion. I don't know to what extent we have given the agency any clarity of direction.

DR. DOYLE: I think quite a bit, actually. And also as was pointed out, long term as well as for this assessment. So thank you all.

DR. ROBERTS: If there are no other comments on this one, let me propose that we take a 15-minute break, and then we'll tackle the last question.

(Thereupon, a brief recess was taken.)

DR. ROBERTS: Dr. Doyle, are you ready to pose the second question to the panel?

DR. DOYLE: I believe, yes.

DR. ROBERTS: I think they are trying to get the question up on the screen. But if you could go ahead and read it for us, that would be fine.

DR. DOYLE: Question 2.

In the Preliminary OP Cumulative Risk Assessment, Section 1 H lists a number of potential follow-up activities proposed by OPP.

This list is far from exhaustive. Does the panel recommend any

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additional follow-up activities or sensitivity analyses beyond those listed.

And does the panel have any thoughts or recommendations about how these additional analyses should be conducted.

Which activities should be receive the greatest priority.

DR. ROBERTS: Thank you. I think that we're going to try and get the list of those activities put on the screen to sort of refresh everyone's memory about what the agency already plans to do.

This question then asks our opinions on any other things and what should be the highest priority.

Before we get into the response to this, let me just tell the panel, let's go ahead and focus our responses on kinds of things that they need to do in terms of follow up.

I realize there is a little bit of a gray area. But as soon as we wrap that up, there are folks that want to bring up some other issues of importance that are not necessarily part of specific follow-up activities.

So let's go ahead and tackle this particular question.

I believe we're going to go a little bit out of order. Dr. Conolly would like to get his comments in first because he has to leave early.

DR. CONOLLY: First of all, I would just like to say that the

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situation here where the agency is actually asking us about how to do it better, differently and better in the future is to be applauded in its own right.

It is really great, I think, to see the agency not only doing a job as well as can be done in the present moment for cumulative assessment for OPs, but also thinking about how to do it differently and better in the future.

My hat off to you on that score.

I just wanted to make one comment about relative potency factors. And this is very much in the spirit of how you might do it differently in the future as opposed to I don't necessarily want you to redo any of the current effort based on this particular comment.

But I do want to get on the record this statement. From a mechanistic, biological perspective in thinking about pharmacokinetics and pharmacodynamics, it's clear that the use of relative potency factors is undesirable.

I made the analogy a day or two ago that RPFs are analogous to thinking of individual OPs as sort of different kinds of fruit like apples, bananas and pears, and then calculating what an average fruit looks like.

Just as there is no such thing as an average fruit, so the use of

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RPFs is at best an approximation to the actual pharmacokinetics and pharmacodynamics of the components of the mixture.

We know we are building an error there. It is unavoidable, of course, when the data aren't available. But there is a science-based solution to this problem, which those of you that know me will know what I'm going to say next, which is to use PBPK models for the individual OPs and then to include the appropriate interaction terms so that the individual models can be combined.

And then when this ideal approach is used, it obviates the need to calculate RFPs as your approach that's being used captures the pharmacokinetics and cholinesterase inhibition kinetics for the individual components of the mixture.

And these are used directly then in the assessment without modification. So there is technical approach to this work that doesn't require calculation of relative potency factors.

I think some of you actually in your thinking about where these kinds of assessments will be going in the future are already thinking along these lines.

I know that one of your future aims in that section of the document talks about developing PBPK and pharmacodynamic models.

So I'm sure you are already thinking along these lines. Really,

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the purpose of my comment is simply to encourage that and to get in the record that there are ways of getting away from relative potency factors.

Thanks.

DR. ROBERTS: Thank you, Dr. Conolly. I think that is an excellent suggestion.

Let me, then, go back to Dr. Hattis for his comments.

DR. HATTIS: I would like to suggest a number of follow-up activities.

And I should stress that these are not necessarily limited to the next three months, but that these are more looking toward the slightly more distant future than that.

And I think that I want to second something that Chris Portier evidently raised a day or two ago.

And that is there is one particular promising avenue that might even be used a little bit in the near term, is some further exploration to compare the modeled distribution of exposures to sets of pesticides that yield a common urinary metabolite.

I understand that urinary metabolites aren't necessarily unique to one. But at least you should be able to know which chemicals are reflected in a particular metabolite to yield some comparisons of what

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you would expect by applying a basic pharmacokinetic urinary excretion model to the exposures to those things that yield that same metabolite and say, okay, what does the distribution that you would predict looks like for the current exposures of the U.S. population and what is the distribution that is evident from the NHANES 3 study.

Because that seems to me that that -- it is too strong to call such a juxtaposition an attempted validation.

It seems to me that that would give you a clue as to how you might want to tweak the model to make it more faithful to the bottom line biological exposures that seem to be indicated.

Some of the basic tweaking that you could think of is in fact by assuming some different degrees of auto correlation of the dietary exposure that occur on different days.

Although, by and large, by urinary measurements, these are likely to reflect a very limited number of days, if not just one day of exposure. So it may be that it doesn't tell you anything about auto correlation, but it may well tell you a lot about how reasonable your model of daily exposures distributions is -- are.

I think it is also important to pursue this issue of multi-day modeling in the actual buildup of cholinesterase inhibition over time in the face of reversal regeneration rates in people.

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You are not going to have that for the reign. But you will -- you should be able to get some information about red cell and plasma cholinesterase reversal from observations on people who have been poisoned.

And then, you know -- there is going to be a body of data. There is going to be a body of maybe observations from more -- less seriously exposed people that were exposed during occupational populations and then followed with regeneration -- with recovery rates followed over time.

Comparing those with some expectations from -- the direct projection from animals may give you important clues.

And I think an important longer term effort is to some extent respond to the point that was made several months ago in a panel meeting by Dr. Needleman, and he put it in terms of validating the relative potency measures for various effect endpoints, behavioral respiratory enervation, behavioral developmental changes versus brain, versus red cell cholinesterase, versus plasma cholinesterase in the experimental animal systems.

I tend to avoid the words like validation because I think it's more a one way comparison. But I think that nevertheless, some juxtaposition of whether the relative potencies you get out of the rat,

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brain system are the best measures of relative potency for predicting all the different effects of anti cholinesterase agents is, I think, a worthy investigation.

And also would give you some beginning clue as to reevaluating this whether you want to choose in fact the ED 10 for rat brain cholinesterase as your point of departure or whether you want to choose some other level depending upon, say, the relative sensitivity of younger animals versus older animals for subtle neuro developmental effects.

It is not obvious that the ED 10 is the idea -- it is a good first guess, but it is not necessarily the golden truth that is going to last for a decade.

I think that some derivation of distributions of human -- that's right. I already said that.

The next item that I think should -- there should be some attempt in the near term but maybe more fully attempts later on is right now the analysis is purely a variability analysis.

There is no uncertain analysis. There is some modest amount of sensitivity analysis perhaps that you can do with the current system by relaxing specific assumptions, eliminating particular pathways, eliminating particular chemicals that get useful information.

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But at some point it seems to me people are going to ask you, maybe people in Congress might ask you even, for some more formal uncertainty analysis.

So how well do you know this answer. And you are going to need to develop uncertainty distributions that reflect --

This is now, again, going to this issue of two dimensional. But essentially, you have a certain guess about different factors that cause people to vary in their exposures and their responses. You have information from Dr. Setzer's wonderful work about the uncertainties even of the relative potency factors.

So it seems to me you should try to propagate some of those uncertainties that can relatively readily be defined to, say, okay, if we are -- have a -- instead of median estimate of the relative potency factor for this one, if for some reason we were at the 90th percentile of our estimate of that, holding everything else constant, how much would it change the results, or you could do the whole system propagating uncertainty -- some reasonable estimate of the uncertainties of several different kinds of parameters describing both base levels of exposures and different toxicity relative potency issues.

I think the suggestion made by one of the regulated company representatives was reasonable if it is true that there are cases where

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the model uses more than 24 hours a day, that then some limitation should be imposed on the modeling so that that doesn't happen.

It seems to me that should be a relatively modest adaptation that would avoid the need to explain why it is reasonable to assume more than 24 hours a day if it is true.

I think that to the extent that there are volatility of particular organophosphate agents, it would be reasonable to add some inhalation exposure to the lawn type scenarios.

Or to the extent that there is, you know, dust being kicked up, then you could inhale some of the entrained dust.

I think it is certainly reasonable to explore this issue of school day exposure, school or day care exposure even more appropriately for an exposure for very young children.

It's by no means unreasonable to expect that diazinon or something else was used at one time for control of cockroaches in day care centers. Maybe it's -- maybe those uses have been phased out. I don't know that. But that's possible.

Finally, there is a need to collect in the long run some longitudinal data sets for dietary exposure particularly, perhaps for some other kinds of recurring exposures.

You don't need the same thousands of people that are routinely

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done in the Department of Agriculture studies. But it seems to me that some modest amount of data that, say, spend a few weeks per person for three or four periods during the year would be invaluable in allowing you to assess the degree of auto correlation of the dietary exposures and calculate long term accumulated measures of internal exposure and cholinesterase inhibition.

And that would just avoid a whole lot of hand ringing. And also more appropriately, allow you to estimate risk.

I think the current model is very good for pointing you in the direction of what is the most likely source of controllable exposures of, you know, giving rise to high days, but in a long run for evaluating dietary exposures.

In particular, you are going to need to know about this auto correlation that you can only get really by some modest amount of additional observations to answer this point.

DR. ROBERTS: Thank you, Dr. Hattis.

Dr. Rhomberg?

DR. RHOMBERG: I think those are some good suggestions that I would endorse them. Obviously, I made just a bunch of suggestions already. So I won't add, I won't reiterate them, only to point out that I think the issue of cross pieces extrapolation has to be more explicitly

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and carefully looked at.

There is a lot to be done in tying levels of cholinesterase inhibition to toxicity, both in the short term and the longer term. And I think I expounded on that before. I won't go on too much about it anymore.

I frankly would have liked to have seen an attempt to try to combine roots by the degree of cholinesterase inhibition rather than this margin of exposure harmonic mean averaging.

The harmonic mean method implicitly has linearity in it.

Now, it is probably not too bad because it probably is more or less linear for cholinesterase inhibition.

So it probably works okay, and I don't really expect you to get a different answer. But I guess I would prefer that if you are really doing it on cholinesterase inhibition, to do it on that. That's a common currency. I know there are some technical difficulties to doing that.

And I would also like to see taken seriously the home gardening -- food from home gardening exposures, which seems to me to be something several people have mentioned. And I agree as a potentially important thing that should probably be brought in.

DR. ROBERTS: Thank you.

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Dr. McConnell?

DR. MCCONNELL: I too will not add to what has been said before. But it is sort of a taking what Dr. Hattis said maybe a step further.

I had a brother-in-law that was a time study engineer. I guess now they call them efficiency engineers.

And I talked to him -- used to talk to him a lot about how he did his job and stuff. He said that the first thing he does is when he went into a factory or whatever was take a look at it and see where the bottlenecks were.

In terms of bottlenecks, for me, it looks like one of your bottlenecks as was explained to us yesterday that you can't get as many water samples as you would like because of the chemistry involved.

So as I explained yesterday, I think it might be worthwhile to have your chemist sit down -- and I would certainly encourage industry more so because I think your chemists are paid more and you probably have a lot more of them to do the same thing that I'm going to propose now.

And that is to sit down and find a quick efficient, by that I mean not technically difficult, and inexpensive way to find total

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organophosphates in water and other media.

I'm not a chemist, but I'll bet you you would be surprised that if you posed the question to your people you might be surprised what they could come up with.

And certainly, the worst answer that you would get is we don't know of anything better, more efficient, less expensive. I mean, that's an answer. But if you never pose the question, you will never find out. So I would like you to do that.

And certainly, if you could come up with a technically easy method of analysis, it doesn't -- you need to be in the ballpark for what I'm talking about. You don't need to be to the parts per trillion.

If I can get down parts per billion, even parts per million, I know whether I have a problem or don't have a problem with that particular sample.

Second is I'm wondering if in terms of acetylcholine evaluations, if there couldn't be an invitro system developed.

After thinking about that, I have a few ideas. I won't get into them now. But I bet there is a biological method that you could use to determine -- the potency, is what I'm talking about, in a very efficient way.

Again, I'm not an expert in this area. But if you don't ask the

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experts the question, again, you will never find out.

And finally, as I propose at every one of these meetings, occasionally you need to do a reality check.

And by that I mean that after you estimate all these levels that you think a person is exposed to, certainly, there has got to be ways of evaluating people that are exposed via their urine or some other invasive way to find out what the levels of the metabolites or products are in their urine to see how close your estimates of exposure were.

I mean, are these off by an order of magnitude or by a factor of one or two. At least you will know that we're overestimating, underestimating the true dose by doing those kind of things.

And with that, I'll stop.

DR. ROBERTS: Thank you, Dr. McConnell.

Dr. Durkin?

DR. DURKIN: I only have two things. And really one of them Dale has beaten me to the punch on. I just want to endorse it rapidly.

Again, this is not necessarily a criticism or something that need be done in three months, but just something to start thinking about.

I totally agree with Dale that you have done some fascinating dose response work here. And I think it could be useful to attempt to incorporate the uncertainty -- on the uncertainty, the variability, the

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whatever, squishiness of your dose response assessment into your risk characterization.

I don't think that is a trivial matter to do. I'm not sure it is super simple. I think when you actually got down to look at the code for all of that, it might even get a little hairy. But it is something to think about.

The other thing that is again very short and is just a soap box of mine, the work that you have done on addressing the potential toxicologic interactions of the organophosphates has gotten progressively better with every draft.

I don't pretend to assert that I think it's a show stopper here. But the agency has recently come out with guidelines for mixtures risk assessment. I know that you are aware of those. They probably get thrown in your face daily.

You may want to expand your discussion somewhat. I totally endorse and agree with your basic assessment that in the low dose region things will indeed be additive or at least noninteractive.

The nasty point gets to be defining low dose.

So it is just something for you to think about over the longer term, because people will raise to your attention repeatedly the well-known interactions and the complexities of the

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organophosphates.

DR. ROBERTS: Thank you, Dr. Durkin.

Dr. MacDonald, you are up next.

DR. MACDONALD: First of all, we were asked to pick from your menu in 1 H. So from that menu, I will select under Hazard Assessment Number 2, long term, research to develop and implement physiologically based PBPK models, which people have talked about.

And under food exposure, my favorites would be Number 1, series of sensitivity analyses for input parameters. And Number 3, detailed analysis of food exposure to identify major contributors to risk.

And in addition to that, I'll just elaborate a bit.

I think especially the discussion today has shown to me that we need a better understanding of the short and long term health risks from chronic and acute exposure.

And I think that this understanding will lead to better supported POD, perhaps even different PODs for different segments of the population.

And another point made earlier today, but sensitive, analysis for auto correlations in the activity diet and residue inputs to the model should be done. And if important, they will certainly emphasize that

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we'll need more longitudinal data on these inputs in particular.

DR. ROBERTS: Thank you, Dr. MacDonald.

Dr. Harry?

DR. HARRY: I have a couple of brief comments. One is I really would like to encourage as much as you possibly can to back up the comments that were made earlier about trying to use the CDC data and THE NHANES data for evaluating and testing out what your exposure predictions were as to what is really there.

In addition to that, I'm not sure exactly how that data is, but if there is any way that a tweaking of that system could give you an idea of what coexposures might occur in people, I know you are getting the metabolites, but if there is any way you can pull out of there a little more idea of what actual in a way dose as we were suggested that dose was different than exposure, what actual mixture dose may happen of the organophosphates. If that is a source, it would be great, or any other human data that we might have for that.

Just encourage going after that a little bit more.

The other one is there has been a number of suggestions of doing modeling of your lumpy versus peaky exposure curves.

And while it is really nice to model and while it is really nice to have the pharmacokinetics, if we go into the neurotox endpoints of

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those things, there is a lot of other dynamics that are going to be playing a role in recovery and that type of aspect.

It would be nice to have some experimental data to back up what predictions you might have if you start to model.

So if you had animals that were at a steady state like subthreshold steady state, do they actually respond differently to a peak than a naive animal. So does the exposure history do that.

And I don't know if you already have that data or not, but it seems to keep coming up as a difference. It would be nice experimentally to know if in the animals there really is a difference with the exposure history if it influences the response.

It is not going to be an easy thing to design and not kill an animal, but to try and get a feel for whether it does. It might give you a little handle, at least a little direction about what might be the most important one of those multiple exposure dynamics you could look at or at least to test back out your modeling.

As this will be opened up for general comments after this question, I know that there are a number of thoughts running around, I would like to take this opportunity as it goes on exposure assessments only, is that -- and it may be that the organophosphates and the use of them is different. So forgive me for that part of my naitivity if I'm

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not sure about that, but we talked about institutional, and we talked about that in the form of schools and day care centers. And we have talked about some other studies that were being done. This is really sort of bad to say, but the oldest age we heard was 56.

I would like to argue that we have two extremes of susceptible populations. And it is not just the children. And it may be that the reason that the elderly have not had quite as much visibility in this is that they don't have their parents around to protect them as their children. So they don't have that group.

But you have as vulnerable a population, as dependent of a population on others on an environment and somewhat as trapped a population within their actual environment whether it's a nursing home or it is just their home type thing.

So I really would hate for that population to get lost in here. It may be that the strategy is that if we protect for one susceptible population, that that should cross over to another.

If, however, we start to think about nervous system effects, the dynamics of why they are susceptible are very different. And you may not be doing that. I just, since we continue to come up with children, and I know that that's a focus of this exercise, I would just like to take my soap box as the people eating the home grown foods that we also

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think about the entire population -- because it is a public health, and that we don't give the appearance that we're looking at social impact so we're concerned about people under 50 or children that we would have a long term as in length of time social impact that we look at the whole population.

DR. ROBERTS: Thank you, Dr. Harry.

Dr. Adgate?

DR. ADGATE: Coming at the wrong end. I don't have a lot to say, other than I concur. And I agree with the point just made about the elderly.

One thing I noticed in looking at a lot of these, your charts, I was interested to see that I think they go from age 50 to 110, which was an interesting -- I don't know if that was on purpose or not. But I was intrigued by that when I saw it.

I have nothing else to add.

DR. ROBERTS: Let me, then, open it up to other members of the panel who may also have their views about what the most appropriate next steps are.

Dr. Richards?

DR. RICHARDS: Even though it appears to be a relatively unimportant pathway, I guess I better stick up for water here.

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I wanted to comment just briefly on the list of items that's there under issues to deal with for water and suggest a few others.

The first one, I think, is an interesting one. It deals with the assumption that the applications all come on the same date and what impact that has on the assessed concentrations. And I think it is one that is worth exploring.

Clearly, it is going to lead to a higher concentration on some given day that's a response to that integrated, sort of simultaneous application.

But the difficult question is how is that going to relate to the timing of the next event to move this stuff. And that's going to be a stocastic question that is going to play itself out in the interplay between those two variables.

And I think, therefore, the conclusion about what impact that has on the overall results is really unclear and deserves what should be a fairly simple and sort of a kind of sensitive analysis. But it should be pretty easy to do.

There is a question in here about the proportion of the model residues that are or would be below detection limits of monitoring. Certainly worth looking at.

I imagine it will be a fairly good percent. Maybe as many as 40

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or 50 percent. Maybe even higher. But I also suggest it's probably not going to have any important impact on the outcome because those concentrations are so low that not really having much of an impact on overall exposures.

Certainly, one of the things that we have identified the need for throughout this whole section is sensitivity analyses of various sorts.

And you list in one of the questions several that would be appropriate to do.

The one that I think I would add to that that might be the most useful would be some kind of an attempt to look at the possible impact of spatial heterogeneity within the region on the simulation results or the possibility that by having a place where you have concentrated use, quirky meteorology, whatever you want to pile together in that one local area that you would actually find that your supposedly worst case scenario is not protective of an area like that.

I think that's worth looking into in some more detail.

In terms of possible needs that aren't mentioned specifically, I think one of the things that would probably bear more useful information in several of the points you have actually listed would be developing the capability to create realistic simulations of concentrations in rivers and streams.

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As it is now, you can only look -- you sort of used the reservoir as a surrogate for those. And it is not a very good surrogate in some respects.

So that is something that would be -- seem to have priority for development.

Another thing that several people in the water group are concerned about is the incomplete dealing with the degradates, particularly the ones that are produced in the treatment plant. And something needs to be done to address those.

And I guess the final thing is I guess I would put in a plug as Dr. Hattis did for what we can call a longitudinal study, I guess, and some long term detailed monitoring so that we actually have the data to look at the simulations and see how they work out.

That will only cost a few billion dollars a year.

Thank you.

DR. ROBERTS: Other suggestions?

Dr. Adgate.

DR. ADGATE: Just one thing I forgot to mention or the question I was going to ask, I notice the agency was asking about specific advice about prioritizing these lists that are presented.

And at least for the residential exposure part, a lot of what is

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here, there are several points that allude to sensitivity analysis. And I think that's key.

And I think you have heard the other answers so you can infer them from our comments about certain conditional probabilities over time in longitudinal versus cross-sectional variability estimates.

DR. ROBERTS: Yeah. I agree, Dr. Adgate. I was going to mention that myself.

There are so many different kinds of data that you folks need. There are so many needs. And obviously, I think the best way to prioritize that in some respect is through sensitivity analysis.

I know that you folks are actively working on that. I guess we would expect you to be guided to a significant degree by what that sensitivity analysis tells you in terms of what the most eminent needs in terms of data might be.

Dr. Bull?

DR. BULL: I have not too much to say. But I did want to -- first of all, I was going to reinforce a couple points at least that Dr. Richards made, particularly about the steam. Because I'm not convinced that one shouldn't at least track these more flash -- what you might call flashy events that might occur in exposure instead of pesticides.

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It may not -- and particularly the OPs because of the nature of the beast.

But if for no other reason, to know how often that might be encountered. There are places where that could be more important than others.

But the thing I would like to kind of come back to, because I think it is kind of the -- there is one thing -- I'm a toxicologist, so I have certain kinds of worries that other people might not have.

But one of the things that bothers me a little bit about focusing so much on mechanisms, what we perceive as being mechanisms of action, we have at least two groups of chemicals -- mechanisms that we're worried about -- because sometimes we lose sight of the other things.

And one of the -- and this has come up, and maybe not so explicitly stated as it should be, is that there really is a straightforward thing, this is a simplification of trying to determine what toxicities arise from cholinesterase inhibition or others.

Because you test a series of 10 compounds and they all inhibit cholinesterase to the same extent. And one compound doesn't give you the toxicity. Obviously, it is associated with something else.

And we tend to be lumping things. The endocrine assumption

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thing is somewhat the same thing. You saw how the National Academy was really put off by that terminology. That was the reason, because you don't -- just because something has a property, the toxicity you worry about is not necessarily expressed by that mechanism.

And the cholinesterases are specific for -- the organophosphorus compounds are not specific for cholinesterase. That has been known for 40 or 50 years. They affect almost any hydrolase, however named, that has a serine hydroxyline (ph) active site.

So there is a lot of possibilities for other things to happen.

And I just get worried that we decide the only thing we need to focus on is cholinesterase and we don't need to do reproductive and developmental toxicities that may have these compounds that may have nothing to do with the cholinesterase activity.

I didn't hear that said by anyone else, so I thought I would say it.

DR. ROBERTS: Let's perhaps wrap up our discussion on this particular question. And we can perhaps get into some other general issues.

Are there anymore suggestions on next steps? Priorities for next steps?

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I would have to say I think there have been a number of excellent ideas. I didn't hear a single suggestion that I disagreed with.

I think the issue obviously for the agency is priority. There were several people around the panel that echoed the desire to do some ground truthing for the model by comparison with human data wherever possible.

And I think that I guess that would emerge sort of as a priority based on the frequency of mention if for no other reason.

And the sensitivity analysis, I think, in terms of data for specific model components would be very important in terms of guiding the agency in terms of prioritizing those things.

Any other comments from panel members on this question before I open to general issues?

Before we move on, would you like any clarifications on our responses to Question 2?

DR. DOYLE: No. No particular clarifications. Just I would like to point out that we agree with a number of the -- well, all of them.

We have actually started some work on a number. We do have a schools project going on to try to get a handle on that.

We have a project to look at urban rural interface and try to

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determine the magnitude of that population.

And there are a number of others that we have started. Certainly, not the breadth that is here, but we appreciate your input.

DR. ROBERTS: Thank you.

Let me then, as promised, open this final part of the session to discussion among panel members about issues that were not raised previously because they weren't part of a question or more general in nature.

I know that some panel members would like to discuss perhaps the endpoint and the appropriateness of it. There is perhaps some interest in discussing some margin of exposure issues as well.

So let me just open it for discussion. Let me just ask the panel, though, sort of to minimize sort of ping-ponging among topics. If someone brings up a topic and we have some discussion on it, let's go ahead and bring that to some closure to the extent that we can before we take up another one.

So who would like to start things off? Dr. Durkin.

DR. DURKIN: Thank you. I have two topics. And I would like to bring up the more minor one first. It is actually almost an improvement. I almost tried to sneak it in. It is really too to revisit an issue that we talked about on the first day.

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And that is the issue of combining the studies. My understanding of what you did is that you took all of the studies that had been submitted to you by registrants that had been "accepted."

And then my understanding of what is accepted is it follows the protocol that at least was specified at the time of submission. Someone reads the study, they do a DER, data evaluation record, and it gets marked acceptable.

Then you turn that over to your statistician who plugged it in and came up with the dose response assessment. That's what I think happened.

The only thing that I would suggest, because I think we all nodded our heads and said, that's fine, and it might be fine, but I did want to open the discussion up to revisit that issue, because I have talked to some of the staff people here, and as a risk assessor, the one thing that I would intuitively recommend is simply that when you have a multiple number of studies, and your general expectation is that they all really ought to represent the same thing, perhaps follow approximately the same dose response assessment and you plan on plugging them all into a model at one time, I didn't hear any discussion of judgment, because it is not uncommon if you have, let's say, three or four studies on either kinetics or toxicity to have maybe two or

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three of them hang together very nicely, one study is way off base.

And even though that way off base study could be acceptable in terms of your data evaluation record, it is the kind of thing where I think you can look at it and either using statistical wizardry or judgment say you are better off dropping that study.

And I know that's a little bit messier, but I would like to recommend that at least you think about it and perhaps hear what other panel members think.

DR. ROBERTS: Dr. McConnell, not to put you on the spot, but I think that was an issue that you had broached on the first day as well.

Comments by other panel members on the idea of sort of inserting another -- a layer of judgment in terms of evaluating the data?

I'll go on the record as concurring with Dr. Durkin. I think that there may be some desirability in that. I think that -- if you look at enough of these things, all studies are got created equal.

I realize the agency might want to -- might be reluctant to do anything that might suggest bias in terms of evaluating the data.

Obviously, if they threw out data sets, that should be accompanied by some explanation of why a study's value was

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downgraded or that sort of thing.

That should be a fairly transparent process that people could look at and see and agree or disagree with the agency.

But I think the opportunity to exercise some judgment would be perhaps a good thing.

DR. DOYLE: Actually, during the initial pass instead of evaluating the tox data, we did start a process such as that.

But we found that we were constantly throwing out more and more data and became concerned about the extent to which our criteria were not appropriate, too rigorous, how ever you would like to define it.

So we then reversed the process and began reinserting them because we weren't certain that we weren't biasing the analysis in just the opposite way of eliminating too many. Because you can significantly change the outcome that way.

So we decided to err on being inclusive rather than too exclusive.

DR. DURKIN: If you look at statistical methods, you might use a more objectively determining -- if you have four studies and one of them appears to be way off base, I believe, again this is not my -- I'm still not a statistician, but I think that the wizards can tell us that there

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are indeed ways to do that very objectively.

What I'm getting at here is we have a tremendous amount of uncertainty in risk assessment.

And this is one way to maybe take off some of that burden in a very objective manner.

DR. ROBERTS: Any other comments or responses?

Dr. Hattis, then Dr. Harry.

DR. HATTIS: I guess I should defer to the real statistician down the table there. But I just would urge that one -- if you use a statistical, a purely statistical criteria, you are correct that there are statistical criteria floating around there, sometimes people choose relatively liberal criteria for defining what is a "outlier." And sometimes people are relatively conservative.

I worry unless when it is pretty damned conservative. One such criterion is by saying the outlier study has to be more than X standard deviations from the mean determined by the set of other studies.

And I would just suggest that X be in a pretty convincingly large, you know, four or five or something of that sort, otherwise, one does get into the difficulty that you have thrown out in some sense real cases.

DR. DOYLE: Yeah. One of the concerns that we had we did

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look from the standpoint of I think goodness of fit. Is that correct?

One of the things we found was that some of our toxicologists disagreed with which studies actually were more reflective of what was going on.

They felt that the goodness of fit test, they disagreed with the outcome of some of those tests that were conducted. So it put us in a bit of a quandary that in fact their judgement in interpreting the data did not match what statistical methods were used.

DR. ROBERTS: Dr. MacDonald, did you have a comment?

DR. MACDONALD: I would be pretty careful about using statistical goodness of fit methods in particular. It just means that the smaller samples will show better fits and the large samples will show bad fits.

I think you have to use more than just looking at the numbers because you could easily get three bad studies and one good study.

And I wouldn't even guaranty the one good study was the outlier. It is not an easy problem. You need an awful lot of judgment.

DR. ROBERTS: There may be attributes of the study that as you say lead you to conclude that the one study is in fact good and three of them are bad.

I agree that it is not an entirely statistical decision. But I sort

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of sense that some people, the panel is sort of opening the door to that possibility of exercising that judgment.

But obviously recommends that it be done very cautiously.

Dr. Heeringa?

DR. HEERINGA: Actually, Dr. Durkin and I had this discussion yesterday. I think as a statistician you are trained never to throw away data. In fact, there is information even in bad data. It may be about the reliability of the test procedure, about the types of errors you can commit in conducting these tests or missing variables that are present in one study and not in another.

So I think when we talked about it, I tend to be very conservative about throwing out data. And I also agree with Peter that simple statistical tests on distributional fit tend to be overly powerful for any sort of reasonable sample size, and probably not very reliable when you get to be too small.

I think some of it is sort of interocular tests where you just look at things and then investigate.

And I had one example that I would point out as a starting point. That is the dose response curves that are fit to phosmet.

If you look at the curves that are produced in the document or on the CD, you have one sort of dose response curve that seems

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reasonable to me.

And that is it is -- at the origin in terms of dose, it has a very low suppression of cholinesterase activity.

A second study apparently without even dosing these animals the curve is already suppressed 40 or 50 percent or at least at really very low doses. It literally has the appearance of two different curves to me. Not even sort of a normal scatter.

The first thing that occurs to me in that particular case is that something happened in one of these studies or the conditions are so radically different in one of these studies that it really shouldn't be combined.

I only pick on that as sort of the extreme case that I noticed in looking at these as to the type of thing that --

What you do find when you look at the data is that the main OPs, particularly methamodophos, that these curves and these studies are all actually very consistent. And as we discussed the other day, I think are generally amenable to this mixed effects model that is being fit.

What happens when you only have two or three studies, I don't think you can -- as Peter says, you can never tell which one is the odd person out here.

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So I think we need to be cautious on this. But I think it is something worth revisiting and clearly in cases where it can be either because the studies are extremely old or the conditions under which they are conducted can't be validated or verified, I think it is worth considering at least refitting the model with some outliers removed to see what impact that might have.

DR. ROBERTS: Thank you.

Dr. Harry.

DR. HARRY: Just one quick one to go off on those. A comment I was trying to make the other day is especially when you are trying to equate potency across chemicals across studies that you really have to be careful to try to ensure that everything is as equal and as precise and as sensitive as it can possibly be in there.

And I don't know about your practices, but is this an opportunity like if you are going back through these studies and you are finding the ones that you disagreed on or the interpretations or things there, is there any mechanism that the agency has to offer additional guidance?

I know the guidelines are set down a certain way. But is there any guidance that is offered to people submitting the data as in how to run, you know, what works best as in running these assays or anything

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like that or is it just sort of set up to how they design it?

DR. DOYLE: Pretty much the testing guidelines at this time refer to study design more than conduct.

I know that the conduct of cholinesterase evaluations has been discussed a lot of times at various, I think, SAPs even.

One thing that we are looking at is testing guideline revisions. And some of the issues that we do want to consider are the very sorts of things that are coming up here about how our studies are not meeting our needs.

So I think this is very helpful.

DR. ROBERTS: I think we have just about reached convergence in terms of consensus on this issue.

Let's go ahead and move on to another one.

Pat, do you want to bring up your Number 2?

DR. DURKIN: Yes. My Number 2 is a biggy for me. And I really think we need to get some response from the committee here, because I misunderstand.

Shortly before coming down, I received a packet from you folks, some comments from Brian Dementе. Brian had been through the wars with malathion. Brian and I are both veterans of a malathion war because I have recently been through a very detailed risk

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assessment for USDA on malathion.

So brian and I may both be suffering from the same disease.

Having said that, I came down here and Dr. Sass kind of reinenforced my malady. Where are the kids here? This bothers me. It bothered me before I got anything from you.

And what is concerning me here, like, if the story is that we're going to address kids at some other point, I'll say that's fine.

But don't give me margins of exposure for kids. Because you are basing that on exposure to the kids, which is good, and we have talked about that, but then the relative potencies that you are coming up with are based on adults.

And I will contend strongly that that is absolutely incorrect and wrong.

For some of the OPs, malathion is a very good example. It is not very toxic to adults. It is substantially more toxic to neonates. So I am a little angst, in fact I'm very angst, that you present that assessment prior to coming up with a separate set, which I think you need, totally separate set of relative potency parameters for neonates and apply that to the exposure assessment for kids.

I think that's the only rational way to go about this.

For some of the OPs, I know it does not make a great deal of

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difference. For others it does. And that's why you have to consider kids as a separate group.

Right now I think the margin of exposure that I get for kids is a margin of exposure for very small adults.

So that is something that I think does have to be addressed as part of the revision to the document. And I think it is a substantial assessment unless I totally misunderstand things.

The one minor point that I'll make, though, and Dr. Demente made this as well, and I want to endorse it, when you did your 1998 assessment, I believe, on the application of the FQPA uncertainty factor, you based it largely. You covered all of the OPs. And that's very commendable. You based it, I believe, exclusively on studies that have been submitted to you for registration.

I would encourage you, because I know it makes a huge difference with a malathion, I would encourage you to look out in the open literature, because we have known for a while that malathion is more toxic to neonates than to adults and it's not an uncommon pattern with OPs, although it is not a universal pattern.

It is tricky, and I think it has to be handled on a case-by-case basis. So that is my strongest most vigorous criticism of your effort here.

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And I would like to hear some consensus from the committee. If I am just a victim of my malathion risk assessment, please just wrap me up and send me home.

But if I am correct, and this is a very, very important issue, then I think the committee has to very, very strongly and clearly state that this cumulative risk assessment will be in no way ready for a final review until those differences in sensitivity are quantitatively addressed and put into the risk assessment.

DR. ROBERTS: I would like to let Dr. Doyle respond before we get more input from the rest of the committee.

DR. DOYLE: There are several components to what you said, of which I'll try to march through at least as many as I can remember.

First of all, I would be interested in -- we are doing the rat on malathion now. And I would like to see a risk assessment, if you can share it.

Second, is we, I don't know the year, but a DCI for something called Developmental Neurotoxicity Study was issued for all the OPs.

We are in the process now of receiving those. We have not received many, but we have received malathion among the five that we have. And we are aware of the issues around that.

One of the discussions that you haven't heard or seen in the risk

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assessment is what the appropriate MOE will be because of the FQPA issue, the relative sensitivity.

So we have not yet frankly finished formulating how to do that.

We have guidance that we drafted that were put out that is generic. We are also putting out a specific statement the next several two or three months, by the next two months, I guess, is what we have left to do this, on how we propose to deal with the FQPA issue based upon what data we have in, which right now is, like I say, a total of five neurotox studies, including relative sensitivity data for cholinesterase inhibition in the brain and how we hope to factor in that and our lack of understanding for other chemicals.

So we have not overlooked that, but we cannot tell you yet what approach we will take. But you will be certainly free to comment at that time.

We also have not yet determined a number of other issues around how to deal with special subpopulations. So we do appreciate that children are not miniature adults. But we also are limited in what data we have available. And we have to figure out how to apply it appropriately. There is no pretence.

I'm very well aware of Dr. Demente's comments. I received copies of them myself. And I have read them and I understand them

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quite well.

But we don't yet know how best we can address that. That's under development.

DR. DURKIN: May I put a footnote in in response?

DR. ROBERTS: That's fine.

DR. DURKIN: One of the reasons that I am -- we're all concerned about kids.

The rest of the world looks at you for guidance here. And in my risk assessment for USDA, which I will leave with you, they elected to defer any decision to your analysis, which I support, but I am just trying to underscore the importance of how you handle it is going to make a huge difference and appropriately so to how it is handled by the rest of the government.

DR. MULKEY: Maybe I could add one thing to what Beth said that might help clarify. As we have worked through each of these individual organophosphates, we have worked through this issue about the, what we call the FQPA safety factor, but the analysis of whether we think we have enough -- we have uncertainty about the differential impact on young, what information we do have, whether we believe we need additional safety factors, or, that is, we're aiming for a higher MOE.

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So in addition to the work we will do in connection with this cumulative assessment, we are working through that for each of the individual assessments.

Malathion is one of those that we have not yet completed. And Dr. Demente is working, of course, he is one of our respected scientists, and he is working with us as we work through at that level as well as the issue regarding the cumulative risk assessment.

DR. ROBERTS: Thank you, Ms. Mulkey.

Dr. McConnell?

DR. MCCONNELL: Yeah. Maybe I can help Dr. Durkin here a little bit too.

Having chaired one of the meetings where this was dealt with, it was a conclusion of the science advisory panel, and I think the EPA adopted that, that the best place to bring in the differential potency between adults and children was, if you will, after the risk assessment had been done and you came up with a number.

Then you would say, now, based on your information, we need to further protect by lowering that number for children.

DR. DURKIN: Lowering the MOE.

DR. MCCONNELL: The MOE for children. Because if you start doing it during the process, it becomes quite complex and you

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lose it in the mix. And it gets multiplied three or four times during the exercise in addition, that it was just cleaner to do it -- you do the whole risk assessment and then you decide, now, I'm going to evaluate whether there is a unique problem for children or not.

DR. ROBERTS: Did you want to respond, Dr. Durkin?

DR. DURKIN: Yes. That approach works if the difference in sensitivity between the neonate and the adult is consistent across chemicals.

Regrettably, with the organophosphates, as far as I can determine, now I am not a total expert on DOPs, but I believe that there is not a consistency.

So then it depends upon the mixture that you have and a uniform approach to saying we're just going to lower the MOE may not be appropriate.

DR. MCCONNELL: This was for individual OPs.

DR. DURKIN: Oh. For individual OPs, it is fine. But for the cumulative risk assessment here I think it doesn't work.

DR. MCCONNELL: The second question I was going to ask of you, when you were talking about relative potency, I assume you are talking about relative potency in terms of children versus adults.

DR. DURKIN: Right.

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DR. MCCONNELL: You weren't saying that if I study a malathion in an adult rat and I give it a one X and I study another OP in an adult rat and it is twice as potent that you would expect that to change those relative potencies in the neonate?

Is that what you are suggesting?

DR. DURKIN: Yes. It could.

DR. MCCONNELL: Anything can happen. But I mean --

DR. DURKIN: I believe that that is known to happen, that for some of the OPs there is very little difference. For other OPs, there is large difference in relative potency between the child and the adult.

DR. MCCONNELL: No, no. That wasn't the question. The question is if a given OP A is more toxic than B, are you suggesting that, in the neonate, B would be more toxic than A?

That's relative potency too. But it's a different kind of relative potency.

DR. DURKIN: I don't really know. I think that it could be.

DR. MCCONNELL: You think it could.

DR. DURKIN: I think it could. And I think malathion might present an example. But I honestly am not -- I cannot come up with an example.

DR.L MCCONNELL: Malathion versus which other OP, would

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be my question.

DR. DURKIN: I don't know. I would have to look -- I think one might possibly be methamodaphos, but I'm not sure. I would have to look at the data.

And I do agree that we have limited information. And I fully understand that.

What greatly disappointed me in the document maybe was at least the really lack of any acknowledgment of this issue. And that, I think, could be relatively easily corrected.

DR. ROBERTS: Dr. Doyle?

DR. DOYLE: I think you will find that there will be a full discussion of that in the June document.

However, at this time we have the difficulty that not having made the decision we wanted to provide the intersection of the exposure and the toxicity data for evaluation and not hold that back waiting for the decision on how to handle special sensitivity.

So I think that that was a deliberate omission on our part. Not that we don't realize this error, but we felt that we were not ready to release it.

DR. ROBERTS: Dr. Harry has been waiting patiently to weigh in on this issue.

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DR. HARRY: I think in a way you answered some of it that you are going to be putting this out a little bit later.

But one of the questions was, and I think you are going to find it a little more complicated, but I have one, first question before I get into that is, you are going to look at each of the individual compounds, and you do have the enzyme inhibition data on these compounds. You said you have five in now.

When you go to look at a cumulative on those, are you also assuming that it will be this enzyme inhibition that will be a common mechanism that you can use at which to look at potency?

DR. ROBERTS: Dr. Doyle?

DR. DOYLE: In this case, yes. We're going to continue to use -- our common mechanism here across the board is going to be cholinesterase inhibition.

That does not say that we do not realize that OPs in some cases do other things. And they in many cases do a surprising variety of things, everything from cancer to developmental effects.

But for this particular exercise as defined in the act itself, we are focusing on this particular mechanism.

DR. ROBERTS: Dr. Harry?

DR. HARRY: Then I have a couple other questions. And they

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are more -- you don't have answers for them, but just to keep them in mind. And a lot of them have been raised in the sense that there are other components of toxicity that can happen that are not necessarily related to this process.

The effort that the agency came up with, as well as outside academic researchers, to identify that this could be a common mechanism of action is a lot of work that was put on adult animals. A lot of the characterization of the adult versus the steady state.

What I would like to ask is are we proposing to skip that effort in the developing animal? I mean, is the acute the same as it would be in the adult? Is the steady state reached at 21 days? Is this being done under the EPA developmental neurotox protocol dosing regiment as is in there or is it direct dosing to the pups.

There may be a lot of things you are going to have to look at before it is even worth thinking that it is going to be a common mechanism of action that would be accepted.

You can do an awful lot of work and come back and say, we really shouldn't have done this. We lumped these together incorrectly. And given that you have a number of questions that are being raised now about which chagrin after everything you went through to get this, that it may not be the right endpoint. Then you are going to have

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to go through those hurdles again developmentally and not just make a tacit assumption that it's going to work through there.

I think you are going to find it a lot harder than what you really want it to be or probably as hard as you expect it is going to be.

DR. ROBERTS: Dr. Doyle, do you want to respond?

DR. DOYLE: I think that she summed up a lot of issues.

Part of our limitation now again is we have limited data. And we have mixed protocols. You have identified a number of points. Yes.

But again, I just can't really tell you how we're going to come out with it.

DR. ROBERTS: Other panel members with viewpoints?

Dr. Hattis.

DR. HATTIS: One way in which you could get a lack of parallelism in the relative potencies between at least neonates and adults is in fact if a substantial fact -- modifying factor for the toxicity is in fact detoxification by specific liver enzymes.

Because some of the P 450 enzymes in particular seem to turn on in the first few months of life but after birth, so that half lifes of some chemicals -- in fact half life for many chemicals, many drugs, in neonates can be of the order of two to fourfold larger than they are in

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adults because of the immaturity of that metabolism system.

So chemicals that are detoxified substantially in the liver versus those that aren't could well have a lack of parallelism in that systematic way.

DR. ROBERTS: And the ontogeny of P450 development is different in rats than humans. Actually, substantially. So that's a further complicating factor, unfortunately.

DR. HATTIS: Okay. I don't know in rats at all.

DR. ROBERTS: Other comments?

Dr. Harry?

DR. HARRY: Just one more to put as a red flag for your comparison, because I'm not sure that it's appreciated by everybody except the ones that are working with the data set, is that your adult neurotox test battery is actually a relatively crude battery.

The developmental, it is not only supposedly looking at a more sensitive organism and time point, but it is also looking at it much more in depth.

You actually have some learning tests and measurements in there, which you don't have in the standard adult battery.

So as you are looking at that, if you just say you have a positive response at a lower dose on the development, it is not necessarily

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going to mean that they are more sensitive. You have a sensitive test battery to look at.

So a lot of that is going to be presenting exactly what you are comparing. And they are going to be different. It is not going to be a tacit assumption that you -- you may just be picking up something because you have more sensitive tests to pick it up.

DR. ROBERTS: Are there any other comments by panel members on this particular issue?

I don't see any.

Are there other issues that panel members want to bring up?

Dr. Harry, are you signaling me?

DR. HARRY: No. I'm looking around.

DR. HATTIS: I just wanted to say that I had -- I thought that the EPA staff did a wonderful job on the expanded model for trying to assess nonlinearities at intermediate lower doses.

I thought that was entirely an excellent implementation of the mechanism-based understanding that we had. I was not here on the first day, so I thought I would insert that here.

DR. ROBERTS: Thank you.

Any other issues to be raised by panel members?

Are there any clarifying issues that the agency would like to

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raise with the panel while we're all here?

DR. DOYLE: No. But I would like to thank you all for your discussions and your inputs. And I think we have a lot of work ahead of us. If you don't see these show up in the June documents, we certainly hurried them and they will show up in subsequent rounds. Thank you very much.

DR. ROBERTS: Thank you, Dr. Doyle.

I would also like to thank the agency for some tremendous presentations trying to clarify a lot of information for us. You did a great job.

I would like to thank the panel members for coming, for being very prepared. We had some excellent focused discussions.

I would like to thank Dr. Kendall in his absence for chairing the first two days and getting us to the point where we could complete our agenda today.

And, of course, I would like to thank the SAP staff for the tremendous amount of work it takes to put one of these sessions together. They work behind the scenes. They do a lot to make this all very possible.

Ms. Mulkey, did you want to say something?

MS. MULKEY: I would like to make some very brief remarks.

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I would like to thank on behalf of the agency the panel for its work. I would like to thank you for the balance you gave between offering us advice that we can practically use within the practical limitations and asking us to reach beyond that.

I will say that if we had sat here this time last year and heard these suggestions, I think we would have felt overwhelmed.

The distance we have come has given us a lot of confidence about how far we might yet eventually be able to go. But we also appreciate your awareness of the distance we have come and the practical place that we are.

So we found this constructive, helpful. And to the extent that your report can make it clear the kinds of things you are saying to us about priorities and near term ideas, that is particularly useful to us as we face the next few months.

Thank you again.

DR. ROBERTS: We will do our best on the report.

Also, I neglected to thank the public commenters. They provide valuable input for SAP. We appreciate their input and suggestions as well.

Is there any other business or comments anyone on the panel would like to raise?

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None. This session is closed. Thanks again.

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[Whereupon, at 5:05 p.m., the meeting concluded.]

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FRANCES M. FREEMAN

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FRANCES M. FREEMAN
21168 Wildflower Square
Ashburn, VA 20147
703/723-3550

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