March 19, 2002

MEMORANDUM

SUBJECT: Transmittal of the Final Report of the FIFRA Scientific Advisory Panel Meeting Held February 5-7, 2002

TO: Marcia E. Mulkey, Director
Office of Pesticide Programs

FROM: Paul I. Lewis, Designated Federal Official
FIFRA Scientific Advisory Panel
Office of Science Coordination and Policy

THRU: Larry C. Dorsey, Executive Secretary
FIFRA Scientific Advisory Panel
Office of Science Coordination and Policy

Vanessa T. Vu, Ph.D.
Director
Office of Science Coordination and Policy

Please find attached the final report of the FIFRA Scientific Advisory Panel open meeting held in Arlington, Virginia from February 5-7, 2002. This report addressees a set of scientific issues being considered by the Environmental Protection Agency regarding methods used to conduct a preliminary cumulative risk assessment for organophosphate pesticides.

Attachment

cc:

Stephen Johnson
Susan Hazen
Adam Sharp
Janet Andersen
Peter Caulkins
Anne Lindsay
Denise Keehner
Elizabeth Leovey
Linda Moos
Lois Rossi
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Antonio Bravo
Douglas Parsons
David Deegan
Don Barnes (SAB)
OPP Docket

SAP Report No. 2002-01

REPORT

FIFRA Scientific Advisory Panel Meeting, February 5-7, 2002, held at the Sheraton Crystal City Hotel, Arlington, Virginia

A Set of Scientific Issues Being Considered by the Environmental Protection Agency Regarding:

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

SESSION 1: HAZARD AND DOSE RESPONSE ANALYSIS

SESSION 2: ASSESSMENT OF FOOD EXPOSURE

SESSION 3: ASSESSMENT OF DRINKING WATER EXPOSURE

SESSION 4: ASSESSMENT OF RESIDENTIAL/NON-OCCUPATIONAL EXPOSURE

SESSION 5: RISK CHARACTERIZATION

NOTICE

This report has been written as part of the activities of the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), Scientific Advisory Panel (SAP). This report has not been reviewed for approval by the United States Environmental Protection Agency (Agency) and, hence, the contents of this report do not necessarily represent the views and policies of the Agency, nor of other agencies in the Executive Branch of the Federal government, nor does mention of trade names or commercial products constitute a recommendation for use.

The FIFRA SAP was established under the provisions of FIFRA, as amended by the Food Quality Protection Act (FQPA) of 1996, to provide advice, information, and recommendations to the Agency Administrator on pesticides and pesticide-related issues regarding the impact of regulatory actions on health and the environment. The Panel serves as the primary scientific peer review mechanism of the EPA, Office of Pesticide Programs (OPP) and is structured to provide balanced expert assessment of pesticide and pesticide-related matters facing the Agency. Food Quality Protection Act Science Review Board members serve the FIFRA SAP on an ad-hoc basis to assist in reviews conducted by the FIFRA SAP. Further information about FIFRA SAP reports and activities can be obtained from its website at http://www.epa.gov/scipoly/sap/ or the OPP Docket at (703) 305-5805. Interested persons are invited to contact Larry Dorsey, SAP Executive Secretary, via e-mail at dorsey.larry@epa.gov.

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INTRODUCTION

The Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), Scientific Advisory Panel (SAP) has completed its review of the set of scientific issues being considered by the Agency pertaining to methods used to conduct a preliminary cumulative risk assessment for organophosphate pesticides. Advance notice of the meeting was published in the *Federal Register* on January 15, 2002. The review was conducted in an open Panel meeting held in Arlington, Virginia, on February 5 -7, 2002.

The Agency's methodology and subsequent meeting consisted of five components/sessions: Session 1: hazard and dose response analysis; Session 2: assessment of food exposure; Session 3: assessment of drinking water exposure; Session 4: assessment of residential/non-occupational exposure and Session 5: risk characterization. Ronald J. Kendall, Ph.D. and Mr. Paul Lewis served as SAP Session Chair and Designated Federal Official for the hazard and dose response analysis, assessment of food exposure, assessment of drinking water exposure sessions, respectively. Stephen Roberts, Ph.D. and Ms. Olga Odiott served as SAP Session Chair and Designated Federal Official for the assessment of residential/non-occupational exposure and risk characterization sessions, respectively.

Ms. Sherry Sterling (Office of Science Coordination and Policy) opened the meeting on behalf of the Agency. Ms. Marcia Mulkey (Director, Office of Pesticide Programs) provided opening remarks. Ms. Margaret Stasikowski (Office of Pesticide Programs, EPA) made introductory remarks, highlighting the goals and objectives of each session. The methodology presented is the first time that the Agency had assessed risk combining multiple sources of exposure for multiple chemicals acting via a common mechanism of toxicity.

Public comments providing overall remarks about the meetings were presented. In addition, public comments relevant to specific sessions were also provided and listed in this report under the respective session. Below is a listing of the overall public comments.

PARTICIPANTS

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, Lubbock, TX

Designated Federal Official
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Patrick Durkin, Ph.D., Vice President, Syracuse Environmental Research Associates, Inc. Fayetteville, NY

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

Jean Harry, Ph.D., National Institute of Environmental Health Science, Research Triangle Park, NC

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

Ernest McConnell, D.V.M., President, Toxpath Inc., Raleigh, NC

Peter Macdonald, D. Phil., Professor of Mathematics and Statistics, Department of Mathematics and Statistics, McMaster University, Hamilton, Ontario, Canada

Nu-May Ruby Reed, Ph.D., Staff Toxicologist, California Environmental Protection Agency, Department of Pesticide Regulation, Sacramento, CA

Lorenz Rhomberg, Ph.D., Principal, Gradient Corporation, Cambridge, MA

PUBLIC COMMENTS

Oral statements were made by:
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

Jeffrey Driver, Ph.D., 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

Ray McAllister, Ph.D., Crop Life America, on behalf of the FQPA Implementation Working Group

Abraham Tobia, Ph.D., Aventis CropScience, on behalf of the Farm Family Exposure Task Force

Written statements were received from:
FQPA Implementation Working Group
Natural Resources Defense Council

PANEL RECOMMENDATIONS

The Panel concluded that the Agency's "Organophosphate Pesticide Preliminary Cumulative Risk Assessment" (PCRA) background document was responsive to recommendations by previous Panels on this topic and did address deficiencies with methods to conduct a preliminary cumulative risk assessment for organophosphate pesticides. In addition, the Panel noted that such limitations would not hinder the Agency in preparing such a cumulative risk assessment. However, the Panel acknowledged such a methodology may need to be refined or provide greater analysis for other chemicals/chemical classes. While further refinements are needed, the Panel acknowledged that some can be accomplished in the near term while others are long-term improvements that should be pursued after the initial cumulative risk assessment is prepared. Specific comments and/or recommendations are presented below. Please see the specific sections of the report for a more detailed discussion.

Hazard and Dose Response Analysis

The Panel recognized that a single measure had been provisionally chosen both as a reference point to determine relative potency factors (RPF) and as a point of departure (POD) for calculating margins of exposure. The majority of the Panel continued to provisionally endorse the use of the BMD10 for both purposes (as recommended at previous SAP meetings). This Panel, as with previous Panels, continues to recommend the use of the nonlinear mixed effect model and noted that the Agency had corrected many problems to model dose response relationships of OP exposure to cholinesterase inhibition. The success of the expanded model in describing the low-dose shoulder on dose-response curves for some OPs should encourage the Agency to explore physiologically based pharmacokinetic models more thoroughly. Although it is biologically inspired, the expanded model should not be considered a substitute for a physiologically based pharmacokinetic model. While the Panel was impressed by how

the expanded model could lead to a simple, practical enhancement to the exponential model, they were concerned that the expanded model was only used to fit 14 out of 29 OPs, raising the question as to whether the model is universally true for all OPs.

Assessment of Food Exposure

The sensitivity analysis performed by the Agency is what is needed for a better understanding of modeling OP exposure in food. The Agency should provide explanations and support for assumptions in the PCRA, specifically that the food exposure component is assumed to be uniform across the geographic regions and over all seasons. The Panel encouraged the Agency to include violative samples from the PDP database in its dietary exposure assessment. For analyses designed to investigate chronic exposures of individuals over periods of consecutive days, weeks or months, the Panel acknowledged limitations with the Continuing Survey of Food Intake by Individual (CSFII) data and the Calendex algorithm and emphasized the need for longitudinal data on food consumption by individuals.

Assessment of Drinking Water Exposure

The Panel agreed with the Agency that exposures to OPs from drinking water are likely to be a minor part of total exposure in almost all cases. However, fuller characterization and interpretation of these analyses would increase confidence in the present analysis and set the stage for subsequent cumulative risk assessments of other pesticides. If exposure via drinking water is potentially greatest for some well defined subpopulations (e.g. young infants bottle-fed formula made from powder and water), such exposures should be characterized. More explicit inclusion of transformation products, particularly the oxons, is essential. The Agency should also consider the potential effects of spills and non-agricultural OP uses to drinking water, as well as the effect of water treatment processes on OPs and their transformation products. In terms of regional drinking water assessments, the Panel concluded that the regional assessment would generally be protective of the region as a whole, not just of the reservoir modeled. Finally, the Panel noted that an important consideration is not what a population is typically exposed to but the probability that an unusual exposure might occur.

Assessment of Residential/Non-occupational exposure

The Panel concluded that the draft residential/non-occupational exposure assessment should show simulation results for all age groups of children. Model parameters that must follow logical constraints (e.g., proportions of the yard that are garden and not garden cannot total more than 100%) and co-occurrence of uses (e.g., of both scenarios and product use within scenarios) need to be dealt with systematically so that realistic longitudinal use patterns are reflected in the assessment. Institutional exposures (i.e., schools, day care centers, etc.) should be explicitly addressed in the document. The Agency also should consider adding the consumption of home grown vegetation, exposure from drift in agricultural applications and inhalation exposures to

volatile active ingredients to the lawn scenario, particularly to children, in its analysis. While the Panel endorsed the use of probabilistic techniques for residential exposures, it believes that the widespread use of uniform distributions in the draft cumulative risk assessment unrealistically distorts the variability and uncertainty in parameters to which it is applied. The Panel encouraged the continued use of calender based models to refine the residential exposure assessments to the extent that such models can be shown to lead to plausible estimates of significant levels of exposure. Finally, the most important priority for the Agency in the area of residential exposure should be updating the assessment based on this guidance and to conduct a formal sensitivity analysis of the model to determine the chemicals, routes, and scenarios that drive the major exposures under the model.

Risk Characterization

The Panel recommended against the single-day approach and instead supports a version of the running-average approach, with modifications. Specifically, the Panel recommended that an approach be chosen that explicitly addresses the persistence of cholinesterase inhibition, in an agent-specific and species-specific way if possible. Such an approach should include only the current and previous days within the averaging window (and not future days), and it should give greater weight to more recent days than to less recent ones, on the grounds that the amount of inhibition persisting from a day's exposure decreases with time.

While the Agency acknowledged that other endpoints, besides cholinesterase inhibition, will be considered for each OP, the Panel concluded that the risk assessment process must still depend upon a full evaluation of the toxic potential of individual products and not simply be tied to a single endpoint. Such a position needs to present a balance by the Agency, clearly stating that a cumulative risk assessment does not address all the potential risks.

The Panel highly recommended that the PCRA for OPs be expanded to provide an evaluation to other susceptible subpopulations, specifically infants, children and the elderly. The Panel strongly maintains the position that this risk assessment cannot be completed without such an evaluation. In addition, there are sufficient issues with regard to collection and use of data from developmental studies that the Panel recommends such topics require additional Agency analysis and independent scientific peer review.

The Panel recognized that a PBPK approach is unlikely to be realizable in the time-frame that the Agency has available and that other approaches to address the dosimetry issues will be needed in the short term. Nonetheless, a PBPK approach should be feasible, and it would help answer important questions about interactions and saturable steps in metabolism, as recommended by previous Panels. It is recommended that such an approach be investigated in the longer term.

SAP Report No. 2002-01

REPORT:
FIFRA Scientific Advisory Panel Meeting, February 5-7, 2002, held at the Sheraton Crystal City Hotel, Arlington, Virginia

A Set of Scientific Issues Being Considered by the Environmental Protection Agency Regarding:

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

SESSION 1: HAZARD AND DOSE RESPONSE ANALYSIS

Mr. Paul I. Lewis
Designated Federal Official
FIFRA Scientific Advisory Panel
Date: March 19, 2002

Ronald J. Kendall, Ph.D.
FIFRA SAP Session Chair
FIFRA Scientific Advisory Panel
Date: March 19, 2002____

Federal Insecticide, Fungicide, and Rodenticide Act
Scientific Advisory Panel Meeting
February 5, 2002

METHODS USED TO CONDUCT A PRELIMINARY CUMULATIVE RISK ASSESSMENT FOR ORGANOPHOSPHATE PESTICIDES
SESSION 1: HAZARD AND DOSE RESPONSE ANALYSIS

PARTICIPANTS

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

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Peter Macdonald, D. Phil., Professor of Mathematics and Statistics, Department of Mathematics and Statistics, McMaster University, Hamilton, Ontario, Canada

Nu-May Ruby Reed, Ph.D., Staff Toxicologist, California Environmental Protection Agency, Department of Pesticide Regulation, Sacramento, CA

Lorenz Rhomberg, Ph.D., Principal, Gradient Corporation, Cambridge, MA

PUBLIC COMMENTERS

Oral statements were made by:
Tim Pastoor, Ph.D., Syngenta Corporation, on behalf of the FQPA Implementation Working Group

Written statements were received from:
FQPA Implementation Working Group

INTRODUCTION

The Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), Scientific Advisory Panel (SAP) has completed its review of the set of scientific issues being considered by the Agency pertaining to methods used to conduct a preliminary cumulative risk assessment for organophosphate pesticides. Advance notice of the meeting was published in the *Federal Register* on January 15, 2002. The review was conducted in an open Panel meeting held in Arlington, Virginia, on February 5, 2002. The meeting was chaired by Ronald J. Kendall, Ph.D. Mr. Paul Lewis served as the Designated Federal Official. 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) summarized the hazard/relative potency factor analysis.

CHARGE

1. 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.

A) 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.

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).

DETAILED RESPONSE TO THE CHARGE

The specific issues to be addressed by the Panel are keyed to the Agency's background document "Organophosphate Pesticide Preliminary Cumulative Risk Assessment" dated December 3, 2001, and are presented as follows:

1. 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.

A) Please comment on how the Agency addressed the recommendations listed above (I.B and III.B.3).

Overall, the Panel concluded that the Agency's response was appropriate and supportive of recommendations of previous meetings of the SAP on approaches for conducting a Preliminary Cumulative Risk Assessment (PCRA) for organophosphate pesticides (i.e. September 5-6, 2001 SAP report). Several members commended the Agency staff for the impressive accomplishment in the relative brief interval since the last SAP meeting. The SAP suggested additional areas of further refinement. While certain remaining deficiencies or uncertainties in the hazard and dose response analysis were also noted, the Panel acknowledged that these deficiencies were not necessarily limitations that must be corrected before implementing the PCRA. Instead, they were seen to a large extent as reflections of the still evolving nature of the field and the inherent difficulties in attempting to combine disparate data sets derived from systems of great underlying complexity. Specific points raised for Agency consideration are as follows:

(1) Derivation of adjustment factor "B"

The present approach is more sophisticated and more objective, because it eliminates arbitrary procedures such as a "default to zero" for residual cholinesterase activity (the horizontal asymptote designated "B", or the related parameters PB, tB). Instead, as described in the draft Agency background document (1B 12-15), this parameter is estimated in the course of fitting the basic or expanded model equations to the data set using standardized nonlinear regression methods. This approach guarantees a best fit to the available data and eliminates the need for subjective choices. The Panel was satisfied with the new approach.

(2) Formal analysis of residuals

The PCRA document contains an appropriate analysis of model residuals, which demonstrates that, when the appropriate basic or expanded model is chosen to fit the OP dose-response data, there is a random distribution of error about the fitted curve. This result increases confidence in the assumptions of the models and in the use of such models for further analysis of other chemicals/chemical classes, including the estimations of relative potency factors.

(3) Minor revisions to the OPCumRisk program (goodness of fit, etc).

These were accepted without comment.

(4) Consideration of appropriate measures of relative potency.

The issue of measuring relative potency received extensive discussion. The Panel recognized that a single measure has been provisionally chosen both as a reference point to determine relative potency factors (RPF) and as a point of departure (POD) for calculating margins of exposure. At the September, 2001 SAP meeting, the Panel recommended the use of BMD10 for these twin purposes. At the present session, this use was debated in light of the necessary tradeoff between a need to minimize adverse effects at the POD, and a need to optimize the precision of RPFs. Because OP inhibition curves often deviate from the classic shape in the low dose region critical for regulation (shoulder effects), the ED50 is not appropriate for determining relative potency here. On the other hand, even though a POD should certainly not be associated with definite adverse effect, a NOAEL cannot be measured precisely at all. The BMD10 is a compromise choice that appears to be justified. It is much more precise than a NOAEL and it represents a very modest level of effect for cholinesterase inhibition. Although some questions about BMD10 were raised during the Panel discussion, recognizing that we are dealing with inhibition of brain acetylcholinesterase, there are two reasons why concern is not great. First, for some OPs, a 10% inhibition of brain cholinesterase is below the level that is generally associated with overt neurologic signs in rats (Nostrandt et al, 1997; Sheets et al, 1997). Second, if the BMD10 is established in animal studies with an appropriate safety factor for extrapolation, allowed human exposures should not generate this level of inhibition.

With these considerations in mind, the SAP is prepared to provisionally endorse the use of BMD10 as presently contemplated. The Panel recommends, however, that the Agency carry out additional analysis of its data sets to determine the relative precision of BMD1, 5, 10, and 20, for example, and to determine how many of the different BMDs fall in or out of the range of observation. The Cumulative Risk Assessment document would be strengthened by including such information as an objective basis for the Agency's preferred choice. Meanwhile, the Panel considers BMD10 as being far superior to a NOAEL or an ill-defined LOAEL as a POD. In fact, several Panel members believed strongly that LOAELs and NOAELs should not be applied to any of the data. Instead, regression-based methods should be extended to all available data so that reasonable comparisons can be made between like items. One Panel member asked for illustration of one or more cases where the NOAELs and LOAELS must be used, reasoning that failure of convergence with regression methods is more likely to reflect deficiencies in the data set than problems with the analysis per se.

Another Panel member noted that a fundamental condition for using the relative potency approach - consistent proportionality among chemicals throughout the dose-response range - was not met by the OP data. While the Agency may have to use this approach nonetheless as a practical matter, at least in the near term, the Panel member encouraged the development of estimates of the potential magnitude of error introduced into the PCRA by its use.

(5) Expression of inhalation and oral exposures in same dose units.

The SAP was satisfied with these minor but significant improvements in the revised document.

(6) Consideration of impact of individual animal data instead of summary information.

In the absence of convincing evidence that the use of group averages does not compromise the analysis, the current Panel supports its recommendations from the previous meeting. During the September 5-6, 2001 SAP meeting, the Agency asserted it could be demonstrated that the use of individual animal data would not impact the assessments:

"If the background document is intended to serve as a model for the assessment of cumulative risks, it is important for the analysis to be reasonably rigorous and transparent. In this respect, **the decision to use group averages based on the data evaluation records (DERs) was inappropriate.** The Agency has the ability to retrieve quickly full text copies of all of the studies submitted to EPA. Further, the studies will typically have tables that give the responses in individual animals. Using group averages ... results in a substantial loss of information. The whole point of the document under review is to use a statistical analysis to reach or support a conclusion. **Therefore, individual animal data should be used regardless of the dose-response model that is selected.** "

–SAP Report No. 2001-04, p. 20, bold added for emphasis

Documentation for the Agency's assertion of group averages was expected in the current revision. Instead, the issue is addressed only briefly in III.B.3.h of the Agency's background document. The Panel recommended that the Agency address this issue more thoroughly and in the main body of the text.

(7) Derivation of oral doses from actual dietary intakes.

This issue was addressed satisfactorily in the present documents.

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.

The Panel commended the Agency for the progress that has been made in the modeling of dose/response relationships of OP exposure to cholinesterase inhibition. The consensus of the Panel is that the nonlinear mixed effects model approach developed by the Agency has corrected many problems highlighted in the previous review. For most OPs with dose response data from multiple studies, the inclusion of random effects for individual studies is a practical and effective approach to the "meta analysis" designed to develop a single fixed dose response curve based on all the available data.

The Agency has proposed an elegantly simple "expanded" exponential model that provides improved fit for many OPs with small response effects at low dose levels. Several members commented that the mathematical elegance of the model has a cost, specifically a greater demand on the data to support the estimation of the additional parameters. The amount of data (study repetitions, numbers of observations) available to estimate the nonlinear mixed effect model varies widely for the OPs. The basic model appears to perform extremely well for compounds with rich dose response data (e.g. methamidophos, fenthion) while poorly for others where study data are limited (e.g. azinphos, phosmet and trichlorfon). During the session, the Agency reported that the expanded model was chosen over the basic model in 14 out of 29 OPs. In the Agency's background document, the expanded model was chosen 8 out of 29 times, but the Agency later explained that correcting computer errors since that time had resulted in improved performance of the fitting program for 6 more OPs.

The Panel encourages the Agency to provide a standard formal definition of the full mathematical model(s) in the documentation of its preliminary risk assessment. This formal model specification would include the model equations (including the random error term) that are currently provided in Section 1.B of the Agency's background document, notation for the fixed and random coefficient parameterization of the model, formal statements of the distributional assumptions for the model error (normality) and the random effects (i.e., mean zero, variance, and independence of errors). For clarity, the Agency is encouraged to use exposure/dose terminology in its background document

to reflect contemporary thinking in related risk assessments. In this regard, it would be useful to refer to the latest Guidelines for Carcinogen Risk Assessment.

The Panel cautiously endorses the general use of profile likelihood analysis to fix values for the asymptote parameter, B, of the basic model or the shape (S) and displacement (D) parameters of the extended model when simultaneous estimation for all parameters in the model fails (profile likelihood analysis is valuable to diagnose problems of convergence failure). The Panel would prefer to see the Agency apply formal optimization methods for boundary value problems in the estimation to address convergence problems that in this assessment were managed through the profile-likelihood technique.

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).

The success of the expanded model in describing the low-dose shoulder on 14 of 29 OP dose-response curves should encourage the Agency to explore physiologically based pharmacokinetic models more thoroughly. Experimental studies could lead to more realistic models, a better understanding of the toxic effects of OPs, and perhaps a better understanding of why female rats appear to be more sensitive than male rats.

While issues related to this question are presented in response to question 1b, the Panel offered a few specific observations on the expanded model.

The Panel was impressed by how the expanded model, a simple but reasonable pharmacokinetic model, could lead to a simple, practical enhancement to the exponential

model, expressing "internal dose" in terms of "administered dose" in a way that reproduces the low-dose shoulder observed on many dose-response curves. Panelists described the expanded model as "elegant" and worthy of further experimental study. Nevertheless, the expanded model was only used to fit 14 out of 29 OPs, raising the question as to whether the model is universally true for all OPs.

In the attempt to develop a simple model, the Agency tried to take into account various aspects of both the underlying biology and the methodology applied in the various study designs. This raises one issue with regard to the data used in the models. In the case of the brain enzyme inhibition, the assays used are equivalent in the level of precision, thus comparing various chemicals across different assays does not present a major problem. However, this may not be the case in future situations for other chemicals or chemical classes where other types of biological data are used.

While biologically inspired, the expanded model should not be considered a substitute for a physiologically based pharmacokinetic model. It is important to think through what is known about biological effects that could be acting to produce the phenomenon. Consideration is needed to determine if such a correction is plausible in view of the processes known to operate, and at the dose levels at which they are thought to operate. Such an approach should also raise the issue of the effects of those processes, should they actually be operating, on low doses. For example, if there really is liver-based detoxification (presumably by carboxyesterases not inhibited by the OPs) and if it can be saturated at relatively low doses by some OPs, then in a mixture of OP exposures, the saturation of detoxification may well affect the kinetics, and hence the low-dose potency, of other OPs in the mix if they are acted upon by the same enzymes. Some OPs are direct-acting and others require metabolic activation for toxic effects. The approach implicit in the expanded model assumes that these processes are essentially linear over the dose range considered, and only the liver-based carboxyesterase detoxification contributes significant nonlinearity. This approach could be addressed by a more sophisticated pharmacokinetic analysis.

An important consequence of the shoulder effect in the dose response curve is that relative potency of a pair of OPs is not expected to be constant over all dose levels. This is an important consideration of the effect of simultaneous exposures to low levels of several OPs. By basing the calculation of relative potency at a higher dose level (at the BMD10), the actual degree of ChE-inhibition in the exposure of interest can be either over- or underestimated.

One Panelist contributed the following additional comments on the mechanisms involved, with reference to the Agency's background document.

(Ref.: I.B p. 2 ff.). The inhibition of cholinesterases of different types and in different tissues is discussed in descriptive terms, assuring the reader that such inhibition reaches a pseudo-steady state within 21-28 days. It would be useful to indicate that these descriptive data are consistent with both the kinetics of inhibition and the kinetics of reversibility of inhibition (whether by regeneration or synthesis of new enzyme). The regeneration rates depend very much on the character of the phosphate ester and could

easily explain the observed variability between the sexes and the non-linearity of the response in the low dose region, as can the pharmacokinetic explanation for non-linear behavior. These factors will be the major determinant of how long it takes to reach this state. Differences in enzyme resynthesis rates may also provide some insight into whether the fetus is more or less sensitive than the adult to cholinesterase inhibition. Greater support for use of these descriptive data would occur if it were consistent with general mechanisms involved in ChE inhibition and the reversal of that inhibition.

Despite the above comment, the statement that there are insufficient pharmacokinetic and pharmacodynamic data to characterize all of these OPs means that the overall cumulative assessment cannot rely on detailed knowledge on how the above factors modify the toxicological hazard with each compound. Therefore, the Agency's use of the descriptive data for the cumulative risk assessment is justified.

(Ref.: I.B p. 30). The Agency should explore the potential rationale for the greater sensitivity of female rats with the identified OP pesticides. A simple, systematic difference in sensitivity of acetylcholinesterase between the sexes is not a viable explanation. The fact that the differences in sensitivity were not observed uniformly is a strong argument that other factors have to be involved. It is probable that sex-related (or age-related) differences in sensitivity are due to differences in the rates of metabolic activation or deactivation of the OP compound (or factors that affect disposition of the parent or metabolite) or to differences in the rate of enzyme resynthesis after inhibition. Since these differences were not observed with all of the compounds, one would prefer to rely on an understanding of why this occurs rather than a broad statement that the female is generically more sensitive. The choice of females is now justified by the data at hand, but the process remains descriptive and empirical (i.e. subject to change) until such time that the mechanistic bases contributing to this variable behavior is understood.

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SAP Report No. 2002-01

REPORT:
FIFRA Scientific Advisory Panel Meeting, February 5-7, 2002, held at the Sheraton Crystal City Hotel, Arlington, Virginia

A Set of Scientific Issues Being Considered by the Environmental Protection Agency Regarding:

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

SESSION 2: ASSESSMENT OF FOOD EXPOSURE

Mr. Paul I. Lewis
Designated Federal Official
FIFRA Scientific Advisory Panel
Date: March 19, 2002

Ronald J. Kendall, Ph.D.
FIFRA SAP Session Chair
FIFRA Scientific Advisory Panel
Date: March 19, 2002

Federal Insecticide, Fungicide, and Rodenticide Act
Scientific Advisory Panel Meeting
February 6, 2002

METHODS USED TO CONDUCT A PRELIMINARY CUMULATIVE RISK ASSESSMENT FOR ORGANOPHOSPHATE PESTICIDES
SESSION 2: ASSESSMENT OF FOOD EXPOSURE

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Oral statements were made by:
Ingrid Kelley, Ph.D., Bayer Corporation, on behalf of the FQPA Implementation Working Group
Judith Schreiber, Ph.D., on behalf of the New York State Attorney General

Written statements were received from:
FQPA Implementation Working Group

INTRODUCTION

The Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), Scientific Advisory Panel (SAP) has completed its review of the set of scientific issues being considered by the Agency pertaining to methods used to conduct a preliminary cumulative risk assessment for organophosphate pesticides. Advance notice of the meeting was published in the *Federal Register* on January 15, 2002. The review was conducted in an open Panel meeting held in Arlington, Virginia, on February 6, 2002. The meeting was chaired by Ronald J. Kendall, Ph.D. Mr. Paul Lewis served as the Designated Federal Official. William O. Smith, Ph.D. (Office of Pesticide Programs, EPA) and Mr. David Miller (Office of Pesticide Programs, EPA) provided an assessment of food exposure.

CHARGE

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 99.9th 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.

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 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.

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.

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?

DETAILED RESPONSE TO THE CHARGE

The specific issues to be addressed by the Panel are keyed to the Agency's background document "Organophosphate Pesticide Preliminary Cumulative Risk Assessment" dated December 3, 2001, and are presented as follows:

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 99.9th 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.

The Agency is to be commended for the impressive effort and progress in dietary exposure assessment. The sensitivity analysis that the Agency presented with varying commodity input is precisely what is needed for a better understanding of the output and serves as a mechanism of quality control for the model and its use. Simulation tests of the type reported in Addendum Table 1 of the Agency=s background document are important to confirm that the modeling of OP exposure through food is performing as expected. The question here centers on explanations for the non-intuitive result that the extremes of a composite variable distribution for OP MOEs are not substantially affected when three major food contributors are removed from the distribution of daily composite food residues.

Dietary exposure evaluation model (DEEM)/Calendex models daily OP residues on foods by first taking draws of residue values for individual food items, converting them to dose equivalents for the reference compound (i.e. Methamidiphos) and then adding these random residue variables together to create a daily dose. Daily exposure is then computed by dividing the value of this stochastically generated composite residue value by the kilogram body weight of the CSFII reference individual (here children age 1- 2). The composite distribution for single day individual exposures is therefore a complex distribution that is a function of: 1) the food items and amounts consumed in the reported daily diet; 2) independent stochastic draws of a residue concentration for each food item; and 3) the sample individual=s weight in kilograms. Since stochastic draws of residue concentrations are independent across food items, the mean of the composite exposure distribution is the sum of the expected values for the contributing food residues. (In actuality, there is a linear scaling that occurs to reflect the fact that exposure values require division of the composite daily residue by individual body weights). The variance is the sum of the variances from the individual residue distributions from each food source.

Removing foods A, B, and C, which are major OP contributors in children=s diets, alters the mean and variance of the composite distribution of exposures. These changes are clearly evident in the results presented in Table 1 of the Agency=s background document. The importance of foods A, B, and C to the composite distribution is obvious. Comparing the simulated composite exposure distribution with foods A, B, and C removed from full distribution of the preliminary cumulative assessment, the following changes were observed: (1) 3.5 fold increase in the mean MOE; (2) an almost 4-fold increase in the 95^{th} percentile of MOE; (3) roughly a 2.5 fold increase in the 99^{th} percentile and 99.5^{th} percentile of MOE and; (4) 2.0 fold increase in MOE for the 99.9^{th} percentile. Therefore, removal of food groups A, B, and C does have a major impact on the distribution.

Why is the impact on the extreme values not greater? The distribution of the 99^{th} and 99.5^{th} percentile values and other order statistics of the composite distribution follow the general formula for the distribution order statistic (i.e. percentile value)

$$f_k(y_k) = n!/((k-1)!(n-k)!) [F(y_k)]^{k-1} [1-F(y_k)]^{n-k} f(y_k)$$

where:

$f(y_k)$ = the probability density function for the composite exposure evaluated at the value of y_k corresponding to the quantile of interest

$F(y_k)$ = the cumulative density function for the composite exposure, also evaluated at y_k

n = total number of observations

k = order of the value y_k in $\{y_i; i = 1, ... ,n\}$ - e.g. 995 of 1000.

For these highest quantiles, this distribution is influenced by the extreme tails of each of the many residue distributions that can contribute to the composite residue values but is relatively unaffected by the body of the distribution. The probability of an extreme draw in the composite distribution is a function of the probabilities of extremes for the individual components. The probabilities of extreme draws from the residue distribution for any food group are very small—for the 99.9th percentile value it is 1 in every 1000 times that the food appears in a daily menu for a sample individual. The probability of 99.9th percentile values on independent draws from two or more foods in the same daily diet are very small (1/1,000,000 for two, 1/1,000,000,000 for three).

The routes by which the foods A, B, and C affect the extreme values are based on two mechanisms: 1) a large but not necessarily extreme baseline draw for a residue value to which a very large or extreme residue draw outcome on another food generates the extreme percentile composite exposure and; 2) a very extreme draw of a residue for foods A, B, or C. The probability that the first mechanism is producing extreme values is much greater than the second—hence the observation that foods A, B, and C are common in daily diets that have high exposures. This is also the primary reason why the upper tail of the daily exposure distribution "contracts" when contributions of A, B and C are removed. The second mechanism applies not only to foods A, B, and C but to every other food that may appear in the diet. These other foods may be less common in the diet so their contribution to the body of the composite distribution is less than that of A, B or C. However, stochastic draws of very extreme residues for these foods can still occur at very low probabilities. Even though the probability of an extreme draw for any given food item in this set is very small, the probability of an extreme draw for any one of them is the sum of the extreme value probabilities for the separate residue distributions.

The explanation provided in the previous paragraph is not intended to completely discount the possibility that there are anomalies or computing errors in the modeling of exposures. If simulation tests produce illogical or unstable results, DEEM/Calendex provides the ability to tag and replay the simulation inputs and stochastic draws for subsets of cases. The Panel encourages the Agency to use this capability to analyze the specific determinants of the extreme quantile values (99th, 99.5th and 99.9th percentiles) in this simulation exercise.

Regarding the multiple sets of analyses with removing high contributing commodities A, B, and C, it was noted that the dynamic interplay of the many factors

involved could change the relative contribution of these commodities as they are removed one by one. It would be beneficial to re-examine the Critical Exposure Contributor (CEC) file after the removal of a commodity. Pulling one commodity could very well alter the profile of top exposure individuals in terms of demographic pictures, the eating pattern, etc.

Another way to conduct the sensitivity analysis could be to observe the change of model output through stepwise removal of high contributing chemicals. This exercise could give some understanding of the dynamics in the $Residue_{IE}$.

The characterization of the entire high end (e.g., 95th to 99.9th) is very helpful. This format of presentation should be carried all the way to the risk characterization phase such that the final analysis of risk is not presented as a single point across the risk distribution.

The PCRA should provide explanations and support for the assumptions that dictate the direction and scope of the current dietary exposure analysis. For example, the food exposure component is assumed to be uniform across the geographic regions and over all seasons. Also, it was assumed that the pattern of PDP residue data provided little evidence for seasonal and geographic variation. Moreover, the single unit residue profile presumably was not significantly different from the profile for the composite samples. These assumptions appeared counter-intuitive to a reader. The common thinking would more likely be that there are seasonality and geographic variations in food consumption patterns and residue profiles, at least for some foods that could significantly contribute to dietary exposures (e.g., commonly consumed by infants and children). Thus, the reader is left with speculations and unanswered questions. Could it be that the key to the assumption of uniformity is in whether acute or longer-term exposure was being assessed? Could the uniformity assumption stem from the Agency=s belief that seasonal and geographic variations would not be substantial in the bigger picture of cumulative exposure? Could some of these assumptions be based merely on the Agency's extensive experience in these areas? It is important to orient the reader to the dietary component of the cumulative exposure by providing sufficient support to these decision-making processes. In addition, the presentation of the assessment could also be enhanced by clearly delineating the scope of the assessment as constrained by the availability of data. This might clarify some concerns raised by the Panel, such as: how or why the exposures from home gardening products are not included in the assessment; how certain population subgroups (see examples given under Question 2) might not be represented in the assessment based on the CSFII.

There was considerable debate concerning the use of violative samples from the PDP database. The Agency discarded violative samples from the PDP data when calculating the predicted distribution of exposures. The Panel encourages the Agency to include these residues in the prediction of a distribution of exposures for the general population. Two basic reasons were given. First, it was argued that regardless of the acceptable level of contamination, it is likely that some violations will occur and the residue data provides some information on the frequency and severity of these violations. In addition, since we are in some way trying to decide if there is a problem in the general

population at the present time, these residues seem the most appropriate. It is noted that as a regulation gets modified to reduce residue levels, it is likely that the severity of the violative residues is also reduced and hence moves the entire distribution of exposures. This could be addressed through a sensitivity analysis.

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 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 Arolling 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.

The two methods of summarizing exposures over multiple days can be characterized in 2 ways. In the first most extreme case, the same food exposure is used for all days in the analysis, the distribution for single days matches the distribution for multiple days and the comparison against single days is most conservative. At the other extreme, days could be considered completely independent over the multiple days and the average would then have variance that was a factor of n-days smaller than the original 1 day samples. If all distributions were normal, the tails of the two distributions (1 day versus n day) would differ by a factor of the square root of n. For non-normal distributions, other changes would be expected and these could be calculated. By looking at changes in the mean exposure and changes in the tail behavior relative to the completely independent days distribution, one can assess the degree to which a chosen day-to-day resampling scheme is conservative (most near the single day distribution) or not.

If moderate chronic exposure proves to be important, then longitudinal data on diet is needed. By way of a sensitivity analysis, longitudinal series could be created

artificially from CSFII data, to see if this impacts on the estimation of chronic exposure. The assumption that diet is uniform across the country and seasonally invariant needs to be tested.

In conclusion, the Panel is well aware of the challenges involved with collecting reliable longitudinal data on food consumption by individuals. The CSFII data are good for models of daily exposure but not suitable for models where the accumulation of exposure over time is critical. The need for longitudinal data has come up as a consistently recurring theme at all recent SAP meetings concerned with exposure to pesticides. Having said this, the Panel accepts that the CSFII data are the best data currently available and the Agency will have to use the CSFII data if they are to move forward at this time. However, in the long term there will be a need for longitudinal data not artificially created from CSFII files.

Further explanation of the Panel=s conclusion is provided below.

The rolling average will introduce autocorrelation into the dietary series for each individual; this will mitigate the effects of sampling non-consecutive days in the CSFII but any extreme values in the series will tend to be smoothed out in the process. For young children with a limited range of foods in their diets, flipping back and forth between the two sampled diets in CSFII may not be unrealistic. For most households, diet is expected to be serially correlated. Not only are leftovers likely to be consumed on consecutive days, but so will fruit, milk, juice and other perishable commodities bought in quantity.

The CSFII record of an individual=s eating pattern in a single day is applied for estimating the single day dietary exposure. However, it is well-recognized that the CSFII data lack the longitudinal characteristics for an individual=s long-term eating patterns. The current analysis of multiple-day rolling average through repeated sampling of two non-consecutive days' consumption records has the apparent limitation of not representing the individual=s diverse eating pattern over an extended period of averaging. The Panel recommends that alternatives to this mode be explored. Specifically, the Agency should pursue the Panel=s recommendation made in the September 2000 SAP review of the Calendex model that addressed this same issue. Briefly, it was recommended that a dietary consumption profile could be constructed according to the demographic characteristics corresponding to each population subgroup of interest (e.g., children 1-2 years old, 3-5 years old). Then, the multi-day sequential dietary exposure can be drawn from this distribution instead of just 2 data points. It is understood that the consolidated dietary consumption pattern alone would no longer allow identifying an individual. However, individual exposure patterns can still be assessed. When individual profiles are considered as they are here, it becomes clear that prior exposures are important in assessing a one day exposure. Thus, examining individual exposures maintains to be important.

Finally, the hypothesis that diet is uniform throughout the country needs to be tested. As an example, in areas such as region 11, the Texas fruitful rim, as well as some of the other predominantly Hispanic growing areas where the diet for the total U.S. is

based on CSFII, CSFII may not be appropriate for these regions. One approach would be to look at CSFII diets from Region 3 and some other region such as Eastern Uplands or Northern Great Plains, where the demographics are different, and assess whether the diets of young children or adults differs.

The Panel is also concerned that CSFII may under-represent minorities in its sampling. A diet rich in corn, wheat tortillas, and beans is very different from the Atypical@ American diet, yet it may predominate in some areas of the country. It might be possible to address this issue by evaluating census data for those areas and adjusting the diet proportionally based on census characteristics, using the ethnicity data available with CSFII. To the extent that CSFII data are inadequate to represent seasonal, ethnic and regional differences, patterns of food consumption can be constructed to examine potential high end exposures.

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?

The Panel commented on both the nature of PDP data and the limitations of the current DEEM/Calendex to address the issue of linking days of exposure from leftovers and the same batches of foods. PDP data are used in both modes of food exposure analysis using Calendex. In terms of the single day exposure mode, there may be some concern regarding the composite nature of the PDP sample. The residue in a single serving unit could be higher than what is detected from a composite sample consisting of many single serving units. The Agency's PCRA document does not elaborate on how the composite samples may differ from a single serving unit with respect to Index Equivalent Residue ($Residue_{IE}$). In terms of the multiple day rolling average mode, the composite nature of the PDP data is compatible with the repeated exposure scenario. However, the concern of linking days of exposure from leftovers and/or the same batch of food cannot be addressed from the standpoint of PDP data alone.

Calendex incorporates the sample survey data from the CSFII studies to build a cumulative risk assessment that proportionately represents the demographic, physical (weight), and dietary characteristics of the U.S. household population. Ideally, these surveys would provide a longitudinal series of daily diet observations of up to a year in length that would support detailed empirical studies of food consumption patterns over time. Such series would support modeling of dietary variation (day to day and seasonal)

and would provide direct support for modeling some food consumption patterns that must be correlated over short, if not longer, periods of time. These Aideal@ data would also enable modeling of common residues on food lots (e.g., bag of potatoes or apples, gallon of orange juice) that are purchased and then consumed over a period of several days. The CSFII data provide individual diet observations for two nonconsecutive days. As such, these data support single day analyses well.

However, for analyses designed to investigate chronic exposures of individuals over periods of consecutive days, weeks or months, the CSFII data and current Calendex algorithm have clear limitations. The first of these is lack of variability in the diet over time. The current algorithm fixes each individual=s diet to as few as one or two discrete combinations of foods. The major drawback to this fixed diet for the CSFII sample person is that it also fixes the association between the particular diet and the age, gender, and body weight of the individual. While age and gender may be associated with diet, it is probably artificial to preserve the diet and body weight association in a calendar year simulation. The Panel suggests a modification of this approach in which diets for CSFII respondents of the same age range are placed in a pool and daily diets for individuals are randomly chosen from the pool (as opposed to being fixed at their one or two survey reports). The second possible limitation of the current model algorithm is the lack of dietary correlation for some foods across consecutive days (e.g. apples, grapefruit, orange juice). Unfortunately the CSFII data alone does not provide empirical evidence on just how important day to day serial correlation in food item consumption.

There are many ways to fine-tune the model, and it is hard to tell in advance which way is worth pursuing. As a common practice in applying the concept of Atier approach@ to risk assessment, whether to further refine the current model of independent daily draw should be based on its need, with the rationale for the decision-making process clearly presented in the risk assessment document. The sensitivity analysis with foods A, B, and C, discussed in the previous question, was simple and informative. Similar sensitivity analyses could be performed with correlated food consumption and residues over consecutive days. A model with reasonable assumptions about the patterns for major foods items (e.g., juices, fresh fruit, vegetables, peanut butter, jams) would provide an informative simulation exercise based on DEEM/Calendex to introduce serial consumption of two, three, or more days and measure the impact of such patterns on the distribution of MOEs from the cumulative risk assessment. Of course, the simulated multi-day, sequential consumption of a food batch should be coupled with a common draw of the residue concentration for the food item.

SAP Report No. 2002-01

REPORT:
FIFRA Scientific Advisory Panel Meeting, February 5-7, 2002, held at the Sheraton Crystal City Hotel, Arlington, Virginia

A Set of Scientific Issues Being Considered by the Environmental Protection Agency Regarding:

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

SESSION 3: ASSESSMENT OF DRINKING WATER EXPOSURE

Mr. Paul I. Lewis
Designated Federal Official
FIFRA Scientific Advisory Panel
Date: March 19, 2002

Ronald J. Kendall, Ph.D.
FIFRA SAP Session Chair
FIFRA Scientific Advisory Panel
Date: March 19, 2002

Federal Insecticide, Fungicide, and Rodenticide Act
Scientific Advisory Panel Meeting
February 6, 2002

METHODS USED TO CONDUCT A PRELIMINARY CUMULATIVE RISK ASSESSMENT FOR ORGANOPHOSPHATE PESTICIDES
SESSION 3: ASSESSMENT OF DRINKING WATER EXPOSURE

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Oral statements were made by:
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Judith Schreiber, Ph.D., on behalf of the New York State Attorney General
Jennifer Sass, Ph.D. on behalf of the Natural Resources Defense Council

Written statements were received from:
FQPA Implementation Working Group

INTRODUCTION

The Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), Scientific Advisory Panel (SAP) has completed its review of the set of scientific issues being considered by the Agency pertaining to methods used to conduct a preliminary cumulative risk assessment for organophosphate pesticides. Advance notice of the meeting was published in the *Federal Register* on January 15, 2002. The review was conducted in an open Panel meeting held in Arlington, Virginia, on February 6, 2002. The meeting was chaired by Ronald J. Kendall, Ph.D. Mr. Paul Lewis served as the Designated Federal Official. Mr. Kevin Costello (Office of Pesticide Programs, EPA)

and Mr. Nelson Thurman (Office of Pesticide Programs, EPA) provided an assessment of drinking water exposure.

CHARGE

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?

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?

DETAILED RESPONSE TO THE CHARGE

The specific issues to be addressed by the Panel are keyed to the Agency's background documents "Organophosphate Pesticide Preliminary Cumulative Risk Assessment", dated December 3, 2001 and are presented as follows:

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:

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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?

The Panel concluded that the Agency's approach to addressing drinking water was correct and agreed with the Agency's position that OPs from drinking water are likely to be a minor part of total exposure in almost all cases. However, fuller characterization and interpretation of these analyses would increase confidence in the present analysis and set the stage for subsequent cumulative risk assessments of other pesticides. It was suggested that the Agency conduct a sensitivity analysis of their modeled results to better understand the reasons for the variations in exposure and better define the extent of exposure. In the future, more explicit inclusion of transformation products, particularly the oxons, is essential. If exposure via drinking water is potentially greatest for some well defined subpopulations (e.g. young infants bottle-fed formula made from powder and water), such exposures should be characterized. The Agency should also consider the potential effects of spills and non-agricultural OP uses on drinking water. More quantitative assessment of the effect of water treatment processes on the OPs and their transformation products should be included. Finally, the Agency should make better use of the existing monitoring data and continue to collect new

monitoring data for validation of the modeling predictions. An elaboration of the Panel's conclusions are provided below.

The Agency should be commended for its efforts in estimating the exposure of OPs in drinking water given the time and data constraints. They have followed and exceeded the recommendations of previous Panels for modeling the water portion of the cumulative assessment. The efforts have elegantly extended the PRZM modeling tool by incorporating multi-chemical with multi-application scenarios using realistic characteristics for the modeled watershed. Sufficient work may have been completed already that could be used to generate a journal article(s) documenting the performance of PRZM/EXAMS and the Index Reservoir modeling approach.

The Agency presented a conservative approach to estimate pesticide exposures in water. In addition, based on monitoring observations, the Agency correctly suggested that drinking water derived from surface water will yield greater exposures to OPs than drinking water derived from ground water.

The Panel acknowledged that the effort to characterize the contribution of drinking water to overall exposures to OPs is limited by the nature of the field data that are available. The Agency's determination that monitoring data are too sparse and not sufficiently well coupled to use patterns in generating cumulative risk assessments is partially justified. The Panel concluded that more could have been done with the monitoring data than just comparing the maximum values on a regional basis.

While the Panel acknowledged that the current model is a useful tool for first tier assessments, the Agency should consider other tools. Modeling may need to move beyond the surrogate fields and index reservoir approach. A number of investigators have used GIS approaches with existing databases to scale models such as PRZM/EXAMS to large areas. GIS techniques were used to apply the GLEAMS model (similar to PRZM) to all of Indiana (see http://danpatch.ecn.purdue.edu/~napra/ for details). Such approaches could be used in applying PRZM/EXAMS to watersheds throughout the US at the scale of interest.

Monitoring should always be considered an integral part of assessing the drinking water exposure route. It would be good to conduct additional, well-planned monitoring activities to help validate modeling predictions. The Agency might also look into developing a quick and sensitive bioassay that would detect the OPs as a group to be used as a screening tool on a monitoring program.

The spray drift addition to the modeling approach is an excellent addition and seems reasonable. It will likely provide estimates of pesticides in water that are conservative (higher than those likely to occur). The spray drift component however is very small relative to the overall levels of pesticides likely to reach the reservoir. The occurrence of airborne pesticides from agricultural applications should also be included in the inhalation exposure of the cumulative assessment. From the literature of pesticides in rain and air, it is known that there is transport away from agricultural fields and that people are exposed to a low concentration for extended periods of time. This is one

potentially important route of exposure that is currently not included in the cumulative assessment.

While generally conservative, there are a few ways in which the PRZM/EXAMS modeling scenarios could be underestimating the effect of the OP pesticides. First, the extent of the incorporation of transformation products in the water, as an output of the PRZM/EXAMS, is probably not adequate. The transformation products, especially the oxons, could be a very important component of the water assessment. From the literature, it is known that substantial transformation occurs in the field and, thus, the transformation products, including the oxons, are available for transport into and through the surface water system. The current documentation is unclear as to how the OP transformation products are being included in the PRZM/EXAMS model. Also, a better estimation of transformation by oxidants used in drinking water treatment needs to be explicitly addressed. This is a problem not limited to the OPs.

The Agency is correct to bring attention to the potential transformation products of OP pesticides in drinking water. This is especially true of the oxidation products that are produced as a result of the disinfectants routinely used in the treatment of surface waters, and of ground waters under the influence of surface water. This has not been a factor recognized in the development of drinking water standards. Therefore, it is essential that the Agency and registrants begin to address this issue for those compounds whose use patterns are such that they have some probability of impacting water supplies. It is important to recognize that this problem is not peculiar to OP pesticides. Pesticides that have a moiety that can give rise to dimethylamine result in the formation of N-nitroso-N-dimethyamine (NDMA) with the chlorination and especially chloramination of drinking water. Other amine precursors are likely to give rise to other nitrosoamines. The Agency has not yet considered the potential of ozonation, another common disinfection process, to create transformation products. Neither has it considered the effect of sorption process (activated carbon, anthracite) on the removal of the compounds from water. In general, this area of the effect of water treatment processes on the removal of parent compounds and the creation of transformation products needs continued and increased attention with a more quantitative approach.

Second, the PRZM/EXAMS tool only models the non-point runoff processes. A few of the highest concentrations that have been observed in monitoring pesticides in north-western Ohio do not appear to be due to this non-point runoff. They do not occur during storm runoff, and may not occur at times of year when high concentrations are expected. Quite possibly they represent spills or improper disposal practices (intentional dumping of excess pesticides). These are not expected to occur more frequently than once in ten years for any given watershed, but such an event might increase the average concentration in the year of the event by 30% or more. Although spills or improper disposal practices fall outside the regulatory mandate of the Agency, it is important that they be included in a cumulative risk assessment.

Third, the contributions of non-agricultural uses of the OPs are not included in the PRZM/EXAMS modeling for drinking water. This would include outdoor residential uses, public health uses, and indoor uses that reach the sewers (e.g. pet shampoos).

These non-agricultural sources to surface waters have been shown to be important and should be considered in the overall assessment of drinking water.

Fourth, subsurface drainage (i.e., tile drains) is not also considered in the current modeling effort. The subsurface transport and delivery may or may not be significant for the OP pesticides, but it will be important for other pesticides. One method that may be used is to assume that pesticides that leach below the root zone are partially returned to surface water in tiled areas. A quantitative estimate of this can be made by multiplying the concentration of the pesticide in the leach water by the percentage of subsurface drainage in a county/watershed. Subsurface drainage estimates can be obtained from the USDA Census of Agriculture data (only available in older 1970s/1980s Census of Agriculture databases). In addition, irrigation may play an extremely important role in the movement of pesticides for some regions. How well does PRZM capture the influence of irrigation on OP runoff? Additional details on how irrigation was treated by the model should be included.

Fifth, the twelve geographic regions modeled are quite heterogeneous. There are within-region variations that are almost as large as across the nation. Major crops are frequently highly localized within these regions. This may be reflected in uses of particular pesticides that are locally intense rather than being spread across all the arable land in the watershed. The lack of homogeneity can be reflected over relatively small areas. It could be that the choice of modeled areas might not provide concentration estimates that are as conservative as hypothesized. The choice of the Willamette Valley in the Pacific Northwest would be one example.

Sixth, the current approach to modeling drinking water exposures assumes that the most vulnerable watersheds have been identified, that areas of the highest pesticide use will give the greatest concentrations of pesticides in water, and that the model provides reasonable estimates of pesticide movement to water (again points out the importance of a validated model). There are likely other significant assumptions. Many of these assumptions are stated in the Agency's background documents. Such statements of assumptions are useful to the readers of the documents. Further, such explicit statement of assumptions can be helpful in minimizing misuse and misinterpretation of the modeled results. A review of the assumptions stated in the documentation is appropriate in order to insure that the most significant assumptions are documented.

Seventh, the Panel commented that the Agency chose a very vulnerable area of the region but used typical application rates and typical application timing. In order to better show that the model predictions are protective, it would be useful to conduct a sensitivity analysis of the PRZM/EXAMS model. This might include varying the application rate, application timing, K_{oc} values, field dissipation half-lives, and other parameters over the true range that could be expected in the given watershed. The effect of the timing of pesticide application may be particularly important. In reality, not all pesticides are applied on the same day and the date of the maximum application within a watershed can vary greatly from year to year. It is not clear that the current assumption of applications occurring on a single day with the 30-40 years of weather data really provide a "worst" case scenario. It is possible that a distribution of application dates

might result in a "worst" case scenario. The use of longer weather records may be better for identifying "worst" case scenarios with the current assumption of pesticide application on a single day. Also, the weather data used is not always very "local". For example, for the "Heartland" region, the watershed is in Illinois and the weather data used is from Ohio. Could this be improved? Finally, with regard to water consumption, exposure to some sensitive groups may not be adequately addressed. Drinking water provides virtually all the fluid intake of a young infant bottle-fed formula made from powder and water. Exposure to this group requires attention and examination.

It must be pointed out that the current modeling effort lacks realism. There is not a direct connection between the modeling scenarios and surface-water-derived drinking water systems. The assumption was made, based on field observations, that drinking water derived from surface water will yield greater exposure to OPs than drinking water derived from ground water, and thus the results of the PRZM/EXAMS modeling would be protective of all drinking water sources. Considerations that could influence the accuracy of estimates include the fact that reservoirs in much of the country are sited in protected watersheds. As an example, this is found in mountainous regions of the U.S. Even in such circumstances, there are steps usually taken to protect the reservoir. Furthermore, drinking water intakes on rivers or reservoirs are often times placed to minimize the withdrawal of water from vulnerable parts of the river. There are important differences in temporal patterns of concentration in rivers/streams versus reservoirs, and the reservoir model does not do a good job of mimicking the river concentration patterns. Average concentrations in rivers and streams may be somewhat higher because average residence time is smaller. Certainly the day-to-day variability will be higher in rivers. Whether or not this is important depends on the linkage between exposure and effects. If the health effects are determined only by medium to long-term average exposure, then this is not an important difference. But, if the fluctuation of exposure from day to day is important ("acute" exposures), the approach may not be sufficiently realistic for populations that take their drinking water from rivers.

How does the Agency believe the exposure profile provided by PRZM/EXAMS/ Index Reservoir model compares with what would really be present in *the same hypothetical reservoir*? While comparisons are made between model results and maximum observed concentrations, what about the rest of the predicted or potentially observable concentration distribution? Are there aspects of the modeling that might lead to *over predicting* by an order of magnitude the mean concentration, or even the upper percentiles of concentration, such as the delivery of 100% of the edge-of-field runoff to the reservoir, assumptions about timing of application to fields in the watershed, and so forth?

The current document indicates that observed regional OP detections in water exceeded the PRZM/EXAMS and Index Reservoir modeled estimates in some cases. Further investigation of these cases would seem appropriate to determine the likely cause of the differences (e.g. is it due to extreme weather, pesticide spills, urban influences, etc?). Furthermore, it would be useful to compare the complete distribution of concentrations observed in field observations to the predicted concentrations from the PRZM/EXAMS modeling. The NAWQA studies were not designed to meet the

Agency's needs for OPs, but they do provide considerable general information about how factors on the watershed influence contamination of water. If the Agency were able to match these analyses with the temporal pesticide use patterns in this area, it might even serve to validate some of the assumptions at relatively small cost. In other words, there seems to be a possibility of a more robust use of the NAWQA data than is implied on page IE25 in the Agency's background document as the Agency goes forward with the concept of cumulative risk assessments.

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?

The Panel commended the Agency for its extensive work to develop a detailed regional assessment methodology that strives to be conservative and protective, yet realistic in its treatment of regional differences in climate, soils, application of OPs, and mechanisms of movement from the land to the water.

The Panel concluded that the regional assessment would generally be protective of the region as a whole, not just of the reservoir modeled. Exceptions might be found among a few small surface water-based water supplies, particularly in areas of concentrated OP application. Exceptions might also occur at infrequent intervals when a water supply was impacted for a short time by an extreme runoff event, or by events not included in the model, such as spills or intentional dumps of pesticides into watercourses.

For drinking water exposure, the concern may be not what a population is chronically exposed to, but the probability that an unusual exposure might occur. These events are sufficiently rare that they are not subject to regulation, and events such as spills are not likely to be detected in monitoring programs such as those used in the present analysis or especially those mandated for drinking water compliance monitoring. It is unclear how spikes from spills might be detected, unless some mechanism for timely reporting of the spill itself were in place to trigger intensive sampling downstream. The appropriate questions for OPs are whether such events are likely to exceed acute toxicity thresholds, and whether they are of sufficient magnitude and duration to lead to multiday (e.g. 21-day) averages that exceed chronic levels of concern.

Several respondents asked the Agency to provide further information about the relationship between the model results and actual exposures from drinking water in the regions. What can be learned from occurrences of observed concentrations that are under predicted by the model? How often and to what extent does the model over predict concentrations, both average and extreme, for water systems within the assessment region?

Most of the concerns expressed by the Panel addressed details of the modeling approach or ways in which the approach might be insufficiently developed for application to groups of pesticides other than OPs, particularly if the drinking water exposure pathway were more important than it appears to be for the OPs.

Many of the concerns could be addressed by sensitivity analyses. Such an investigation should explore the following issues:

(1) Whether the assumption that all OPs are applied on the same day is conservative.
(2) The importance of spray drift.
(3) The impact of using weather data drawn from a different place in the region than the place chosen for locating the modeled reservoir.
(4) The importance of transformation products (i.e. degradates) to the overall exposure.
(5) The impact of heterogeneity within the region: in climate, soils, land use, and use of OPs.
(6) Whether the model is sufficiently conservative to be protective of all geographic segments of the region.

The Panel raised concerns about applying the current model to other as yet undesignated groups of compounds. These include: (1) insufficient resolution to reflect conditions that are truly local in scale, rather than regional as is the model; (2) correspondence between the model and "reality": Does the model provide exposure profiles that are not sufficiently protective, and if so in what parts of the distribution or under what circumstances? Are the results overly protective, and if so to what degree do they overestimate the distributions of concentrations at sites throughout the region?; (3) the model is not adequate to address groups of compounds for which the major pathway to human exposure is through ground water.

Finally, the Panel recommended that the Agency should develop a better ability to model urban uses of pesticides, subsurface drainage, and irrigation, and expand its capability to model the effects of treatment in the drinking water supply plant.

SAP Report No. 2002-01

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A Set of Scientific Issues Being Considered by the Environmental Protection Agency Regarding:

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

SESSION 4: ASSESSMENT OF RESIDENTIAL/ NON-OCCUPATIONAL EXPOSURE

Ms. Olga Odiott
Designated Federal Official
FIFRA Scientific Advisory Panel
Date: March 19, 2002

Stephen Roberts, Ph.D.
FIFRA SAP Session Chair
FIFRA Scientific Advisory Panel
Date: March 19, 2002

Federal Insecticide, Fungicide, and Rodenticide Act
Scientific Advisory Panel Meeting
February 7, 2002

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SESSION 4: ASSESSMENT OF RESIDENTIAL/NON-OCCUPATIONAL EXPOSURE

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PUBLIC COMMENTERS

Oral statements were made by:
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Written statements were received from:
FQPA Implementation Working Group

INTRODUCTION

The Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), Scientific Advisory Panel (SAP) has completed its review of the set of scientific issues being considered by the Agency pertaining to methods used to conduct a preliminary cumulative risk assessment for organophosphate pesticides. Advance notice of the meeting was published in the *Federal Register* on January 15, 2002. The review was conducted in an open Panel meeting held in Arlington, Virginia, on February 7, 2002. The meeting was chaired by Stephen Roberts, Ph.D. Ms. Olga Odiott served as the Designated Federal Official. Mr. Jeffrey Evans (Office of Pesticide Programs, EPA) provided an assessment of residential and non-occupational exposure.

CHARGE

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 PCRA, 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.

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?

DETAILED RESPONSE TO THE CHARGE

General Comments on the Residential and Non-occupational Exposure Assessment

- The Panel concluded that the PCRA should show all age groups of children for transparency purposes.

- Conditional probabilities (e.g., proportions of the yard that are garden and not garden cannot total more than 100%) and co-occurrence of uses (e.g., of both scenarios and product use within scenarios) need to be dealt with systematically, so that realistic longitudinal use patterns are reflected in the assessment.

- Institutional exposures (i.e., schools, day care centers, etc.) should be explicitly addressed in the document.

- The most important priority for the Agency in the area of residential exposure should be to update the assessment based on the guidance provided by the Panel and to conduct a formal sensitivity analysis of the model to determine the chemicals, routes, and scenarios that determine the greatest exposures under the model.

The specific issues to be addressed by the Panel are keyed to the Agency's background documents "Organophosphate Pesticide Preliminary Cumulative Risk Assessment", dated December 3, 2001, and are presented as follows:

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.

While the Panel endorsed the use of probabilistic techniques for residential exposures, it believes that the widespread use of uniform distributions in the draft cumulative risk assessment distorts the variability and uncertainty in parameters to which it is applied. Even with existing uncertainties and small data sets, it is possible to assign

shapes to distributions using data, decision criteria, and professional judgment, thereby providing more defensible assessments. More formal sensitivity analyses should not be performed until this guidance on appropriate use of uniform and other distributions has been incorporated into the analysis. A more detailed response to the Agency's question is provided below.

Use of Uniform Distributions in Probabilistic Assessments

The Agency staff should be commended for a good initial effort to apply the techniques of distributional analysis to represent the population variability of residential/non-occupational exposures to pesticides. Unfortunately, the choice of the uniform distribution as a default assumption for generic application to limited data sets and summary statistics is often ill-advised.

Past Panels of the SAP recommended the use of the uniform distribution in cases where data were sparse or uncertain. The uniform distribution, which sets a minimum and maximum and assumes each value within that range is equally likely, is the simplest way of representing uncertainty in model input. Its use is appropriate if a range of values that are possible can be identified, and all values seem equally likely. This notwithstanding, the assumption of uniform distribution may seriously distort the character of a cumulative risk assessment because cases where all values are equally likely are relatively rare. Using a uniform distribution means that extreme values may be weighted more heavily than their real contribution would be if the shape of the original distribution were used instead. For example, if the original data had an exponential distribution, those few high values when placed in a uniform distribution might be sampled more frequently in the model.

In the experience of one Panel member who has reviewed many probabilistic risk assessments over the past several years, the uniform distribution is the single most over-used distribution, and nearly always significantly distorts reasonably available information about the variability or uncertainty of the parameters to which it is applied. This 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 is often an impression, as stated in the text paragraph introducing this question, that "it relies on easily established values such as the minimum and maximum…" In fact it is not so easy to appropriately establish true minimum and maximum values from observed ranges of data from limited sets of empirical observations. It is incorrect to assume that the largest and smallest values in a group of 10-30 data points or fewer represents the true minimum and maximum values that the parameter can assume.

Moreover, there are few cases where the mechanisms that cause measurements or estimates of exposure-related parameters to vary among people create situations where there is no greater chance of producing a case near the center of a distribution than at its extreme end (as required for the uniform distribution to be correct). Much more commonly, factors that cause exposure to differ from one individual to another tend to

interact multiplicatively—leading, when these factors are numerous, to expectations of a lognormal distribution. Sometimes, where a categorical factor or two is likely to have a strong influence (e.g., wearing short sleeved shirts versus long sleeved shirts; or short pants vs. long pants influencing dermal exposure from hand spraying on page 14 of section 1D) it is good to create mixtures of lognormal distributions, weighted by their expected frequency, to represent the influence of those different known cases.

The uniform distribution is appropriate in cases where: (1) it is physically impossible for the parameter to take on values outside the limits and (2) there really is no greater likelihood for values close to the center of the range rather than at either end. For example, using a uniform distribution to represent the day of the week that a meteor might land is an appropriate use of the uniform distribution. It is the experience of one Panel member that the uniform distribution is often selected in cases where there can be no solid assurance that the parameter cannot take on values outside the stated range. In attempting to select a defined absolute range, the analyst is very vulnerable to the psychic trap of overconfidence. Overconfidence, the general underestimation of uncertainty and or assigning confidence limits that are too narrow, is one of the best documented phenomena in risk analysis. This applies to both subjective evaluations by experts and non-experts (Tversky and Kahneman, 1974; Alpert and Raiffa, 1982; Lichtenstein and Fischoff, 1977), and to supposedly objective numerical calculations by physicists (Shlyakhter and Kammen, 1992).

Unfortunately, the current PCRA document does not provide a detailed description of the data underlying its various choices of uniform distributions in the text. The Panel provided summary comments on the various specific applications of the uniform distribution described in Section 1D of the Agency's background document "Organophosphate Pesticide Preliminary Cumulative Risk Assessment", dated December 3, 2001:

On page 9 of the PCRA, a journal article by Vinlove and Torla (1995) is cited as reporting average and median lawn sizes as similar at about 13,000 square feet. This does seem rather large. However, at least for the types of housing developments considered, the similarity of means and medians would ordinarily suggest use of a normal distribution. The consideration mentioned in the paragraph—that the stated central estimate neglects such subtractions from lawn size (decks and gardens), which reportedly can take up as much as 50% of the lot not occupied by the lawn, could be represented by a variable multiplier. The effect of other types of housing, such as the townhouses mentioned in the next paragraph, should probably be represented by a distinct mode with its own mean and standard deviation (or log mean and log standard deviation, if a lognormal is chosen). One aspect that should be considered is that larger lawns will often require a longer time of pesticide application (and therefore direct exposure), or the use of more automated methods of application with potentially different characteristics of emissions and resulting transfer efficiencies.

On pages 11 and 13 of the PCRA, fourteen applications of the uniform distribution are mentioned. In general, the ends of the ranges provided differ from one another many fold (e.g. 7-fold for inhalation exposure from a hand pump sprayer; over 1800-fold for

inhalation exposure from a hand garden duster). Such large multiplicative ranges, based presumably on data sets with limited numbers of observations strongly suggest use of lognormal distributions.

One exception to this is the number of treatments per season, which clearly must be represented by a distribution that can take on only discrete integral values. A Poisson distribution is a possible choice in that it can be estimated from only a single piece of information (e.g. the mean number treatments per season per home). A binomial distribution is another possible choice.

A modified Poisson distribution can also be useful for cases where there is a defined upper limit to a process (e.g. the fraction of pesticide in soil on fingers that is removed on inserting a child's fingers into his/her mouth). In this case, the fraction clearly must have an upper limit of 1.

One Panel member suggested a lognormal distribution of transfer rates k among children, and then modeling the fraction of soil particles/molecules transferred as the fraction that receives one or more absorption "hits" defined as:

Fraction Absorbed = 1 – Fraction of molecules with 0 Poisson "hits" = $1 - e^{-k}$

As k goes to large values, this naturally approaches the upper limit of 100% absorption.

Special attention is in order for the last application of uniform distributions mentioned on page 13 of the PCRA—a separate uniform distribution for each of six sample periods for observations of emissions of DDVP from pest strips over 90 days combined with a limited set of air concentration data. This merits more extensive attention because it appears to be an influential mode of OP exposure for higher percentiles of the population distributions in some regions. Rather than a uniform distribution for a series of several periods, it would be better to fit a plausible continuous function modeling the loss of material from the strips over time. Air concentrations should be modeled in part using data on the variability of house sizes and air exchange rates during relevant seasons of the year. Much data of the latter type for houses is available from the literature describing indoor air radon exposures.

In summary, the uniform distribution represents the first step in a continuum that runs from uniform (the simplest case) to well-characterized distributions (normal, log-normal, gamma, etc.) based on well-understood phenomena and/or large unbiased data sets. As the Agency chooses the distributions for various parameters for probabilistic residential exposure assessment, it is important to apply a systematic process to determine or assign distributions to uncertain variables. Choosing the correct distribution requires both a clear set of decision rules and experience in the process of distributed analyses. The following section briefly outlines the Panel's conclusions as the most important issues in this process. Several examples in the following text discuss some of the analytical process the Panel suggests adopting to make decisions on choosing the right distribution.

Assigning Distributions Under Uncertainty

Assigning a distribution to sparse and/or uncertain data requires both decision rules and professional judgment. Some on the Panel concluded that the decision should be largely based on what is suggested by the existing data, even when sparse. Others on the Panel advocated use of judgment and experience with the underlying phenomena for determining the properties, such as shape and central tendency, of the distribution. These are two complementary approaches, and the Panel is united in the view that the uniform distribution is overused in the residential assessment. Thus, judicious application of these two approaches will result in defensible choices for distributions. The following section describes processes that can be used to determine the nature of a distribution from data as well as some guiding principles and examples.

In examining limited data sets to determine their distributional properties, there are statistical tests that can be employed to evaluate the shapes of distributions of small samples and tests for normality. These include the Kolmagorov-Smirnoff test with Lilliefors transformation (also known as the Lilliefors test) and the Shapiro-Wilkes test. These can also test the hypothesis that the distribution is uniform. If a data set fails the test that it is uniform, then the uniform distribution should not be used.

Parametric input distributions from available data can be developed using an iterative process similar to good laboratory practices for animal studies, procedures that insure that studies used to develop distributions: 1) are done in a scientifically defensible manner; and 2) provide data that is statistically defensible. The first point has to do with performing the study using standard scientific methods, such as standard QA/QC protocols that characterize measurement error and variability. For chemical measurements this means appropriate use of method, field, lab, and calibration blanks; development and tracking of calibration curves over time; and repeat analysis of standard reference materials, internal standards and/or spiked samples. Analogous processes for survey instruments, such as questionnaire validation, internal consistency checks, and error checking on data entry are also appropriate. Statistically defensible data is not merely a question of sample size, but of characterizing the important features of the study design that affect the ultimate derivation of data useful for the PCRA. This means using studies that have large enough sample sizes to characterize temporal, spatial, and intra-individual variability. It also means the resulting empirical distribution of data is a good estimator because it is consistent (i.e., as sample size increases, the measure of central tendency in the sample converges on the population measure of central tendency), unbiased, robust (i.e., relatively insensitive to departures from the underlying distribution), and practical (i.e., it balances the above features with the appropriate time and resource constraints) (Morgan and Henrion, 1990).

A 1994 paper in the journal Risk Analysis (Hattis and Burmaster, 1994) 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 result of the combined action of many factors acting multiplicatively indicates that the lognormal form is most often the best choice for exposure-related data where there is limited information. Both normal and lognormal distributions have just two parameters, and are thus no more complex

statistically than a uniform distribution. Derivation of the parameters of lognormal distributions can be done if a simple range is given together with the number of independent observations that gave rise to that range. Means and other measures of dispersion, such as a standard deviation, can also be used to estimate the parameters of lognormal distributions.

Use of Sensitivity Analysis

One of the Panel's principal conclusions is that widespread use of uniform distributions (by one tabulation, they were assumed in 11 of 21 cases cited in the draft PCRA) will distort exposure, especially in the tails of the distribution. As such, the Panel does not recommend performing a formal sensitivity analysis until more work has been done by the Agency to consider the Panel's recommendations in response to this question.

Nonetheless, the Panel believes that a sensitivity analysis is important for examining the outcomes of the modeled exposures and risks, and once the model is reconstituted, a formal sensitivity analysis should be conducted. This analysis should attempt to see how model outputs change after removing either scenarios or active ingredients. This will be a valuable exercise for examining the routes and pathways that drive the analysis and will provide information for the risk characterization section of the assessment that risk managers will no doubt find valuable.

Ultimately what would be most valuable is to develop confidence limits on the final model outputs. This can only be done if variability and uncertainty are explicitly treated as separate entities in a 2 stage probabilistic analysis. The first stage samples the variability distributions (e.g., measurement error), while the second stage samples from the uncertainty distributions (e.g., as a result of small sample size) and provides output that has confidence limits over the entire range of estimated exposures and risks.

One Panel member proposed a more pragmatic approach. Rather than paying too much attention to the justification for a particular statistical distribution, this Panel member proposed different choices to assess the difference each one makes. The Panel assumes that the simulation has been structured in such a way that the choice of distribution could be easily changed. Lognormal, gamma, Weibull, or, for discrete data, negative binomial distributions should be reviewed. Beta distributions will be useful for coefficients restricted to a [0, 1] range. These are standard two-parameter distributions and fitting them by moments (sample mean and variance) will be adequate.

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?

The Panel encourages the use of calender methods for the general population as well as for special circumstances participating in or living in agricultural areas.

A concern with the exposure assessment as it is currently presented is that risks associated with possibly two very significant activities: (1) the consumption of home grown fruits and vegetables and (2) exposure from drift in agricultural applications, are being overlooked. The Panel does not know the size of these populations but this should be characterized. The Agency may feel that these possibly small sub-populations are not appropriate for the current cumulative risk assessment. If so, this should be acknowledged in the document. Such populations need to be evaluated as special cases.

Incorporating NHAPS should be similar to what has already been performed with the dietary data as the techniques used are probably very similar. The problem with NHAPS is that, even though it is a very rich data set, it is a smaller data set than CSFII, particularly when looking at children. There is also the concern of several versions of the questionnaire which differ in the question format and hence the data analysis.

For the NHAPS data set as a whole, there are both regional and seasonal differences in activities. When utilizing the database for assessing childrens' exposure, in order to maintain a reasonable sample size by looking at all children in the country, the important regional and seasonal detail will be lost. There is a similar issue with the CSFII data. Alternatively, if the datasets are broken down by region and season, then limited data points are available.

Another consideration in the use of NHAPS is whether activities are independent. Many activities are clearly not independent either within a day or across days. Activities for such groups as school aged children, children of people who work outside the home and where/when they are done, all of these factors are driven by their occupations or in the case of school aged children, by school.

In the past, the Agency combined different routes of exposure by taking the route specific points of departure and the ratios of exposures by each route. The Agency needs

to address why it does not take the other approach where the multi-routes of exposure are converted to oral equivalents and related to the oral dose data which are more robust. Route conversion is consistent with PBPK modeling.

To elaborate further, the method the Agency has employed for multi-route exposures needs further consideration. The Agency used direct exposure measures for dermal and inhalation and divides these by corresponding points of departure by the same route. As indicated in the document, the dermal and inhalation studies are in general fewer and of a lesser quality than those available on oral exposure. This limits the quantitative consideration of dose response relationships for these exposure routes. An alternate approach is to use the oral data to estimate the POD and then use methods to extrapolate dermal exposures (using measured or estimated dermal absorption rates) and inhalation exposures (using some estimates of breathing rate and absorption) to approximate units of equivalent oral exposures (this approach would be very consistent with the Agency's decision to develop PBPK models for these compounds). Both approaches have limitations but the Agency may wish to consider the alternatives and the document should at least discuss the rationale for selecting one method over the other.

It is important to keep the daily activity within the confine of 24 hours. In addition, it is also important in the exposure modeling to consider the mass balance of the amount of residue available for contact or exposure. Mass balance should be performed by time or location - if a certain portion is taken up, it is no longer available for the next exposure. Finally, care should be taken to ensure that the transferable amount that is taken up through dermal contact is no longer available for uptake at the next time period.

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SAP Report No. 2002-01

REPORT:
FIFRA Scientific Advisory Panel Meeting, February 5-7, 2002, held at the Sheraton Crystal City Hotel, Arlington, Virginia

A Set of Scientific Issues Being Considered by the Environmental Protection Agency Regarding:

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

SESSION 5: RISK CHARACTERIZATION

Ms. Olga Odiott
Designated Federal Official
FIFRA Scientific Advisory Panel
Date: March 19, 2002

Stephen Roberts, Ph.D.
FIFRA SAP Session Chair
FIFRA Scientific Advisory Panel
Date: March 19, 2002

Federal Insecticide, Fungicide, and Rodenticide Act
Scientific Advisory Panel Meeting
February 7, 2002

METHODS USED TO CONDUCT A PRELIMINARY CUMULATIVE RISK ASSESSMENT FOR ORGANOPHOSPHATE PESTICIDES
SESSION 5: RISK CHARACTERIZATION

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PUBLIC COMMENTERS

Oral statements were made by:
Ray McAllister, Ph.D., Crop Life America, on behalf of the FQPA Implementation Working Group
Christine Chaisson, Ph.D., on behalf of The LifeLine Group
Mr. Edward Gray, on behalf of McDermott, Will and Emery
Jennifer Sass, Ph.D., on behalf of the Natural Resources Defense Council
Judith Schreiber, Ph.D., on behalf of the New York State Attorney General

Written statements were received from:
FQPA Implementation Working Group

INTRODUCTION

The Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), Scientific Advisory Panel (SAP) has completed its review of the set of scientific issues being considered by the Agency pertaining to methods used to conduct a preliminary cumulative risk assessment for organophosphate pesticides. Advance notice of the meeting was published in the *Federal Register* on January 15, 2002. The review was conducted in an open Panel meeting held in Arlington, Virginia, on February 7, 2002. The meeting was chaired by Stephen Roberts, Ph.D. Ms. Olga Odiott served as the Designated Federal Official. Mr. David Miller (Office of Pesticide Programs, EPA) and Elizabeth Doyle (Office of Pesticide Programs, EPA) summarized the risk characterization of the preliminary assessment.

CHARGE

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 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.

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.

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.

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?

DETAILED RESPONSE TO THE CHARGE

The specific issues to be addressed by the Panel are keyed to the Agency's background documents "Organophosphate Pesticide Preliminary Cumulative Risk Assessment", dated December 3, 2001 and are presented as follows:

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).**
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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.

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- **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.**

Summary of Panel Position

The Panel noted that there are two issues regarding patterns of exposure on consecutive days: (1) a fundamentally *pharmacokinetic* issue having to do with the persistence of cholinesterase inhibition for some days past the date of exposure, which would lead to inhibition caused by subsequent days' exposures adding on to a background of persistent effects from earlier exposures; and (2) a fundamentally *toxicologic* issue about the health effects that may be caused by short-term *versus* multi-day periods of different extents of cholinesterase inhibition. The two aspects are not clearly distinguished in the PCRA document and they should be considered separately.

Because of the persistence of cholinesterase inhibition for days past the time of an OP exposure, it would generally be inappropriate to evaluate the toxicity of exposures on particular single days without reference to the recent history of exposure on previous days (the exception is when the ongoing pattern of recent exposure is to very low levels that would be expected to produce negligible accumulated effects on cholinesterase inhibition levels when assessing an episodic "spike" of exposure.) Thus, one alternative proposed by the Agency—to examine each day separately in a day-by-day profile of daily exposures, is not recommended. Such a practice would underestimate total cholinesterase inhibition for each day because the lingering effect of inhibition from previous days' exposures would be inappropriately ignored.

Seen in this light, the rolling-average approach is an attempt to address the influence of recent exposures on the effects of each day's exposure. Since that is the goal, the "averaging" procedure should be crafted to reflect the biological process at work, at least approximately. The ideal solution would be to construct a physiologically based pharmacokinetic model for the joint exposure to all the relevant OPs. Such a model could consider any effects of metabolic activation and detoxification, interaction among pesticides in their metabolism and their binding to cholinesterase, and the compound-specific rates of recovery of OP-cholinesterase complexes plus the effect of cholinesterase resynthesis. The result would be a model of joint effects on the varying levels over time of cholinesterase inhibition, as a function of the history of recent exposures to all the compounds in the common mechanism group. Indeed, since cholinesterase inhibition is the basis for the formation of the present common mechanism group, it makes sense to conduct the assessment in terms of cholinesterase inhibition explicitly and directly, as opposed to indirectly by modifying OP doses by relative potencies for their ability to contribute to a total cholinesterase inhibition that is never explicitly calculated. Among the advantages of such a PBPK approach are that the issue of "parallelism" of dose-response for external dose *versus* cholinesterase inhibition would be obviated, the complexities of interactions could be directly and explicitly addressed, and any differences among sexes, ages, adults-*versus*-children, inter-individual variation, and sensitive subpopulations (by virtue of their Pharmacokinetic) could be addressed by

appropriate variations of the model. The disadvantage, however, is that construction of a model accomplishing all this, although within reach of current science, would require a good deal of data, time, and effort. Therefore, the Panel recommends this approach as an eventual goal, but suggests that the Agency seek a simpler way to accommodate the fundamental issue of cholinesterase-inhibition persistence in assessing multi-day sequences of exposure.

As a candidate for such a simplified approach, the Panel felt that the "rolling-average" approach as currently articulated in the PCRA had several major shortcomings. To address the issue of persistence of ChE inhibition from previous days' exposures, an averaging "window" that extends both forward and backward in time from the index day is inappropriate. In addition, the effects of more recent days' exposures should count more than those of more remote exposures, since the persistence of ChE inhibition is something that decays gradually, with ever-smaller persisting effects from exposures in the increasingly remote past. The Panel recommends that, in the assessment of multi-day patterns of exposure, an approach be adopted that addresses these issues, at least in an approximate and provisional way. Indeed, a logical consideration of such effects would seem essential to a valid assessment of OP toxicity *via* cholinesterase inhibition.

The Panel made two suggestions about appropriate simplified methods that could be undertaken in the short term. First, a simplified pharmacokinetic modeling approach could be undertaken that is more empirical and less data-intensive than a full PBPK modeling approach. The Panel noted that such an approach was successfully applied to the dose-response analyses used for determining RPF, in which an empirical, pharmacokinetically-inspired correction was applied to account for the observed "shoulders" in dose-response curves of exposure *versus* steady-state cholinesterase inhibition. The question for this approach would be what data are to serve as the basis for either empirical patterns to be fit with models or for basic physiological parameters such as metabolism, ChE-binding, and ChE recovery rates.

A second method that was proposed by one Panelist is to modify the rolling-average approach by applying an exponentially-weighted running sum. The exponential weighting would be determined by the OP-specific persistence time of ChE inhibition, a factor that could be estimated from either single-dose experiments or from the time to achieve steady-state in continuous constant dosing experiments (such as were evaluated already in the RPF determinations), with the time to steady-state being about 4-5 half-lives. In this approach, exposures of recent past days are weighted according to the fraction of their initial effect on ChE-inhibition that is expected to persist to the present (as calculated according to the half-life for such persistence), and the contributions from the current and past days summed. (This dose measure is readily converted into an estimate of realized day-by-day cholinesterase inhibition by applying the ratio of doses weighted in this way for the steady-state experiments to the steady-state level of ChE inhibition achieved.) Advantages of this approach include its simplicity, its achievability with data the Agency already has in hand, and its direct incorporation of the persistence of inhibition in a compound-specific way. Its disadvantage is that it will get less accurate as an approximation of total ChE inhibition to the degree that actual pharmacokinetic are nonlinear.

Subsequent to this meeting, the Panel member (Lorenz Rhomberg, Ph.D) prepared preliminary calculations for the proposal noted above. While the Panel did not have an opportunity to review the applications of the model, it is being provided to the Agency for illustrative proposes and is presented in Appendix A of this report.

If the Agency does not adopt one of the above Panel suggestions, it will have to arrive at another approach to addressing the day-to-day persistence of cholinesterase inhibition. That is to say, the Panel finds the current PCRA document incomplete owing to its failure explicitly to address the persistence issue. In any approach, whether it be PBPK, simplified PK, or exponentially-weighted running sum, it will be necessary to address the possibility that humans have longer persistence of cholinesterase inhibition from a given dose, and hence a higher level of inhibition from a given mg/kg/day dose rate, than do rats. Such an effect is expected from the generally slower pace of physiologic processes in larger-bodied mammals and from the comparative pharmacokinetic of other compounds. Panelists noted the use of allometric scaling for such an effect, but it is recommended that the Agency attempt to examine empirical data on cholinesterase recovery rates in humans vis-à-vis rats in order to estimate the magnitude of this effect.

In summary, the Panel recommended against the single-day approach (as presented in the Agency's methodology to perform a cumulative risk assessment), in which doses on individual days are examined one-by-one without any effect of previous days' exposures. In cases where single-day exposures occur in isolation (without significant exposures on previous days), comparison of that dose level with a point of departure based on the repeated daily dose to achieve 10% steady-state cholinesterase inhibition would be unduly conservative, since one exposure day will lead to much less inhibition than would be achieved if that daily dose were experienced daily in an ongoing exposure. On the other hand, in cases where a day's exposure is preceded by non-negligible exposures on previous days, its associated cholinesterase inhibition level will be underestimated if one fails to allow for the lingering cholinesterase inhibition from those previous days.

The Panel instead recommended a version of the running-average approach, but further recommended that it should be modified to avoid the shortcomings noted in the comments above. Specifically, the Panel recommended that an approach be chosen that explicitly addresses the persistence of cholinesterase inhibition, in an agent-specific and species-specific way if possible. Such an approach should include only the current and previous days within the averaging window (and not future days), and it should give greater weight to more recent days than to less recent ones, on the grounds that the amount of inhibition persisting from a day's exposure decreases with time.

The running-average approach in the current draft essentially compares the *average* daily dose within the window to the *constant* daily dose that leads to the POD's level of cholinesterase inhibition at steady state (*i.e.*, 10%). In so doing, the excursions to higher than average inhibition within that window are averaged out with days on which inhibition is less. While this approach may make long-term average inhibition comparable, it will miss identifying sequences of daily exposure that lead to excursions

of greater inhibition. The Panel had recommended several alternative analytical approaches to accounting for recent exposures, the common feature of which is that they aim at tracking the day-by-day variation in estimated cholinesterase inhibition, with each day's inhibition being a function of the exposure on that day and (with diminishing influence) exposures on earlier days. The PBPK approach is ideal, but appropriate modifications of a running-average approach (such as the exponentially weighted running sum) could provide an adequate approximation that can be implemented in the short term.

The Panel also noted that the second aspect of multi-day exposures—that of the toxicological effect of longer or shorter periods of cholinesterase inhibition—is part of the evaluation of the potential effects of a day-by-day profile of inhibition (rather than a profile of exposure). The Panel understands that the questions of adequate margins of exposure and the definition of a POD have yet to be fully addressed by the Agency and were not part of the present document. Nonetheless, the Panel urged that such consideration should address several questions, including the level of cholinesterase inhibition expected in subjects of different ages, the health effects of relatively brief peaks of inhibition *versus* prolonged depression of cholinesterase activity, and the adequacy of 10% inhibition as a POD for acute *versus* chronic effects and for developmental neurotoxicity. Addressing these questions will raise the second aspect of averaging across multi-day exposures—the toxicologic as opposed to the pharmacokinetic one—but the averaging issue for toxicological questions should properly be applied to the profile of estimated ChE inhibition rather than to profiles of OP exposure.

The Panel discussed the applicability of RPFs determined from steady-state experiments to the assessment of shorter-term exposures. The issue is important because, when exposures fluctuate daily, they must be treated as a series of short exposures, and steady state will not generally be reached. Some Panelists suggested that a separate set of short-term RPFs should be generated based on short-duration experiments. Others felt that the steady-state RPFs could be applied, and one Panelist asserted that application of the exponentially-weighted running sum process would make the steady-state RPFs applicable to short-term exposures as well, since the reason for differing effects in the short and long term (*i.e.*, the persistence effect) is explicitly corrected for.

In any case, the Panel recommends that the steady-state RPFs be applied for the present, and the issue of short-term relative potency be addressed to the extent feasible given the time frame. The Panel noted that, in discussing application of steady-state RPFs to shorter exposures, a distinction should be made between the issue of using relative amounts of exposure to achieve a given cholinesterase inhibition (determined at steady state in the current method for defining RPFs, a practice of which the Panel is approving, at least for the present) and the related issue of comparing isolated single-day exposure estimates against a POD daily dose determined at steady state, a practice that the Panel does not recommend. An elaboration of the Panel's position is provided below.

Introduction

The central point to this question is how to arrive at an appropriate measure of exposure when presented with longitudinal profiles representing day-by-day variations in consecutive daily exposures to individuals. Such profiles may be generated from direct longitudinal observation, from modeling, or from a combination of these. They intend to capture temporal patterns in exposure, including day-to-day correlations (positive and negative) that may arise from such factors as ongoing exposures to slowly-decaying residential residues, eating of food items from a single source on consecutive days (e.g., leftovers, fruits from a single bulk purchase), and the tendency of some exposures to preclude others in subsequent days (e.g., varying diet by choosing foods not recently consumed, not re-treating recently treated cracks with a residential insecticide). Such patterns of temporal dependence of exposure can, depending on the particulars, lead individuals to be exposed to either greater or lesser amounts over a few consecutive days than would be estimated if each day's exposure were considered to be independent of the ones that preceded it.

Patterns in consecutive-day exposures are important in the case of OP pesticides because the effects of exposures on the levels of cholinesterase inhibition can persist for days to weeks. To some degree, effects of exposures on consecutive days will tend to accumulate, with the total level of cholinesterase inhibition on any given day being a product of not only the current day's exposure but also of persisting inhibition caused by exposures on earlier days, with the amount of inhibition attributable to past exposures diminishing as the time since they occurred becomes increasingly remote.

In the PCRA, toxicity is being treated as a consequence of sufficiently high cholinesterase inhibition. The toxicity of a day's exposure—even its acute toxicity—is in some way a function of that day's exposure as well as of recent past exposures. Moreover, it is of interest to examine not only acute toxicity arising from short-term but severe cholinesterase inhibition, but also the effects that might arise from prolonged periods of lesser degrees of inhibition—effects that would be detected in animal studies with sub-chronic or chronic dosing. The traditional approach to assessing risks for effects of chronic exposure is to average daily exposures over a period of time similar to that in which the effect was observed experimentally. In the present assessment, the POD is provisionally being defined by the daily dose rate leading to an estimated 10% inhibition of cholinesterase in rats over a period of about 21 days, a time at which steady-state has been achieved for most of the agents in the sense that further durations of dosing at the same rate lead to no further increase in the degree of inhibition.

In essence, Risk Characterization Question 1 asks the Panel to recommend, when interpreting a longitudinal daily distribution of exposures, how to deal with the "averaging" aspects inherent in these phenomena. The PCRA does not make a clear distinction between the question of persistence of cholinesterase inhibition and the averaging times appropriate for assessment of acute or more chronic toxicity. The methods proposed by the Agency are either to conduct no averaging (i.e., treating each day's exposure separately), or to apply a "rolling average" in which each day's exposure is replaced with an average of the exposures over a several-day period centered on the

day in question. The Agency asks for advice as to which is appropriate, and if a rolling average is to be used, what time period is appropriate in view of the 21-day duration of the rat experiments against which the exposures are being judged.

Issues Regarding the Reliability and Representativeness of the Profiles

Even a sound analysis of temporal profiles can be misleading if the profiles themselves are poorly determined. The Panel raised several issues regarding assessment of how well the profiles as estimated in practice represent the real temporal patterns of exposure. To some degree, these issues overlap with discussions of temporal patterns and correlations that were raised by the Panel in considering the PCRA's analysis of food, drinking water, and residential/non-occupational exposures.

The Centers for Disease Control (CDC) have recently released a summary of data on metabolic products of some OPs in humans from the NHANES study. These data could be used in this analysis in two ways. First, one could examine how the distribution of OP exposures in the general human population, as estimated by the Agency, compares to that calculated from metabolite data estimates derived from the CDC data. If there are no obvious concerns from this analysis (assuming that one can get the data from the CDC), then the exposure assessment as done by the Agency is supported. Second, using the CDC data to estimate actual human body burdens, comparisons could be made to body burdens seen in animals and their brain CHE inhibition. This would provide an opportunity to check whether there is sufficient protection of public health built into the system. The human clinical data may also help with this analysis.

Understanding the relationship of the temporal characteristics of the hazard endpoint and the temporal characteristics of exposures from the water, diet and residential pathways requires that the temporal characteristics of the exposure pathways be similar. The PCRA document states (section F, page 2) that "regional differences in pesticide use are major considerations in appropriately estimating exposures from pesticides in drinking water and residential uses." This was not the case for the diet model. This is not simply a matter of wanting consistency in the way the assessments are done across the three areas, but that it is important for the quality of the assessment to take into account regional and temporal (i.e. seasonal) differences in diet and pesticide residues on foods. During the presentation on the water model, a figure of California pesticide use across the year was presented. This exemplifies why it is important to evaluate food pesticide residues and diet by region and season of the year. There are growing areas of the country that restrict importation of commodities that they grow themselves, and the diets of the individuals living in these regions will be influenced by the local foods and their residues more than ones from other areas during the time periods that the local crops dominate the available foods.

One Panelist wondered whether seasonality of food exposures is an assumption or an outcome of market basket surveys. Unless it is demonstrated to be absent or minimal, it should be considered, especially if peaks might be synchronous with those in water and in residential exposures.

Several Panel members also expressed concern that pesticide treatment of home gardens is treated only as an influence on residential exposure but not on diet. It is likely that these occur jointly, since the time period of growing and treating the garden vegetables will also be the time that they are consumed. This adds complexities to the exposure model, but consumption of locally grown fruits and vegetables is common and in many regions of the country important seasonal additions to the diet.

One Panelist asked how bias is defined in this question, pointing out that biases are introduced into the analysis when independence of the data is assumed, if such independence is not characteristic of the real world. In addition, use of uniform distributions does not simply create conservative estimates, but distorts the estimates so that the risks may appear greater than they are, depending on the shape of the distribution of the original data.

In summary, the Panel had some concerns regarding how well existing means for estimating longitudinal exposure profiles for individuals represent the actual temporal patterns and day-to-day correlations in exposure levels. Nonetheless, the main thrust of the present question is not about the adequacy of such profiles, but rather about their use in relation to toxicity questions. The balance of the Panel's comments on this question will, therefore, assume that the individual longitudinal profiles of daily exposure are deemed adequate, and will focus on how such results should be analyzed and interpreted. More specifically, the focus is on the appropriate use of a "rolling average" approach.

Issues Regarding Rolling Averages

There are really two issues to be addressed by some kind of averaging process on the temporal profiles: (1) the pharmacokinetic issue of persistence of the agent—or more importantly, of the cholinesterase inhibition it leads to—over several days, and the consequent dependence of day-to-day variation in inhibition levels on recent past exposures; and (2) the toxicity issue of the consequences of a more- or less-prolonged multi-day period of cholinesterase inhibition above a certain level or at a certain average level, and the averaging time that should be used. That is, the question is one of assessing toxicity of a day-to-day pattern of varying levels of cholinesterase inhibition if toxicity is not simply a function of the peak inhibition level. To a large degree, the difficulty that the Agency has with the averaging-time issue stems from a failure to separate these two aspects, trying vainly to find a single rolling-average method to address both. In fact, they are best treated as distinct issues.

The existence of day-to-day variation in exposure levels has always been present in real exposures; it is only because the cumulative risk assessment has explicitly described this variation that the interpretation issue has arisen. Because exposures from several sources and agents (including ongoing, low-level exposures and episodes of higher exposures) are being considered together, there is a fluctuating level of daily exposure, and a spike may occur in the context of a high or low recent history of "background" exposures. Moreover, ongoing exposures may consist of markedly fluctuating histories of daily incremental exposure, not the approximately constant chronic exposure often assumed.

The basic considerations for matching the duration between the exposure and the toxicity components are not unique to cumulative risk assessment. For chemicals that have the potential of repeated exposures for a prolonged period of time, their risks are generally characterized by 3 - 4 exposure durations: the acute, subchronic, chronic, and for a potential human carcinogen, the lifetime. Short of using an elaborate PB/PK model (provided that it is properly conducted and based on reliable data) to account for the dynamics of dosages at the target tissue, a level of inherent uncertainty has always been present in matching the duration of exposure experienced by humans to the toxicity data observed in laboratory animals. This is irrespective of whether the assessment is addressing single chemical single route, or multiple chemical multiple routes of exposure. The multiple chemical risk assessment through summing the exposures only adds complexity to the group of issues regarding matching durations.

In the usual practice, acute human exposures, such as one-day spikes that may occur from occasional short-term events, are assessed against levels causing acute toxic effects in similarly short-term experiments on previously unexposed animals. The implicit assumption is that the ongoing background exposure in humans is low enough compared to the occasional spike that the subjects are essentially similar to the naïve animals, and any persistent effects of earlier exposures are negligible. For single exposures to naïve subjects (barring the influence of nonlinear pharmacokinetic processes), doses or exposures measured in units external to the organism (such as applied dose) are a good surrogate for the peak of internal concentration they will produce, and so a dose-response relationship for effects after different magnitudes of a single dose are appropriate for assessing the potential acute toxicity of episodic exposures in humans. In the case of OPs, however, this situation does not generally happen; the lingering effect of previous exposures may not be negligible, and so each day's exposure considered by itself is a poor surrogate for the degree of peak cholinesterase inhibition it will produce.

Similarly, longer-term ongoing exposures are traditionally considered as approximately constant, and the long-term average exposure rate is compared against chronic toxic effects in similarly long-term, repeated-dose animal experiments. In this case, animal experiments address the ability to tolerate an ongoing, more-or-less constant dose *rate*. With ongoing constant exposures, the daily dose *rate* in external units (such as mg/kg/day) is a surrogate for the internal steady-state concentration, and (again barring the influence of pharmacokinetic nonlinearities) the dose rate is linearly related to the steady state it eventually produces. At this steady state, the constant daily increment in new inhibition is just balanced by the daily amount of recovery from past inhibition. This situation may not be the case for the OPs either; owing to fluctuating day-to-day exposures, steady state may never be reached in humans, and the average daily dose over any period of time may be a poor reflection of the pattern of cholinesterase inhibition over that time. Unlike the constant dose-rate animal studies, where the steady state level of inhibition is gradually approached "from below" (i.e., from lower levels of inhibition), the inconsistent daily increments of varying exposures will have inhibition levels that go over and under a long-term average. A steady state level is also a maximum, but the average of a fluctuating level has the inhibition rising above and falling below the level that a constant exposure of the same average level would induce.

Daily-dose Averaging and Pharmacokinetic

It may be well initially to review the way pharmacokinetic issues play in the assessment of cumulative risk via cholinesterase inhibition.

The issue at hand is one of a common mechanism among a large group of chemicals. It is important to recognize that one cannot deal with toxicities not produced by this mechanism and that all toxicities associated with individual members of this group may not stem from the inhibition of acetylcholinesterase. This is discussed in further detail in a later question. To perform a cumulative risk assessment, it must be clearly stated that only toxicities arising from this mechanism are being considered. Given that clarity, acetylcholinesterase inhibition is the best integrator of both exposure and toxicity.

Thus, the best way to address the problem is a pharmacokinetic/ pharmacodynamic model that can explicitly consider the impact of a dose of any magnitude and with any duration superimposed upon any given background of inhibition. Such a model will capture the distributive and metabolic factors that control the delivery of the active form of the compound to the enzyme active site and the rate at which the inhibition of the enzyme is reversed.

There are two components of the recovery that have to be considered. One is the spontaneous hydrolysis of the phosphate moiety off the enzyme active site, which is a matter of simple chemistry. The second means of recovery is resynthesis of the enzyme. The former rate should be independent of the animal/human in which the inhibition occurs. The second rate will be dependent upon the different biology represented in the compartment of the animal under consideration. These metabolic and enzyme resynthesis rates should reflect those rates seen in humans of differing sexes and developmental stages.

This draws attention back to the RPF as the means of integrating exposures to the different OP compounds into a common metric. While the rate of enzyme synthesis within a given animal should be independent of the compound that is administered, the rate of chemical regeneration of the enzyme will vary depending upon the chemistry of the phosphate bond to the serine hydroxyl group on the enzyme. This difference, as well as differences in the metabolic activation, distribution and clearance of these compounds will be the variables responsible for differences between the acute and steady-state RPF. The major issue for the current approach is the accuracy of the RPFs. These differences would automatically be taken into account with appropriate pharmacokinetic/ pharmacodynamic modeling.

Clearly pharmacokinetic/pharmacodynamic modeling will be the ultimate method to determine how acetylcholinesterase levels are modified with any exposure magnitude and duration and to determine how today's exposure interacts with the pre-existing inhibition remaining from prior doses. It also can solve the problem associated with the sensitivity of different segments of the population (e.g. fetus, newborn, toddlers, etc.).

Many of the issues that arise in the PCRA for OPs are also considered in detail in the draft Guidelines for Carcinogen Risk Assessment. For example, identification of when children are not at greater risk than adults, evaluation of the MOE, and the benefit of inclusion of some mechanistic data without development of a full case-specific model. The Agency is encouraged to work with the authors of the cancer guidelines to ensure a harmonized approach and to ensure that OPP obtains the full benefit of the thinking that has gone into development of the cancer guidelines.

Appropriate models probably do not exist for all 29 compounds, therefore, the current exercise may have to go forward with the RPF approach. Future cumulative risk assessments for OP pesticides should attempt to make use of pharmacokinetic/ pharmacodynamic modeling. In the meantime, simpler approaches are needed that nonetheless address (if only in an interim, approximate way) the key issues.

The key issue to address in any simple approach to the pharmacokinetic aspect of daily-dose averaging is the persistence of cholinesterase inhibition from previous day's exposures, raising the level on top of which the current day's exposure will have its effect. The degree of inhibition achieved on a particular day will be due to all of the current day's exposure, a fraction of the previous day's (reflecting that part of its initial effect that persists one day), a smaller fraction of the exposure from the day before that (reflecting the smaller persistence from two days ago) and so on, until exposures sufficiently far in the past have no lingering effect on the index day's level of inhibition.

Clearly, a straight rolling-average approach is only a gross approximation to this process. First, if the averaging period is centered on the index day, it averages together exposures from past and future days, and only the former can actually contribute to the current burden of inhibition. One improvement, then, would be to make a rolling average that only considered the current day and some number of immediately past days. (One panelist asked for clarification of the "rolling average" or "window" as used for inputs to the model—diet and residues on food in particular—pointing out that this is a simple way to generate autocorrelation in the data at the expense of smoothing out the extreme values. For this purpose, it doesn't really matter whether the current day is at the middle or the end of the window.)

By weighting each day's exposure (in the window) evenly, however, a straight rolling-average approach overweights exposures in the more distant past, for which influence on current cholinesterase inhibition has largely waned. Moreover, it doesn't address the fact that the lingering effects of earlier exposures should add to, rather than average with, more recent exposures in influencing the degree of cholinesterase inhibition expected. A better alternative would be to employ an exponentially weighted running sum that fully counts the present day's exposure, and adds a "discounted" fraction of previous days', with the contribution of days in the more and more distant past falling off exponentially. Ideally, this exponential discounting would reflect the biological attenuation of the effects of earlier exposures, with the parameter of the distribution of weights set to reflect the half-life of cholinesterase inhibition recovery. This half-life could be different for the different OPs, and if it is possible to estimate such OP-specific recovery times, this would be an important aspect to include, since for some

agents only the quite recent past exposures will be relevant, while for others, more distant exposures could still have lingering effects. If the Agency were to consider the issue of combined exposures of OPs (which have long recovery times for cholinesterase inhibition) and carbamates (which typically have much shorter recovery times), the distinction could be important, and adopting such an approach would provide a solution to the problem of "order of exposure," in which the toxicity of a carbamate followed by an OP dose is less than if the order of presentation is reversed.

Estimating the appropriate half-life (or OP-specific half-lives) is a challenge, but the data in hand on recovery times and on time to achieve steady-state with constant daily dosing could be used to arrive at reasonable estimates for the values in rats. Such estimates could be based on the fact that the time to steady-state is dependent on the time to recovery from a single dose, and that the kinetics will be dominated by the component process with the longest half-life, which is likely to be recovery time of inhibited cholinesterase. It should be remembered, however, that the assessment of human exposures should employ human-specific half-lives, and these are expected to be somewhat longer than those in rats, owing to slower clearance processes and (perhaps) slower ability to recover from cholinesterase inhibition. To the degree that human values for recovery times can be determined, they should be used, but if extrapolation from rats is necessary, it will be necessary to consider possible allometric scaling of the pace of the responsible physiological processes.

Even this more elaborate weighting is an approximation of what are likely to be rather complex pharmacokinetic relationships. Clearly, the ideal would be to construct physiologically based pharmacokinetic modeling for the joint exposure to the relevant OPs, in which interactions, induction of metabolism, competitive and noncompetitive inhibition, and other effects can be considered. The Agency has a PBPK model for three OPs that handles simultaneous exposures (Blancato et al, 2000). This model could be used to evaluate (albeit incompletely) the issue of how AchE inhibition varies as a function of OP exposure scenarios (assuming that the PBPK model describes AChE regeneration and resynthesis).

Development of mechanism-based models (and the thinking process that accompanies their development) always encourages consideration of how the model could be refined (as opposed to the more static situation with policy-based approaches to risk assessment). It is thus necessary to draw a line with respect to the technical development of the various models that are feeding in to the cumulative assessment, freeze the models, and complete the assessment. Refinement of the models and better understanding of the biology can then contribute to future assessments.

The Panel recognized that a PBPK approach is unlikely to be realizable in the time-frame that the Agency has available, and that other approaches to address the dosimetry issues will be needed in the short term. Nonetheless, a PBPK approach should be feasible, and it would help answer important questions about interactions and saturable steps in metabolism as recommended with previous SAPs. It is recommended that such an approach be investigated in the longer term.

The Panel commented earlier on the fact that, in estimating dose-response relationships for cholinesterase inhibition in the RPF-identification analysis, the low-dose nonlinearity introduced to model "shoulders" in the curves would have an impact on the applicability of the RPFs to lower doses. This question would be obviated if PBPK models could link different dose levels of multiple agents (and the recent histories of those dose levels) to the time-varying level of cholinesterase inhibition they would produce.

It would also be possible to undertake a simplified PK-modeling approach, along the lines of the empirical correction factor used to describe the shoulder in individual OP dose-response curves. Such a model would be a slight elaboration of the exponentially weighted running sum approach described above. It could allow for more complex pharmacokinetic processes, at the expense of requiring some basis for estimating the necessary parameters.

In an appropriate simple compartmental model, cholinesterase inhibition would tend to "decay" at a rate that can be inferred from (1) a model of the approach to steady state observable in the available animal experiments, and (2) a human/animal adjustment factor to account for the fact that many processes in humans are slower in animals, approximately by a factor related to the human/animal ratio of metabolic rates/body weight, or about (Human Body Weight/Animal Body Weight)$^{1/4}$. This rule also approximates changes among species in relative toxicity for anti-cancer agents per mg/kg dose (Watanabe et al, 1992; Travis and White, 1998). Hattis et al. (2001) has recently updated these calculations based on a new compilation of data developed by Price et al. (2002). It should be noted that Price's analysis is restricted to directly acting agents, i.e., agents that do not require metabolic activation to exert their biological effects. Based on the distribution of departures of these data for various anti-cancer agents, the most recent results give lognormal uncertainties for the departures from the equal toxic potency per mg/(kg Body Weight$^{3/4)}$ rule for projections between various species and humans as shown in the following table:

Table 1. Distributions of human toxic potency relative to animal toxic potency per unit (body weight)$^{.75}$ inferred from the data of Price et al. (2002) for cancer chemotherapy drugs—human projections based on the most sensitive of the species listed for each chemical

Species LD10 or MTD Information Used	Number of Chemicals	Geom. Mean	Arith. Mean	95th %tile	Log(Geom. Std. Dev.)
Mouse (single species)	54	1.222	2.71	7.07	0.464
Rat (single species)	18	0.888	1.45	4.29	0.416
Hamster (single species)	15	1.722	3.37	12.61	0.526
Monkey (single species)	34	1.139	1.87	7.51	0.498
Dog (single species)	56	0.609	2.14	5.45	0.579

In other words, based on the 18 rat/human projections available to us, the geometric mean human potency for toxic effects for these anti-cancer agents was about 0.888 times that predicted on the basis of the mg/(kg Body Weight$^{3/4)}$ projection rule. The Log (Geometric Standard Deviation) characterizing the spread of these observations was 0.416, meaning that the 95th percentile of the distribution was at some 4.29 times the potency predicted from the mg/(kg Body Weight$^{3/4)}$ projection rule.

If the PBPK approach is not taken, and if the simplified pharmacokinetic approaches or allowances for half-life of recovery of cholinesterase activity described above are not employed, the Agency should attempt to arrive at another means to address the persistence-of-effects issues. It is clear that using one-day exposures in isolation is only appropriate when they are very large compared to all the exposures in the previous weeks, in which case the persistent effects of previous inhibition can be neglected.

The Panel had considerable discussion about the issue of applying RPFs determined at steady state to exposures that are of shorter duration. Several Panelists believed that the short-term application was a different setting from steady state and that applying steady-state RPFs to such exposures was questionable and should be regarded as provisional. Other Panelists were more supportive of the applicability of steady-state RPFs to short-term exposure. The issue is important to the rolling-average question because the RPFs will be applied to each day's exposure, not to ongoing constant exposures expected to lead to steady state, and so the relative effect of the daily amounts of different OPs are being judged under non-steady-state, relatively short-term exposure conditions.

One Panelist asserted that the issue could be reconciled by applying the OP-specific corrections for half-life of cholinesterase recovery, as described earlier. The basis for this is that the one-day amount of new inhibition caused by a day's exposure should be the same for a one-day exposure as for a day's increment in an ongoing constant exposure at the same level, whereas differences in the level of inhibition achieved after one day, or after reaching steady state, depend on the rate of recovery from

that new inhibition. Application of the OP-specific correction for this half-life adjusts for this difference and so RPFs determined at steady state continue to apply to short-term exposures.

Thus, the issue of averaging daily doses for pharmacokinetic reasons is that one must somehow allow for the persistence of cholinesterase inhibition beyond the day of exposure, and for the tendency of inhibition to accumulate from exposures on consecutive days. The best way to do this is by constructing a PBPK model, but this is time-consuming and demanding of data. Simple pharmacokinetic models could be proposed as an interim step. A particularly simple approach, and one that should provide much of the benefit of a full description of kinetics, is to apply an exponentially weighted running sum to the daily exposures to express the persistence of the effects of exposures in the recent past. Whatever approach the Agency takes to this issue, it should reflect the possibly longer persistence of cholinesterase inhibition in humans vis-à-vis rats, which would tend to lead to higher inhibition levels for a given rate of daily intake of OPs.

Dose-Averaging and Toxicity

The issue of dose-averaging and toxicity is quite distinct from that of allowing for the persistence of cholinesterase inhibition from day to day. By addressing the persistence issue, the day-by-day profile of varying exposures or OP intakes (combined over various agents and exposure sources) is translated into a single day-by-day profile of the level of cholinesterase inhibition. This profile will rise and fall as a consequence of the particular recent history of exposures. The further question then arises as to what properties of this fluctuating level of inhibition should be related to toxicity.

One alternative is to assume that the issue is peak inhibition and that the toxicity at issue is the acute consequence of attaining a level of inhibition over a critical level, even if that is suffered only briefly. (In practice, because of inhibition persistence and because of the 1-day minimum resolution in timing of exposure events, peaks of very brief duration are unlikely and in any case impossible to estimate.) Under this view, the way to evaluate a temporal profile of varying inhibition is to assess whether any single day's inhibition level approaches levels associated with acute effects. In the present case, 10% inhibition is being considered as the POD, so for each day's estimated inhibition level, one would evaluate the margin of exposure vis-à-vis the 10% benchmark. (This is different from evaluating each day's OP exposures versus a benchmark defined in terms of OP dose, because the daily level of cholinesterase inhibition will depend in part on lingering effects from previous days.)

It is also possible, however, that prolonged periods of inhibition at levels too low to cause immediate acute responses may nonetheless lead to chronic toxicity. In those cases, one must consider how long must inhibition be maintained at what level to lead to such effects. An example along these lines is of herbicide impacts on aquatic ecosystems, where herbicides act to block photosynthesis and are not directly toxic. Once concentrations exceed a certain threshold, photosynthesis is blocked. If blockage is sustained for long enough, the plant dies of "starvation." If concentrations fall below the threshold before starvation, photosynthesis resumes and recovery is rapid, but there is

"lost" productivity, which may or may not be of ecological importance. To characterize such impacts of duration on effect, one must track durations of excursions above the threshold and of recovery periods. One could do probabilistic analysis of frequency and duration of such excursions. But also here the question is, What is the "allowable" frequency and duration?

Perhaps the BMD10, having been based on rat steady-state experiments, could be conceived of as an assertion that 10% inhibition can be tolerated indefinitely without ill effect. The logic would be that rats exposed continuously at a certain daily OP dose leading to just under 10% inhibition at steady state will never exceed 10% inhibition no matter how long the steady-state condition is maintained by ongoing dosing. If continued dosing at this level does not produce chronic toxic effects, even if prolonged, this is evidence that 10% inhibition can be tolerated indefinitely. (It is noteworthy that the time to achieve steady state does not play much role in this argument, and so the basis for matching consideration of the averaging time for assessing a profile to the experiment duration to achieve steady state is not clear.)

Under this view, a profile never reaching 10% inhibition could be thought of as without chronic effects (setting aside the margin of exposure issue for the moment), but this would be a conservative finding, since profiles that exceeded 10% for brief periods (although not reaching levels producing acute toxicity) but otherwise well below 10% might well be without effects as well.

Once the day-by-day profile of cholinesterase inhibition is estimated, one could then examine it for its potential to cause toxicity occurring at various time scales by looking for periods longer than a day over which certain levels of inhibition are maintained (or over which average inhibition is above some critical level). The challenge is that animal experiments provide a meager basis for defining what periods are relevant and do not provide clear information on what to expect from a profile that varies from day to day. Animal experiments that involve repeated dosing for various periods typically are run with a constant daily exposure level, leading to a steady state internal dose level and inhibition level. Since this internal level is constant, it is difficult to ascribe its impacts to the peaks achieved or to the long-term average, since they will be identical.

Fundamentally, this issue is identical to the "Concentration X Time" issue that is a familiar problem in toxicology. One way to approach it would be to take rolling averages with different window-sizes of the temporal profile of estimated cholinesterase inhibition (but not of the profile of daily external doses). The different window-sizes would inform assessment of toxic effects that are risked when cholinesterase is inhibited to some average level for a corresponding period of time.

The Larger Issue of Toxicity Evaluation

The discussions above make it clear that a further discussion of the expected relation of degrees of cholinesterase inhibition (and the durations of periods of such inhibition) on actual toxic responses needs to be explored. The key to considering the

OPs together as a common mechanism group is that at least a large class of their toxic effects are deemed to be a product of cholinesterase inhibition. There may be other toxic effects by other mechanisms or by related but distinct mechanisms, and these will also need to be considered in the full characterization of risks posed by the various OP pesticides, but the cumulative risk focuses on their joint effects on cholinesterase.

In light of the Agency's limited time frame for completing the cumulative risk assessment of the OP pesticides, a viable approach is recommended. This proposal should not be construed as to discourage the Agency from seeking future refinement in this area. The goal of this recommendation is to characterize the risk of acute ("spike") exposure based on acute toxicity data, and repeated exposure based on toxicity data from repeated dosing. Thus, multiple sets of risk evaluation are conducted.

Several Panelists questioned how the level of cholinesterase inhibition that is to be related to effects, especially to possible effects in children and to developmental neurotoxicity in particular. For instance, one Panelist raised the question whether cholinesterase inhibition itself is the issue, or is it just a measurement endpoint used to reflect some other toxic endpoint? If the latter, what are the health effects it reflects? This seems much more subtle and obscure than the case of a carcinogen or a mutagen, for example. In this context, what is recovery? Clarity on these questions is essential to the proper choice of exposure assessment interval. What kind of risk is associated with shorter duration exposures? Are they qualitatively different from longer-term exposures? How high do concentrations need to be to have these effects? Are these acute effects, or chronic effects guaranteed by a short major exposure large enough to provoke an effect sometime later, whether or not there are other exposures?

Given that we are dealing with cholinesterase inhibition and recovery in the adult female rat as the endpoint, it may be valuable to know if there are differences between adults and young (rats or in humans), the degree of inhibition and in the recovery from inhibition from a similar dose (adjusted for body weight). This is further raised in the Panel's response to the next question.

In the near term, the Agency may have to use a less sophisticated approach to dealing with cholinesterase inhibition over time by OPs. The Panel understands from the Agency that the benchmark response (i.e., a 10% inhibition of cholinesterase) potentially applies to effects over a period of time as short as one day. Because of this, the Agency needs to explicitly consider 1-day intake estimates, particularly since modeling to date indicates that daily intake can vary dramatically, both for a single individual and among individuals in a population. The Agency has been unable to create satisfactory BMD10 values for acute (1-day) exposure, in large part because of limitations in the acute OP dose-response data available. Several Panelists recommended that relevant dose-response data for acute OP exposure be obtained. These dose-response data should be derived in a way that contemplates the potential influence of preconditioning of the animals to OPs on acute response. Since it will take time to develop these data, the Agency should use the BMD10 values from 21-day exposures as surrogates for acute BMD10 values on an interim basis. They have, in effect, done this in their current preliminary draft. NOELs from acute studies suggest that an acute BMD10s would

probably not differ substantially from the 21-day, steady-state BMD10. While there was some question as to the validity of this conclusion, the 21-day BMD10s probably represent the best acute BMD10 estimate available at the moment.

Some Panelists felt that the rolling average intakes potentially correspond more closely with the 21-day BMD10 values in that they represent dose and response integrated over similar time frames. This approach would be preferable to 1-day intakes if the benchmark response was a function of average OP concentration over a period of several days. This does not appear to be the case, at least as the benchmark response is currently defined. The Panel discussed the possibility of defining a benchmark response in terms of both magnitude and time. It is reasonable to suspect that adverse effects from cholinesterase inhibition are a function of both the extent of inhibition and its duration. Unfortunately, an understanding of the relationship between these factors and toxicity is insufficient at present to develop a benchmark response metric that includes a time function. As knowledge regarding the connection between cholinesterase inhibition and OP toxicity increases, the Agency is encouraged to revisit the way in which the benchmark dose is expressed.

Most Panelists felt that the current list of RPFs is applicable for calculating the repeated cumulative exposure. Since these RPFs represent the steady state dose-response at and beyond 21 days of exposure, one Panel member believed that it may not be necessary to extend the moving average exposure further. However, the majority of the Panel noted that this is a question of the duration of elevated exposure that would lead to toxic effects and is not necessarily related to the time to achieve steady state inhibition, but that the ability to tolerate a steady state of inhibition for long durations is informative.

For assessing acute exposures, several Panelists felt that a separate set of RPFs would be desirable. The different pharmacokinetic characteristics of OPs are expected to have greater impact on the variation of their acute toxicities. The Functional Observational Battery (FOB) tests are the most uniform set of studies available for evaluating the acute neurotoxicity of OP pesticides. However, due to the design of these studies, care should be taken in interpreting the ChEI data from acute (single dosing) FOB studies for the purpose of establishing the RPF:

1) The time of ChE measurement: The first ChE measurements (plasma and RBC) are usually taken at the time-of-peak effects (TOPE) which varies from chemical to chemical and is not optimized for peak ChE inhibition (ChEI).

2) The choice of endpoint for RPF: While plasma and RBC ChE activities are monitored on the day of dosing, day 7, and day 14, brain ChE activities are usually measured only at the termination of study (day 14).

A pilot study can be carried out to evaluate the feasibility of establishing acute RPF, starting with a few high contributing OPs. Alternatively, the current list of RPF based on steady state dose-response could be used for estimating the cumulative exposure.

One essential feature in risk characterization is in its description. The final cumulative risk assessment should consist of a thorough risk characterization discussion in which the underlying uncertainties and assumptions are clearly presented to facilitate risk communication and for risk management considerations.

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 question asks both for suggestions of additional follow-up information-gathering and analysis efforts and guidance on priorities for such projects. The Panel believes it is wisest to avoid an effort to directly formulate a priority-ordered list pending a basic effort to systematically explore the effects of the various readily assessable uncertainties on the bottom-line results of the current analysis (the current analysis focuses exclusively on variability in exposure and risk, rather than uncertainty, although there has been some assessment of standard statistical uncertainty in some parameters). The broad outlines of such an uncertainty/sensitivity analysis effort will be provided below.

Before starting that description, however, it is best to clarify how the results of such an uncertainty analysis should naturally feed into priority-setting choices. The basic objective is to make the largest possible positively-valued impact with limited available resources. If the goal is reducing uncertainties in a particular outcome parameter, this means attempting to anticipate how much particular information gathering/analysis efforts are likely to reduce the overall uncertainties in the outcome parameter per unit of expenditure of some limiting resource. For this purpose a "limiting resource" is not necessarily only describable in monetary terms, but can include specialized expertise of various kinds that are not readily fungible in the near term. Where specific kinds of resources are not readily fungible, it is best to have separate priority-allocation systems for the various defined resource types (Hattis and Goble, 1994). Over the longer term, different kinds of resources become more fungible.

Thus, priority allocation choices are best informed by data/judgements of two kinds: (1) how much uncertainty is in the current analysis attributable to particular sources, and (2) how much <u>reduction</u> in each type of uncertainly can reasonably be anticipated for feasible research/analysis efforts of various types and sizes. Formal analyses of the sensitivity of the results of the current assessment to changes in various parameter values and other assumptions will clearly yield information about the first consideration; however judgments about the second consideration need to be added.

There is also an important source of concern in proposing any formal analysis of the magnitude of readily assessable uncertainties as an input to priority-setting. That is, some more fundamental sources of uncertainty, which are not readily assessed statistically, are quite likely to be more important than those that lend themselves to

straightforward quantification. Some of the suggestions that the Panel makes below for more fundamental research reflect a judgment that there are promising opportunities for basic research efforts to fill gaps in our current understanding that at the present time must be bridged with potentially inaccurate assumptions. In at least one other case, the potential use of urinary OP metabolite data from NHANES3, the effort is just to take advantage of an opportunity that is rare in risk assessment: to detect any gross anomalies between actual and estimated exposures, if they are present as the result of unsuspected sources of error in the exposure estimation methods.

Approach for Systematic Exploration of the Effects of Readily Assessable Sources of Uncertainty

There are three basic steps in such an analysis:

1. Identify a "bottom line" outcome parameter that captures as well as possible the basic health concern that could be a focus of risk management decision-making. (If more than one "bottom line" parameter is needed to capture different concerns, the final model calculations should be repeated for each of the needed outputs.) For example, one might choose the 99th percentile of the MOE for the most sensitive age group in a representative geographic region as the focus of analysis. The restriction of the uncertainty analysis to one or a small number of outcome parameters and a single region is meant to reduce the computational requirements for multiple runs of the model, and the cognitive burden to effectively grapple with what are likely to be broadly similar results for different regions.

2. For parameters that are the result of statistical model outputs or other statistical analyses (e.g., the relative potency factors; central estimates of exposure related parameters, and estimates of variability of exposure-related parameters such as geometric standard deviations), estimate the standard errors of the estimates. A standard error is analogous to a standard deviation, but applied to the mean or some other group statistic such as one describing the interindividual variability. If the distribution describing variability is lognormal, then the standard error of the mean log value should be computed from the log transformed values. The uncertainty in the standard deviation of the logarithms (representing the variability among individual values for a lognormal distribution) should similarly be expressed in log terms. In some cases bootstrap simulation methods may be helpful in estimating the uncertainties in particular statistics where inferences about, for example, the extent of interindividual variability in particular exposures have been made from limited summary statistics in published papers rather than the full underlying data sets of individual values.

For other parameters, subjectively assess values that the analyst believes have about an 80% or an 85% chance to be higher than the true value (in contrast to an estimate which is just as likely to be higher or lower than the true value, which should be the baseline value used in the main analysis). By "higher", what is meant here is different from the median estimate in the direction that is expected to increase the risk indicated by the outcome parameter (e.g. lower MOEs). Some parameters will need to be lowered in their values to correspond to the direction producing an increase in risk. A

subjective 80-85% level (approximately 4/5 or 5/6 chances) is preferable for subjective estimation because of the notorious unintentional biases toward underestimation of uncertainties when both lay people and experts attempt to assign more extreme limits to parameters, such as 1%-99% ranges (Tversky and Kahneman, 1974; Alpert and Raiffa, 1982; Lichstenstein and Fischoff, 1977). To help promote consistency in estimates of uncertainties across many different subject areas, it would be helpful for a small team (1-3 people) to be responsible for arriving at the final estimates with the assistance of experts who performed the primary analyses of available information.

3. One by one, substitute input values for the analysis altered by amounts thought to correspond to about one standard error in the direction that produces larger risks (or lower MOEs). Summarize and compare the relative sensitivity of the changes in the bottom line parameter(s) to the comparable standard error changes in the various input values.

Other Suggestions for Information-Gathering/Model Evaluation Efforts

The following recommendations address sections of the Agency's background document. In addition, a "Risk Assessment Methodology" category is presented first because it contains some of the most fundamental and potentially significant issues.

Risk Assessment Methodology

The Agency acknowledges the need to take into account all potential toxicity endpoints for determining individual chemical risk. However, the cumulative risk assessment is based upon one identified mechanism alone. The contribution of any one pesticide may not be associated, via it's effects, on only one mechanism and toxicity. Other mechanisms should be taken into consideration during the process of selecting chemicals to be included or excluded in a cumulative risk assessment. Thus, one practical limitation of a cumulative risk assessment is that it cannot encompass all the potential hazards associated with a group of pesticides. While the Agency stated this position at the meeting, it should also be made clear in the PCRA. The Panel concluded that the practical approach taken by the Agency given the current biological data on these chemicals is sound and should proceed.

Taking into consideration the materials provided to the Panel, one particularly promising area for further exploration is to compare the modeled distribution of exposures to sets of pesticides that yield a common urinary metabolite to the distribution of daily exposures that can be inferred from the urinary metabolite data from the nationally representative NHANES3 data. This is included in the EPA staff list of projects and is enthusiastically endorsed by the Panel. One Panel member added that an identification of the metabolite is needed.

The Panel also believes that it is important to pursue the issue of multi-day modeling and the actual build-up of cholinesterase inhibition over time, in the face of reversal/regeneration rates in humans. This is described in more detail in the response to an earlier question above.

An important issue for longer term basic research is the validation of relative potency measures for various effect endpoints (behavioral, respiratory inhibition, etc.) vs. brain, red blood cell and plasma cholinesterase inhibition in experimental animal species. Also, there needs to be some further exploration of the protectiveness of the chronic rat brain cholinesterase ED10 relative to doses at which toxic and neurodevelopmental effects can be observed following fetal and neonatal exposures over various durations. Comparisons should be made particularly between adult steady state rat ED10 doses and the dose rates that might be observed to give rise to neurodevelopmental effects on relatively short term dosing schedules in very young experimental animals (with parallel observations on ED10's for brain cholinesterase inhibition for those short term dosing schedules in young animals).

In the near term, efforts should be made to mine and analyze the available data to assess the degree of uncertainty in the general assumption that RPF derived from chronic rat brain ED10s are the same as RPF that would be derived: (A) from acute cholinesterase inhibition and toxicity experiments in adult rats; and (B) from cholinesterase inhibition, toxicity, and neurodevelopmental effects observable following exposure in the fetal and neonatal periods. The Panel raised this issue since the Agency's background document reviewed the case of malathion, suggesting differential toxicity between early life and adult exposures relative to that expected for other OPs.

There should also be some effort to utilize available human data to develop distributions of human peripheral (red cell and plasma) cholinesterase inhibition reversal rates. Such analyses are likely to be possible from observations of OP exposed workers following the end of an exposure or growing season or from the limited studies that may be available from human exposure studies (e.g. aldicarb). An example of such research is by Moeller and Rider (1962).

Estimating Risk in Children

The Panel highly recommended that the PCRA for OPs be expanded to provide an evaluation to other susceptible subpopulations, specifically infants, children and the elderly. The Panel strongly maintained the position that a cumulative risk assessment of OPs cannot be complete without such an evaluation. In the current document, risk is characterized as the margin of exposure that is determined by both the POD and the level of exposure. While exposure sections of the current document clearly indicate that children between the ages of 1-5 years are more heavily exposed to OPs than adults, the POD was not derived from studies in animals of comparable developmental periods but rather from studies in adult female rats. The adult POD was applied to children in both the 1-2 year and 3-5 year old age groups (Fig. 1.G-3a and 1.G-3b on pages I.G. 29-30). For compounds that appear to be more (or less) toxic to young animals, this would not be appropriate. A more relevant approach would be to match the population used in the dose-response assessment to the population used in the exposure assessment- i.e., separate exposure and dose-response assessments to be conducted based on comparable ages.

For the OPs, this is a quantitatively significant issue. Under the Food Quality Protection Act (FQPA), an additional uncertainty factor for children is required unless the available data indicate that children are not more sensitive to the chemical than members of the general population (U.S. EPA, 1998). This is intended to address the concern that children may be and often are more sensitive than adults to pesticide exposure. This is the default approach to be taken in the absence of data. However for many OPs, specific data are available and should be used quantitatively in the cumulative risk assessment. Data in the open peer reviewed literature suggest that differences in sensitivity between young and adult animals exist and can vary among the different OPs (Brodeur and DuBois, 1967; Mendoza, 1976; Mandoza and Shields, 1977; National Research Council, 1993). In the absence of a uniform differential susceptibility to OPs in the young, relative potency factors for each OP should be computed and used to convert total exposure to each pesticide to the equivalent total exposure to the reference chemical. Without data to estimate relative potency in children, a default approach could be used based on the available potency estimate for adults until better data are available.

Risk to the Elderly Population

The Panel expressed concern that while children are being considered as a susceptible population warranting additional measures to ensure appropriate protection, the elderly are a large susceptible population that are not considered in a similar fashion. The assumption that the efforts to protect one susceptible population will be inclusive of others requires a scientific basis, as this may not be an appropriate approach. For the central and peripheral nervous system, the basis for susceptibility is different between the age groups, as it is for the immune and respiratory systems.

Hazard Assessment

The Panel encourages the Agency to develop and apply full PBPK/PD models to the cholinesterase inhibition effects of different OPs. In the long term, from a mechanistic and biological perspective in thinking about pharmacokinetic and pharmacodynamic processes, the use of RPFs is undesirable. RPFs are at best an approximation to the actual pharmacokinetic and pharmacodynamic behavior of the overall mixture of OPs to which people are exposed. The long term science-based solution to this problem is to use PBPK models for the individual organophosphates and to include appropriate interaction terms so that the individual models could be combined. This idea would obviate the need for RPFs as the pharmacokinetic, AChE inhibition, and recovery kinetics for the individual components of the mixture would be directly and explicitly assessed without modification.

One Panel member suggested that some effort be devoted to developing or using an in vitro model for measuring the relative potency of OPs using cholinesterase inhibition as the end point. A family of such systems might be helpful in detecting possible interspecies or inter-tissue differences in relative potencies for specific sets of OPs.

Combining Studies

In the cumulative risk assessment process, the Agency combines all toxicity studies classified as "acceptable" to determine RPFs for each OP. Currently, the data sets undergo one level of review for adequacy prior to determining relative potency. In any exclusion of data, the Panel suggested that the Agency should not rely on formal statistical tests such as "goodness-of-fit tests" to decide which studies met such criteria. Rather, judgement needs to be based on the scientific quality of the study with consideration that all available data provides the Agency with some level of information.

Interactions

The Agency's background document discusses the potential for toxicologic interactions in section I.B, pp. 56-57. This discussion has slowly expanded and improved with successive versions of the risk analysis document. The conclusion in the present draft, that low dose interactions are implausible, is necessarily true. If, however, the final risk characterization suggests that some exposures may be in or approach the range of concern, then interactions may be plausible that differ from those expected from simple dose additivity.

While this need not be a major focus of revisions to the current document, given other more pressing issues that the Agency needs to address, the document should cite in this section the recently issued Agency guidelines on the conduct of mixtures risk assessment and clarify the extent to which the current approach is consistent with these guidelines. As time and resources permit, the Agency may wish to consider at least an abbreviated weight-of-evidence assessment for toxicant interactions for those OPs that commonly co-occur in relatively high potency-weighted doses.

Food Exposure Assessment

The Agency needs at least some longitudinal data sets for major modes of continuing exposure, e.g. diet. Preferably, there should be some periods of a few weeks of continuous measurement for the same individuals for a few periods during a single calendar year (perhaps one per season). This should be done for a modest number of people (perhaps 100 if possible) but it is probably not necessary to do it for thousands to develop good estimates of within- and between-season autocorrelation of dietary exposures over longer periods of time (from successive days, to weeks and up to a year).

Drinking Water Exposure Assessment

The current assessment includes an assumption that applications occur as pulses across the entire watershed on a given date. For the final analysis, it would be advantageous to explore how this assumption affects the results. Clearly a coordinated application date would lead the bulk of inputs to the Index Reservoir to occur over a short period of time, but this may not lead to the highest exposures, because a single application date may allow all OPs to be applied long before the rainfall event that moves them to the reservoir, and substantial degradation may occur in the intervening time.

Distributing applications over time makes it more likely that some applications would occur shortly before the first rainfall event, whenever it occurs.

The Agency should do some sensitivity analysis using various assumptions about the heterogeneity of land use, compound use and climatology within regions, especially at a relatively small basin scale. The concern here is that there might be bad-case situations where some basins will not be protected by the conservatism built in to the Index Reservoir model.

To enhance the database for estimating drinking water exposures to OPs, it would be very desirable to develop a rapid, inexpensive and technically easy method for detecting total OPs in "finished" drinking water. The set of positive samples could then be used to select samples for more detailed chemical analysis. Additionally, this kind of tool would facilitate long term detailed monitoring to assess the accuracy of the modeling results. If this can be accomplished, then the method should be developed further for possible use in other media.

The Agency should make a systematic effort to determine the extent to which pesticides are converted to active forms in the treatment of drinking water. This should be done as a requirement for registration following an Agency funded preliminary investigation to explore those conditions most likely to result in activation. The problem is that there are a variety of oxidative processes used in water treatment ranging from the relatively mild oxidative conditions that would be experienced with chloramines as the primary disinfectant, to chlorine, chlorine dioxide, and ozone. In addition to the disinfectants, consideration should also be given to the common use of other oxidants such as hydrogen peroxide and potassium permanganate in water treatment. These studies should recognize that the wide variation in pH found in different drinking water systems may affect the process of activation/deactivation of the pesticides as well.

Finally, there is a need to develop the capability to model drinking water exposures that occur as the result of OP contamination in rivers and streams. These flowing water bodies have lower dilution capabilities and more rapid flows, leading to higher short term peaks of contaminant levels that may occasionally be of toxicological concern.

Residential Exposure Assessment

The Panel had several suggestions for modest expansions to the analysis. First, the Agency should consider adding inhalation exposures to volatile active ingredients to the lawn scenario, particularly for children. There should also be some assessment of school/day-care exposures to pesticides. Finally, the Panel would also like to see a serious effort to assess exposures to OPs in food that becomes contaminated in the course of the same events that lead to the home gardening exposures.

Other issues requiring consideration

While the Agency reiterated their commitment to the inclusion of young children in their final risk assessment, the Panel considered this a significant concern requiring additional review. There are sufficient issues with regard to collection and use of data from developmental studies that the Panel recommended such topics be considered for scientific independent peer review. Such issues include but are not limited to:

(1) The limited number of data sets for evaluation of developmental neurotoxicity of OPs.

(2) The need to use all available information including data in the peer-reviewed literature.

(3) The need to obtain experimental data regarding the influence of background cholinesterase inhibition on the response to episodic peak exposures.

(4) The use of the identified adult common mechanism and cholinesterase inhibition to assess toxicity in the young. There is also a need to consider other mechanisms of toxicity. Several questions were raised with respect to differential toxicity in young animals:

(a) Are RPFs the same in young and old for each chemical or do they differ significantly for certain chemicals?
(b) Should the POD be significantly different in the young animal?
(c) Are there experimental data to support the assumption that the characteristics and inhibition of cholinesterase activity are similar in the developing organism and the adult?
(d) Has it been demonstrated that cholinesterase inhibition as a marker of neurotoxicity is equivalent in the young and the adult?

(5) In view of the differences in route of exposure for developmental and adult studies, can accurate estimates of potency factors be performed?

(6) Could the relative susceptibility of different OPs in the developing organism be different than in the adult?

(7) Can we accurately assess the differential susceptibility of young and adult animals given the differences in the standardized test batteries and the endpoints examined?

(8) Should the performance of the EPA Developmental Neurotoxicity Test Battery be evaluated and compared with the standard test battery used with adult animals?

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Appendix A. Modification of Rolling-Average Approach Through Application of Exponentially-Weighted Running Sum

As noted in the report, subsequent to the meeting, one Panel member (Lorenz Rhomberg, Ph.D) proposed a modified rolling average model through application of an exponentially-weighted running sum. Such an approach would take into account the OP-specific persistence time of cholinesterase inhibition, an important consideration raised by the Panel in the report. While the Panel did not have the opportunity to review the proposed model, the model is being presented to the Agency for illustrative purposes and for their future consideration. The operations of the model are provided below and are available on the SAP web site:

http://www.epa.gov/scipoly/sap/index.htm

The calculations of the exponentially-weighted running sum method itself are simple. They hinge on defining, for each OP, the agent-specific "limiting half-life," that is, the time it takes to recover half of the inhibition of cholinesterase caused by a day's exposure. This is a measure of the persistence effect, and the essence of the method is that this persistence is reasonably treated as an exponential decay of impact on ChE inhibition. For a given OP, once the limiting half-life is estimated, the steps in applying the exponentially-weighted running sum are as follows:

Let D_x be the dose of the OP on day x of a profile of daily exposures, with x = 1, 2, 3, … representing the sequential days in the exposure profile. Then

(1) turn the limiting half-life (expressed in hours) into a rate constant by calculating

$$k = \ln 2 / t_{1/2}$$

(2) calculate the factor F as

$$F = \exp(-k*24)$$

(3) For each day x in an exposure profile of daily doses, calculate the "persisting dose" (PD) as

$$PD_x = \text{sum} (D_{x-i}*F^i)$$

where i is the number of days in the past, taking the values 0, 1, 2, 3, …, n. That is, i=0 for today, i=1 for yesterday, i=2 for the day before yesterday, *etc*. The largest value of i should be set so that about 5 times the $t_{1/2}$ is covered.

(4) Calculate J, the OP-specific relation between PD and the degree of ChE inhibition by using the ED10 as follows:

$$J = 10\% / [\ ED10*(1/1-F)\ ]$$

(5) Calculate, for each day x in the profile, the estimated ChE inhibition I_x on that day as

$$I_x = PD_x * J$$

(6) Do steps 1-5 for each OP. Then add the I_x values for the inhibition attributable to each agent to get the total inhibition TI_x estimated for each day x.

$$TI_x = \text{sum over agents } (I_x)$$

These values constitute a daily profile of estimated ChE inhibition that results from the exposure profile to the set of OPs.

Most of the spreadsheet is devoted to demonstrating the idea that a limiting half-life can be defined and to showing that the estimated ChE inhibition from the above calculations closely mimics the calculations one would get from a more fully developed pharmacokinetic model. Thus, in the spreadsheet, a more complex model is made and used simply to provide a "target" for the above simple method to try to mimic.

Under the heading "Model", a pharmacokinetic model is presented for an OP that is eliminated from the body with a certain half-life and that reacts with cholinesterase at a certain rate, dependent on its concentration and on the amount of un-inhibited cholinesterase present. The inhibited cholinesterase recovers at a certain rate that is OP-specific and that has a rate of recovery proportional to the amount of inhibition at any moment. Recovery is not specified as to whether there is resynthesis of new ChE or repair of inhibited molecules--it is assumed that it all goes into one rate. (A more complex model could be created, but the model is only used in the spreadsheet to illustrate principles and to provide a "target" for the simplified exponentially-weighted running sum method to try to predict.)

Under the heading "Variations," the parameters of the model are changed to examine their effects on both the steady-state level of cholinesterase inhibition and on the peak level after a 1-day isolated exposure. A dose rate of 10% steady-state ChE inhibition is selected (where steady-state is assumed to be achieved after 960 hours, the of time for operations of the model).

AVariations@ illustrate the effects of different model parameters on the inhibition, or rather the effect of the parameters on the dose needed to give 10% steady-state inhibition. For each case, the model is run with the same dose and parameters, but for one isolated day. This demonstrates the amount of peak inhibition that would be achieved after a 24-hour exposure to a naive subject if given the dose rate for only one day. If that dose rate were to be continued indefinitely, this would lead to 10% steady-state inhibition. For many cases, the peak inhibition after one day is less than 10% (i.e. a one-day exposure at the daily dose rate that results in 10% steady-state inhibition and leads to less inhibition after a single day of exposure).

The point of AVariations@ is to illustrate that the ruling factor is the "limiting half life," which is the longer of the half-life for elimination and the half-life for ChE

recovery. In practice, the cholinesterase recovery is probably the true limiting factor. The case also illustrates that the time to achieve steady-state inhibition (which can be seen on the right-hand graph of ChE levels over time) is about 4-5 times the "limiting half life", regardless of whether that limit is in OP elimination or in ChE recovery. This can be seen by changing the half-life parameters and observing the impact on the graph.

Under the documentation of the parameter variation is a set of statements that discusses the application to the problem of assessing profiles, assessing the difference between steady-state and one-day inhibition at a given dose rate. The key here is whether the proportionality between these two changes with changes in parameters. For two different OPs (each with its own parameters), the dose rate to get 10% steady-state inhibition will be different (hence the basis for the relative potency factors, RPFs). But for a wide range of circumstances of different parameter values, the steady-state and one-day inhibitions stay in proportion to one another. That is, with different OPs (with different parameters) the relative ability to cause steady-state inhibition is proportional to the relative ability to cause one-day inhibition. This scenario would not be applicable when the limiting half-life is shorter than a couple of days, which is not likely for OPs.

Nonetheless, the inhibition caused after a day's exposure is less than would result at steady-state. The lowest part of the AVariations@ sheet illustrates how to apply the calculation of "persisting dose" (PD). This is considered the exponentially weighted running sum as referenced in the Panel=s report. The basis of the steps 1-3 above is laid out in this section of the spreadsheet. The calculation can be applied to exposures that are neither isolated one-day events nor constant for an indefinite run of days. Thus, it can be calculated for each day in the profile of an individual's day-to-day changing exposure. Since it depends on the limiting half-life, if the different OPs have different such half-lives, one should use the OP-specific values.

The next step results in calculating the amount of inhibition expected on each day from that day's PD values. For each OP, one calculates the PD times the ratio of the steady-state inhibition to the PD for the steady state experiment (steps 4 and 5 above). Then one sums the inhibitions caused by each OP on that day to get the day's total ChE inhibition (step 6).

To illustrate how all this works in practice, the model is further applied by comparing (for a single OP) the full pharmacokinetic model's prediction of varying ChE levels after a series of days with varying daily exposure, and comparing this to the approximate estimate that arises from the exponentially-weighted running sum approach. For two cases, "Peak in Low" and "Peak in High," each on their own sheet, the approximation is shown to be very good in that the estimates from the exponentially-weighted running sum method very closely mimic the calculation of ChE inhibition coming from the full model. (Peak in Low and Peak in High refer to a peak of exposure amid a low background and a higher background of other exposures, respectively.) The slight deviation in "Peak in High" is due to the fact that the peak inhibition is well over 10%. The level of inhibition is the sole nonlinear factor in the model (because it depends both on the OP concentration and on the amount of uninhibited ChE still left), and so the approximation starts to deviate as one gets ChE-inhibition levels over 10%. However,

this is unlikely to be a significant limitation in the real analysis, since such levels are not usually reached.

Finally, the sheet called "Year" shows a hypothetical year-long profile for two imaginary OPs, "Thisifos" and "Thatathion." The first has slower ChE recovery than the second, which has an effect on how the PD rises and falls after a period of high exposure compared to the background level.

The application of the model shows the relations between steady state, one-day isolated exposures and time-varying profiles. It also illustrates that the RPFs calculated based on steady-state conditions can be applied to shorter-term exposures, as long as the effects of the limiting half-life (which are easily calculated) can be considered. In addition, the RPFs apply equally well to exposure profiles where the exposure is a series of different, short exposures following one another so closely that they cannot be considered as isolated days, owing to the persisting effects on ChE inhibition of previous days.

The proposed model is an attempt at turning a profile of changing daily exposures to a series of OPs, each with different propensity to inhibit ChE and with its own kinetics, into a daily profile of the changing levels of ChE inhibition that results. This is a separable step from considering the toxicity, and indeed, it is necessary to investigate the ChE inhibition effects in order to be able to address the toxicological question of what toxic effects one expects after peaks and/or prolonged times with different levels of inhibition.