SAB Consultation on "Enhancing EPA's Risk Assessment Practices"
September 6, 2006

EPA has asked for a second consultation with the SAB to discuss its more recent activities since publication and presentation to the SAB in 2004 of the Staff Paper on Risk Assessment Principles and Practices. This is intended to be part of EPA's continuing dialogue on topics in this area.

The purposes of this consultation are:

1. to briefly review the Agency's key communication activities since publication of the staff paper, and the input EPA has received;
2. to bring the SAB up to date on some current EPA research efforts related to human health risk assessment;
3. to describe specific projects in three Offices to illustrate progress in EPA practices;
4. to outline a few ideas and thoughts about the Agency's future directions; and
5. to provide the public with another opportunity for comment in a Federal Advisory Committee Act (FACA) setting.

1. Brief Review of the History of the Staff Paper, key follow-up activities, and comments

A. History of the Project

In early 2003, the Office of Management and Budget (OMB) asked for comments[1] on Federal Agencies' risk assessment practices. The comments that they received were forwarded to EPA for consideration, and in response, EPA formed a Risk Assessment Task Force. This group reviewed the comments and developed a staff paper to provide a written "snapshot" that described how EPA conducted risk assessment. In March, 2004 EPA published this staff paper entitled, "An Examination of EPA Risk Assessment Principles and Practices" (www.epa.gov/osa/ratf.htm). Chapters of the document addressed a number of themes related to major comment areas: conservatism; uncertainty, and variability, including sensitive populations and lifestages; use of default and extrapolation assumptions; site and chemical specific assessments; and ecological assessments. While not an official policy statement, the paper presented the perspectives of EPA risk assessors on their understanding of how risk assessments were being conducted in EPA. It also presented a number of staff recommendations for strengthening and improving EPA practices with respect to a number of issues. These recommendations included:

development of more chemical specific data to replace default assumptions;
development of more data to support and refine default assumptions;

[1] On February 3, 2003 (68 FR 22, pp. 5492-5527) OMB requested public comment on "ways in which 'precaution' is embedded in current risk assessment procedures through 'conservative' assumptions in the estimation of risk" and "Examples of approaches in human and ecological risk assessment…which appear unbalanced."

better communication of data, assumptions, and defaults EPA use, including how EPA deal with uncertainty;

exploring the feasibility of using probabilistic analysis in all phases of risk assessment; and

the need to continue to develop and apply approaches to address cumulative risk.

B. Outreach Efforts

Since publication of the Staff Paper, EPA has engaged in a variety of activities to foster dialogue about EPA Risk Assessment principles and practices. These include:

Meetings with members of the broad environmental community

- American Chemistry Council and Croplife America (4/27/04);
- National Academy of Sciences (NAS) Board on Environmental Studies (6/4/04);
- Natural Resources Defense Council (7/7/04); and
- EPA's Science Advisory Board (7/26/04) Shortcut to sab_com_05_001.pdf.lnk

Presentations to EPA groups

- ORD's Board of Scientific Counselors (BOSC) Workshop Feb 2-3, 2005 www.epa.gov/osp/bosc/ra_work.htm and Henderson et. al. (2005)
- Regional risk assessors (5/7/04);
- Science Policy Council Steering Committee (7/22/04);
- An Air Toxics Symposium (8/6/04); and
- EPA Tribal Science Council Workshop, Reno, NV (1/25/05) "Assessing Tribal Traditional Lifeways in EPA's Risk Assessment Policies and Procedures"

Symposia and Workshops at professional society meetings

- A discussion at the annual meeting of the Society for Environmental Toxicology and Chemistry (SETAC) (11/04);
- A symposium at the annual meeting of the Society for Risk Analysis (12/04); and
- Co-sponsored a Contemporary Concepts in Toxicology Workshop under the auspices of the Society of Toxicology on Probabilistic Risk Assessment: Bridging Components along the Exposure-Dose-Response Continuum (7/05) www.toxicology.org/AI/MEET/PRA_meeting.asp (papers in preparation)

C. Comments Received

Public comments on the EPA staff paper were taken in 2004 (e-docket ORD 2004-0004). An analysis of all the comments received lists 21 overarching themes and the % of commenters who identified these concerns or issues (Appendix 1). The areas mentioned most frequently related to:

- the level of conservatism from bias, defaults, lack of dose data; or from lack of data on metabolites or all effects or exposed groups (65%);
- the need to advance probabilistic and distributional approaches (52%);

- establishing criteria for generating and using the most scientifically sound data in a variety of settings and from a number of sources (48%); and
- advancing cumulative and aggregate risk assessments (29%).

The BOSC meeting (see links above) focused on Chapter 4 of the *Staff Paper* which discussed the use of default and extrapolation assumptions, and included discussion of high to low dose extrapolation, and extrapolation between species. The BOSC emphasized the promise of genomics and systems biology to begin to test the relevance of high dose toxicity testing for predicting risk from limited exposures, and mode of action information as a potential substitute for default uncertainty factors, and the need for greater consideration of changes in toxicity test design and approaches to quantitative risk assessment.

After the consultation with SAB in July of 2004, two key messages for support were highlighted in their letter (link above): the effort to move towards a preference to use available and relevant data instead of default assumptions; and the application of probabilistic methods, particularly to hazard and dose response assessments.

D. SAB Consultation

For this consultation, EPA will bring the SAB up to date on some current research efforts in ORD or supported by EPA related to human health risk assessment; and describe specific projects in three offices to illustrate progress in EPA practices focusing on:

- Attachment A; cumulative risk assessments in the Office of Pesticide Programs (OPP);
- Attachment B; probabilistic risk assessments in Office of Solid Waste and Emergency Response and the Office of Solid Waste (OSW); and
- Attachment C; recent chemical reviews by the National Center for Environmental Assessement (NCEA) in the Office of Research and Development (ORD);

Then, EPA would like to outline a few ideas and thoughts about some recent developments and the Agency's future directions to address the issues raised by them, and to advance risk assessment practice in EPA.

E. Charge Questions

1. Do the Agency's efforts seem on track to advance EPA risk assessment practices and are they in line with the comments and recommendations received with respect to
    A. the advances in the areas presented and
    B. in the Agency's research
2. What other areas and improvements should be considered and which would be most important?

Appendix 1

Office of Science Advisor Staff Paper—Risk Assessment Principles & Practices
Public Comments (e-Docket ORD2004-2004)
List of 21 Overarching Issues/Themes[2]

1 Addressing the level of conservatism (mentioned by 65% of commenters):
- A Level too high: Default assumptions lack scientific basis
- B Level too high: Systematic/multiple layers of bias
- C Level too high: Default assumption of low-dose linearity
- D Level too high: Exposure vs. dose-response impact
- E Level too high: Concern about other resulting impacts
- F Maintain level: Current approach affords needed level of protection
- G Maintain level: Current approach omits toxic metabolites
- H Need to specify/quantify degree of protectiveness of uncertainty factors

2 Refining/advancing probability and distributional approaches (52%):
- A For toxicity value development
- B For characterizing probability distribution of risk estimates
- C Collecting input data
- D Human health, including aggregate and cumulative RA
- E Ecological assessments
- F For comparative estimates of remedial alternatives
- G Suggested models

3 Establishing criteria for generating/using the most scientifically sound data (48%):
- A In chemical-specific/tox assessments
- B In exposure evaluations
- C Using data from open literature
- D Using human data
- E Need for peer review
- F Weight-of-evidence evaluations
- G Tapping others' approaches (e.g., WHO)

4 Advancing cumulative and aggregate RAs (29%):
- A Clarifying/refining dose and response addition methods
- B Challenges of testing whole mixtures, congeners
- C Recognizing uncertainties, data gaps, and research needs

5 Establishing a better framework for screening level vs. refined assessments (29%):
- A Using empirical data over default assumptions or modeled data
- B Criteria needed for collecting site data
- C Limitations of HQ approach

6 Advancing ecological risk assessment approaches (19%):
- A Moving beyond conservative screening
- B Integrating higher food chain receptors
- C Conducting population-level vs. organism-level assessments

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[2]Represents coding used in *Table 1: Office of Science Advisor Staff Paper—Risk Assessment Principles & Practices: Compiled and Annotated Set of Public Comments (e-Docket ORD-2004-2004) (February 25, 2005)*

Office of Science Advisor Staff Paper—Risk Assessment Principles & Practices
Public Comments (e-Docket ORD-2004-2004)
List of 21 Overarching Issues/Themes (continued)

7 Improving risk assessment decision framework—separating risk assessment from risk management (19%)
8 Quality/validity of models (19%):
- A Need mechanisms to check plausibility
- B Need rigorous peer review
- C Improving exposure/environmental models
- D Statistical applications (e.g., UCL)

9 Clarifying application of reasonable maximum exposure (RME) and central tendency exposure (CTE) estimates (16%)
10 Clarifying risk assessment terminology (16%)
11 Establishing better criteria for low-dose extrapolation (16%):
- A Maintain dichotomy
- B Using mechanistic/MOA data
- C BMD modeling, PBPK modeling

12 Protecting subpopulations (16%):
- A Subsistence and traditional lifestyles (e.g., tribal)
- B Young, old, compromised
- C Environmental justice issues
- D Farm workers

13 Addressing/defining "adversity" in risk assessment (13%)
14 Improving cancer assessment approaches (13%)
- A Addressing variability and uncertainty
- B Interpreting tumor data
- C "Safety assessment" methods

15 Specifying limits of/advancing TEF approach (13%):
- A Need to experimentally validate
- B Use of probabilistic approach, REP distributions
- C Invalid for wildlife receptors, and other eco applications

16 Additional topics for EPA consideration (10%):
- A Comparative risk assessment
- B Consideration of non-U.S. risks
- C Evaluating population impact

17 Addressing data gaps in toxicology knowledge (6%)

18 Addressing nonchemical/safety risks (3%)
19 Better process for assessing residual risks (3%)
20 More consistency needed across EPA regions (3%)
21 Refining exposure point estimates (recognizing uncertainties associated with composite sampling) - (3%)

Attachment A

EPA's Office of Pesticide Programs: Cumulative Risk Assessment and Incorporation of Probabilistic Approaches in Exposure Assessment

In assessing the potential health risks associated with exposure to pesticides, EPA's attention has historically focused on single pathways of exposure (e.g., pesticide residues in food, water, or residential/ non-occupational uses) for individual chemicals, and not on the potential for individuals to be exposed to multiple pesticides by all pathways (and routes) concurrently. Congress passed the Food Quality Protection Act (FQPA) in 1996 which significantly amended the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) and the Federal Food, Drug, and Cosmetic Act (FFDCA). One of the major changes imposed by FQPA was the requirement to take into account when setting pesticide tolerances *"available evidence concerning the cumulative effects on infants and children of such residues and other substances that have a common mechanism of toxicity."*

This new requirement provided EPA's Office of Pesticide Programs (OPP) new scientific challenges including the need to develop approaches for establishing common mechanism groups and developing new guidance and methods for performing cumulative risk assessments. To ensure transparency and use of best available science in the cumulative risk assessments, EPA-OPP has used the FIFRA Science Advisory Panel (SAP) to obtain expert review, advice, and recommendations at each major step in the development of the methodologies. EPA-OPP has consulted with the FIFRA SAP on numerous occasions beginning in 1998 and most recently in February and August, 2005. EPA-OPP has also held numerous meetings with the FQPA Federal Advisory Committees TRAC (Tolerance Reassessment Advisory Committee) and CARAT (Committee to Advise on Reassessment and Transition), which were established under the Federal Advisory Committee Act (FACA).

EPA-OPP has published guidance on conducting cumulative risk assessments. This guidance is available on EPA's website at http://www.epa.gov/pesticides/trac/science/cumulative_guidance.pdf. As mentioned above, under FQPA (1996), EPA-OPP must consider cumulative risk to those pesticides which share a common mechanism of toxicity. When assessing the potential for two or more pesticides to act by the same mechanism, EPA-OPP considers three key principles: 1) they cause the same critical effect(s); 2) they act on the same molecular target at the same target tissue; and 3) they act by the same biochemical mechanism of action perhaps because they share a common toxic intermediate (Mileson, 1998). EPA-OPP has so far established four groups of pesticides as common mechanism groups: organophosphates (OPs; 1999a), *N*-methyl carbamates (NMCs; 2001a), chloracetanilides (2001a), and triazines (2002a). The focus of the remainder of the discussion in this document will be on the OP and NMC cumulative risk assessments. For the OPs, EPA released its Revised Cumulative Assessment in 2002 and more recently the 2006 Update which incorporated new or additional data available since 2002 and risk mitigation or risk reduction efforts taken by the Agency on individual OPs. The Agency released the Preliminary Cumulative Risk Assessment of the NMCs in 2005 and expects the Revised Cumulative

Risk Assessment of the NMCs to be available to the public in 2006. For more information on the OP, NMC, triazine and/or chloracetanilides assessments, see EPA's website at http://www.epa.gov/pesticides/cumulative/. Key aspects of the hazard, food, drinking water, residential and multi-pathway analyses included in the cumulative risk assessments of the OPs and NMCs are highlighted below.

Hazard and Dose-Response Assessment:

EPA has used the relative potency factor (RPF) method to determine the joint risk associated with exposure to OP and NMC common mechanism groups. Briefly, the RPF approach uses an index chemical as the point of reference for comparing the toxicity of the pesticides included in the common mechanism group. Relative potency factors (RPFs) are calculated as the ratio of the toxic potency of a given chemical to that of the index chemical. RPFs are used to convert exposures of all chemicals in the group into exposure equivalents of the index chemical. Dose additivity is a key assumption in the RPF approach and is also the Agency's default approach in mixture risk assessment unless there are data to support a different approach (i.e., more or less than additivity; USEPA, 2001b). For both the OP and NMC common mechanism groups, EPA-OPP has worked with researchers at EPA's National Health and Environmental Effects Research Laboratory (NHEERL) to design and conduct mixture experiments with selected pesticides. These mixture experiments have shown that the default assumption of dose additivity is a reasonable assumption for the both the OP and NMC common mechanism groups (Moser et al, 2005 & 2006; USEPA, 2005). EPA-OPP has worked collaboratively with EPA's National Center for Computational Toxicology to perform empirical dose-response modeling using an exponential model for the OPs and NMCs. In the analyses for both groups, the Agency has calculated benchmark dose estimates using sophisticated statistical procedures which allow the Agency to use data from multiple studies for a particular chemical. The use of multiple studies for each pesticide provides the Agency with robust and scientifically supportable estimates of relative potency and points of departure for extrapolating risk.

- **OP cumulative risk assessment:**
  The OPs have been grouped as a common mechanism group based on their shared ability to cause neurotoxicity mediated through the inhibition of the enzyme acetylcholinesterase via phosphorylation of the active site. OP toxicity accumulates with repeated exposures such that effect levels in animal studies are lower in repeated exposure studies compared with acute (single dose) studies. Toxic potencies for over 30 OPs were determined from the oral route using brain cholinesterase inhibition from female rats measured at 21 days of exposure or longer. Following approximately 3-4 weeks of exposure to OPs, cholinesterase inhibition is no longer increasing following OP exposure. This point where cholinesterase inhibition at a given dose is fairly constant is called steady-state. The Agency has shown that estimates of potency are reliable and reproducible when estimated at steady state. For those OPs with residential uses, brain cholinesterase data from dermal and/or inhalation studies were also

collected. Methamidophos was selected as the index chemical based on the availability of high quality data from oral, dermal, and inhalation studies.

- **NMC cumulative risk assessment:**
  The NMCs have been grouped as a common mechanism group based on their shared ability to inhibit acetylcholinesterase via carbamylation of the active site. NMC toxicity is characterized by rapid increase in cholinesterase inhibition followed by rapid recovery in minutes to hours. Acute toxicity, particularly at the peak time of effect, is the critical duration for NMCs. Toxic potencies for 10 NMCs were determined from the oral route using brain cholinesterase inhibition from female and male rats measured at peak (or close to peak) time of effect. The half-life to recovery was also estimated based on available time course data. For those NMCs with residential uses, brain cholinesterase data from dermal and/or inhalation studies were also collected. Oxamyl was selected as the index chemical based on the availability of high quality data from oral, dermal, and inhalation studies.

Exposure Assessment:

An important aspect of the exposure analyses is to develop exposure scenarios resulting from the uses for each pesticide. Three key pathways of exposure to OP and NMC pesticides–food, drinking water, and residential and other non-occupational settings–have been assessed by EPA. Factors EPA considered in the analysis of exposure by each of these three pathways included duration, frequency, and seasonality of exposure. Evaluation of chemical use profiles allows for the identification of exposure scenarios that may overlap, co-occur, or vary between chemicals, as well as for the identification of populations of concern.

All of the hazard data, exposure data, and exposure scenarios must be combined in a manner designed to produce reasonable and realistic estimates of exposures likely to be encountered by the public in location and time (seasonally). EPA-OPP has used probabilistic exposure methods to evaluate the risk to the food, drinking water and residential pathways along with risk to multiple pathways simultaneously. The models (and the application of these models) described below have been through significant peer review and public comment.

Exposures through residential uses and in drinking water are incorporated into cumulative exposure assessments on a regional basis. These regional assessments are meant to account for differing agronomic uses and reflect the differences in climate, soil conditions, and pest pressures across the entire US. Exposure to pesticide residues in foods is considered to be uniform across the nation (i.e., there are no significant differences in food exposure due to time of year or geographic location). The assumption of nationally uniform food exposure is based on the understanding that, to a large extent, food is distributed nationally and food consumption is independent of geographic region and season. The single national estimate of food exposure was combined with region-specific exposures from residential uses and drinking water in three regions that represent the highest potential for exposure. The following age groups were analyzed in the exposure assessments: infants (children <1); 1- and 2- year olds (i.e., 1 to < 3 years of age); 3- through 5- year olds (i.e., 3 to <6 years of age); 20- through 49- year olds (i.e., 20 to <50 years of age); and 50 years of age and greater. These age groups were selected since they provide a broad representation of potential exposures and because these include age groups that are commonly shown to be the most highly exposed in single-chemical assessments.

Food

The food component of the OP and NMC cumulative risk assessments is considered to be highly refined and to provide reasonable estimates of the distribution of exposures across the US. The exposure estimates for food are based on residue monitoring data from the USDA's Pesticide Data Program supplemented qualitatively with information from FDA’s Surveillance Monitoring Programs and Total Diet Study. The PDP data provide a very reliable estimate of pesticide residues in the major children's foods and account, directly or indirectly through the use of commodity surrogates, for more than 90-95% of consumption for children. These data also provide direct measures of co-occurrence of OP pesticides in the same sample, alleviating much of the uncertainty about co-occurrence in foods that are monitored in the program. The reliability of the food component of this assessment is also supported by the use of the food consumption data from the USDA's Continuing Survey of Food Intakes by Individuals, 1994-1996/1998 (CSFII). The CSFII surveyed more than 20,000 individuals over two non-consecutive days and provides a detailed representation of the food consumption patterns of the US public across all age groups, during all times of the year, and across all 50 states. Thus, EPA has

confidence that the distribution of risk estimates for food is well-predicted and reasonably reflects risks to the US population.

- **OP cumulative risk assessment:**
  Due in part of toxicological considerations and the nature of OP-induced cholinesterase inhibition, the Agency has used DEEM/Calendex™ software to probabilistically evaluate food exposures using a 21-day rolling average approach. In this approach, 21 sequential days are averaged with careful maintenance of the temporal pattern of exposure residues and the regional basis.

- **NMC cumulative risk assessment:**
  The Agency has used DEEM/Calendex™, the LifeLife, and CARES software programs to probabilistically evaluate food exposures to single day exposures to the NMCs. More recently, EPA-OPP has collaborated with EPA's National Exposure Research Laboratory to investigate the potentially utility of the Agency's probabilistic SHEDS model to evaluate single day food exposures to the NMCs.

Water

The drinking water assessment focuses on areas where combined exposure is likely to be among the highest within each of the regions across the U.S. as a result of total pesticide usage and vulnerability of drinking water sources. This analysis is based on a probabilistic modeling approach that considers the full range of data and not a single high-end estimate. Exposures in drinking water to individuals are incorporated into the cumulative exposure assessment on a regional- and source water-specific basis (i.e., ground water and surface water, by region). The regional drinking water exposure assessments are intended to represent exposures from vulnerable drinking water sources resulting from typical pesticide usage and reflect seasonal variations as well as regional variations in cropping and pesticide use. Each regional assessment focuses on areas where combined exposure is likely to be among the highest within the region as a result of total pesticide usage, adjusted for relative potencies, and vulnerability of the drinking water sources. The co-occurrence of pesticide residues in water is primarily estimated by means of modeling. Monitoring data are not available consistently enough to be the sole basis for the assessment. However, monitoring data are used to corroborate the modeling results and have helped confirm locations of potentially vulnerable drinking water sources.

- **OP cumulative risk assessment:**
  Based on the analysis described above, the focus of the drinking water analysis for the OP cumulative risk assessment is on surface water residues. The Agency used PRZM/EXAMS software to develop a time-series of residue concentrations for inclusion in the OP Cumulative Risk Assessment.

- **NMC cumulative risk assessment:**
  The focus of the drinking water analysis for the NMC cumulative risk assessment is primarily on ground water exposure, particularly shallow wells, and secondarily on surface water residues. The Agency used PRZM/EXAMS software to develop a time-series of residue concentrations for inclusion in the NMC Cumulative Risk Assessment.

Residential

Applications of pesticides in and around homes, schools, offices, and other public areas may result in potential exposure via the oral (due to hand-to-mouth activity by children), dermal, and inhalation routes. Potential exposure scenarios include lawn and turf uses, home garden uses, wide-area public health uses, indoor uses (including aerosol sprays and pest strips), and/or pet uses. Several reliable data sources were used to define how pesticides are used, how quickly the residues dissipate, how people may come into contact with pesticides (e.g., via dermal or inhalation exposure), and the length of time people might be exposed based on certain activities (e.g., playing on a treated lawn).

- **OP cumulative risk assessment:**
  EPA used Calendex™ software to probabilistically evaluate residential exposure to potentially exposed individuals across a calendar year. In the case of regional differences, OPP developed one generic regional analysis that included all OP residential uses. This “composite” region (referred to as "Region X") provides a worst-case combination of all OP residential uses and includes worst-case assumptions regarding percent of households treated and application frequency. Thus, this update provides a conservative assessment of risk for which exposures are expected to be higher than would be potentially seen in any single region in the U.S.

- **NMC cumulative risk assessment:**
  EPA used Calendex™ software to integrate various pathways while simultaneously incorporating the time dimensions of the data. Calendex™ provides a focused, detailed profile of potential exposures to individuals across a calendar year. The Agency expects to include some residential analyses using the CARES, model in the Revised Cumulative Risk Assessment in 2006.

Combined Pathway (Cumulative) Assessment:

EPA also evaluated the risk for all three pathways of exposure (food + water + residential) considered simultaneously. Evaluating exposures is significantly more complex when the analyses address the simultaneous exposures to more than one pesticide and when distributional inputs derived from data from surveys and monitoring studies – as opposed to default assumptions or point estimates -- are used. The detailed outputs from the OP and NMC cumulative assessments allow in-depth analysis of interactions of data sets to estimate the possible risk concerns and identify the sources of exposures. This practice permits expression of the full range of values for each parameter and results in an improved ability to interpret the complete risk picture. Examples of the calendar-based output at different percentiles of exposure are provided in Figures 1a-c.

- **OP cumulative risk assessment:**
  EPA used Calendex™ software to probabilistically integrate various pathways while simultaneously incorporating the time dimensions of the data. Specifically, time and population based information from the national diet is combined with time and population based information from the regional drinking water and generic (high end assumption) residential region. Calendex™ provides a focused, detailed profile of potential exposures to individuals across a calendar year.

- **NMC cumulative risk assessment:**
  EPA used Calendex™ software to integrate the food, drinking water, and residential assessments in a probabilistic manner across various population groups and across the calendar year. The Agency expects to includes some analyses using the CARES, LifeLine, and SHEDS models in the Revised Cumulative Risk Assessment in 2006

Summary

Beginning with the passage of FQPA (1996), EPA-OPP has undertaken efforts to develop and implement guidance documents, methods, and approaches for performing cumulative risk assessment of pesticide groups that share a common mechanism of action. EPA-OPP is committed to developing cumulative risk assessments based on the most current scientific information and methods. As part of these efforts, EPA-OPP has collaborated with many scientists from various laboratories and centers in EPA's Office of Research and Development. EPA-OPP has also held numerous external peer-review meetings with the SAP and asked for comment on many issues, including the approaches to grouping chemicals based on a common mechanism of toxicity; guidance for conducting cumulative risk assessment; methods and approaches for dose-response and exposure assessment; and probabilistic exposure models for combining food, drinking water, and residential exposure pathways. In the future, EPA-OPP expects to continue to further refine and develop more sophisticated cumulative risk assessments, including incorporation of physiologically based pharmacokinetic modeling and/or biologically based dose-response models. The OP and NMC cumulative risk assessments provide good case studies for the application of highly sophisticated approaches for developing dose-response assessment using benchmark dose techniques and the application of probabilistic exposure models which assess exposure from food, drinking water, and residential pathways along with multiple pathways simultaneously. Due to their large size and the level of sophistication, these cumulative risk assessments are resource intensive. They do, however, provide the public and risk managers with a novel prospective on potential risk to pesticide chemicals.

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U.S. Environmental Protection Agency 2005 Preliminary N-Methyl Carbamate Cumulative Risk Assessment. Office of Pesticide Programs, U.S. Environmental Protection Agency. Washington, DC. http://www.epa.gov/scipoly/sap/index.htm#sept

Figure 1a. Example of the probabilistic output from Calendex which provides a calendar-based approach for evaluating Margins of Exposure across various percentiles of exposure: 95th Percentile Exposure for Infants from the Mid South Region.

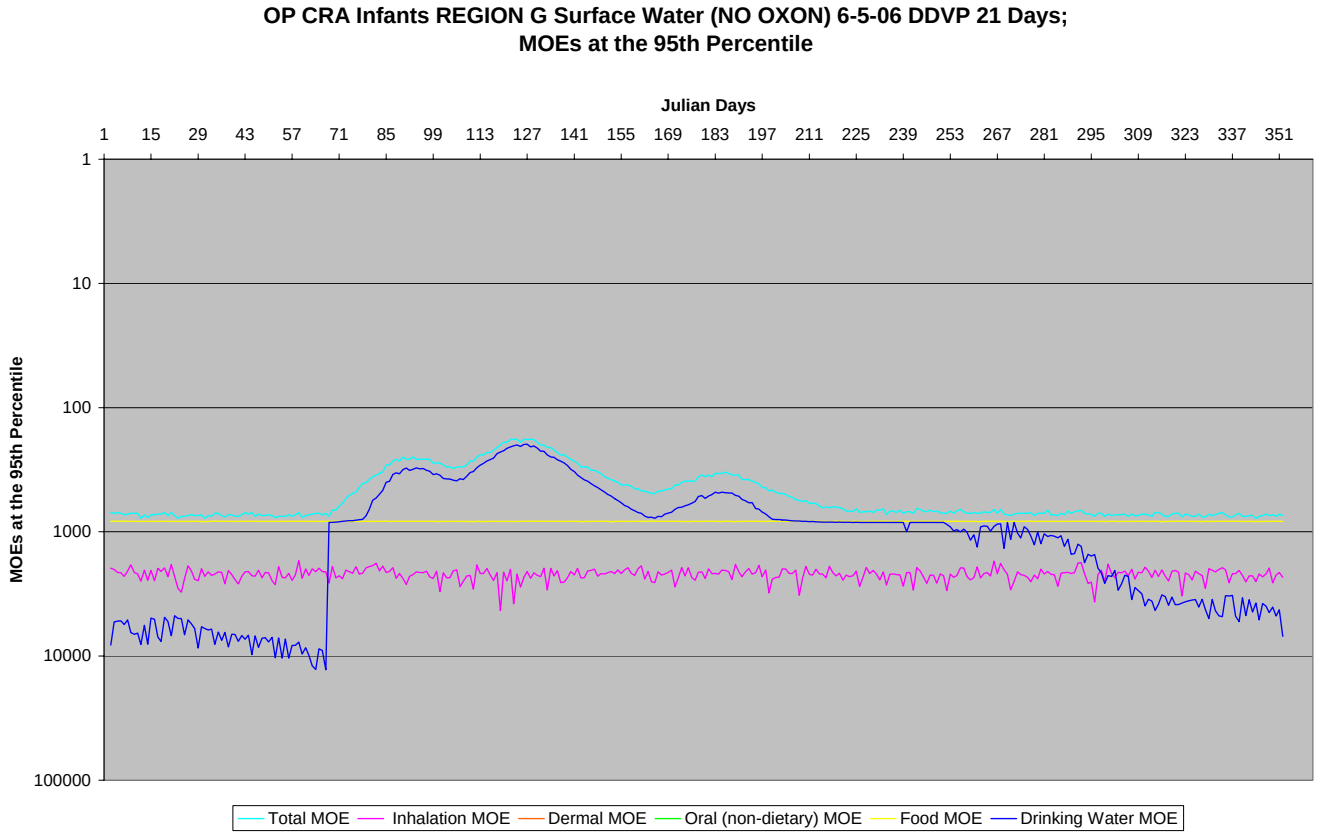


Figure 1b. Example of the probabilistic output from Calendex which provides a calendar-based approach for evaluating Margins of Exposure across various percentiles of exposure: 99th Percentile Exposure for Infants from the Mid South Region.

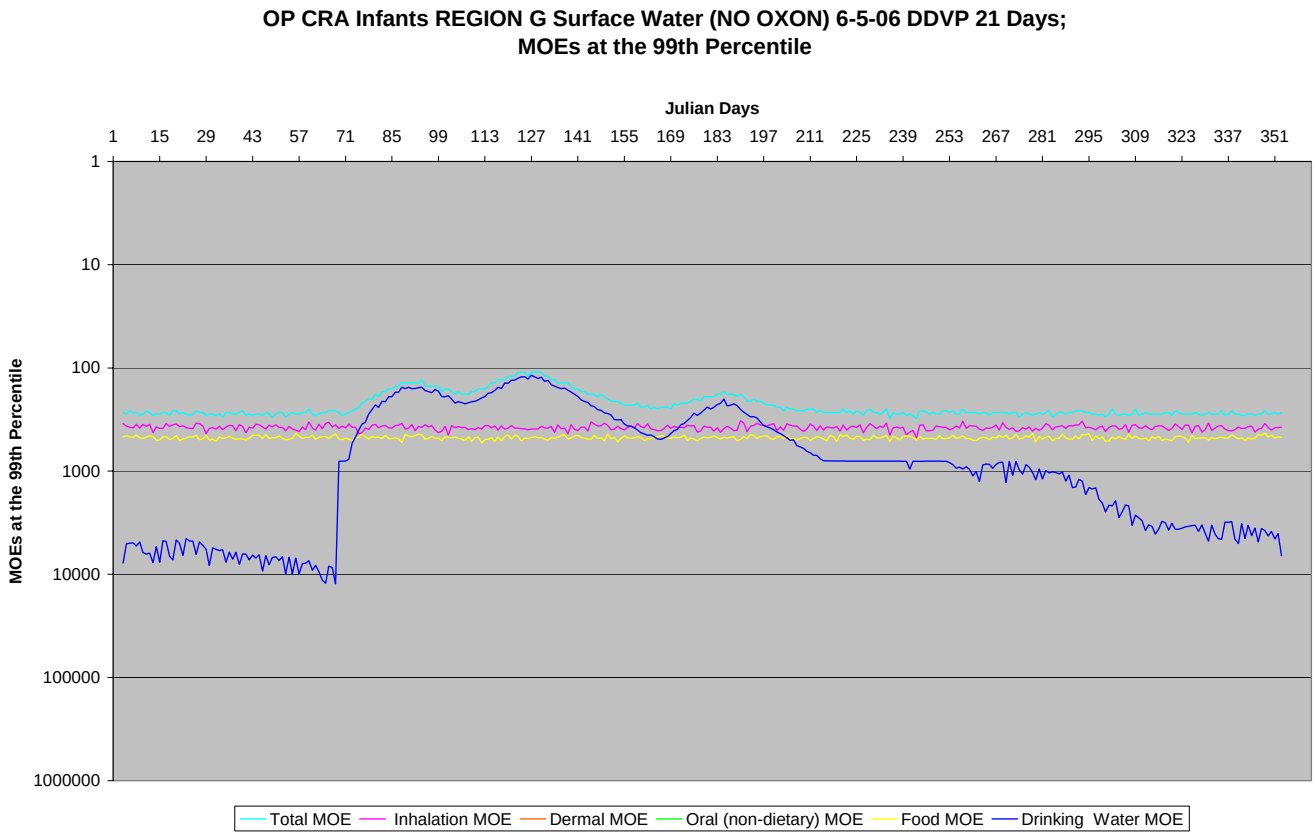
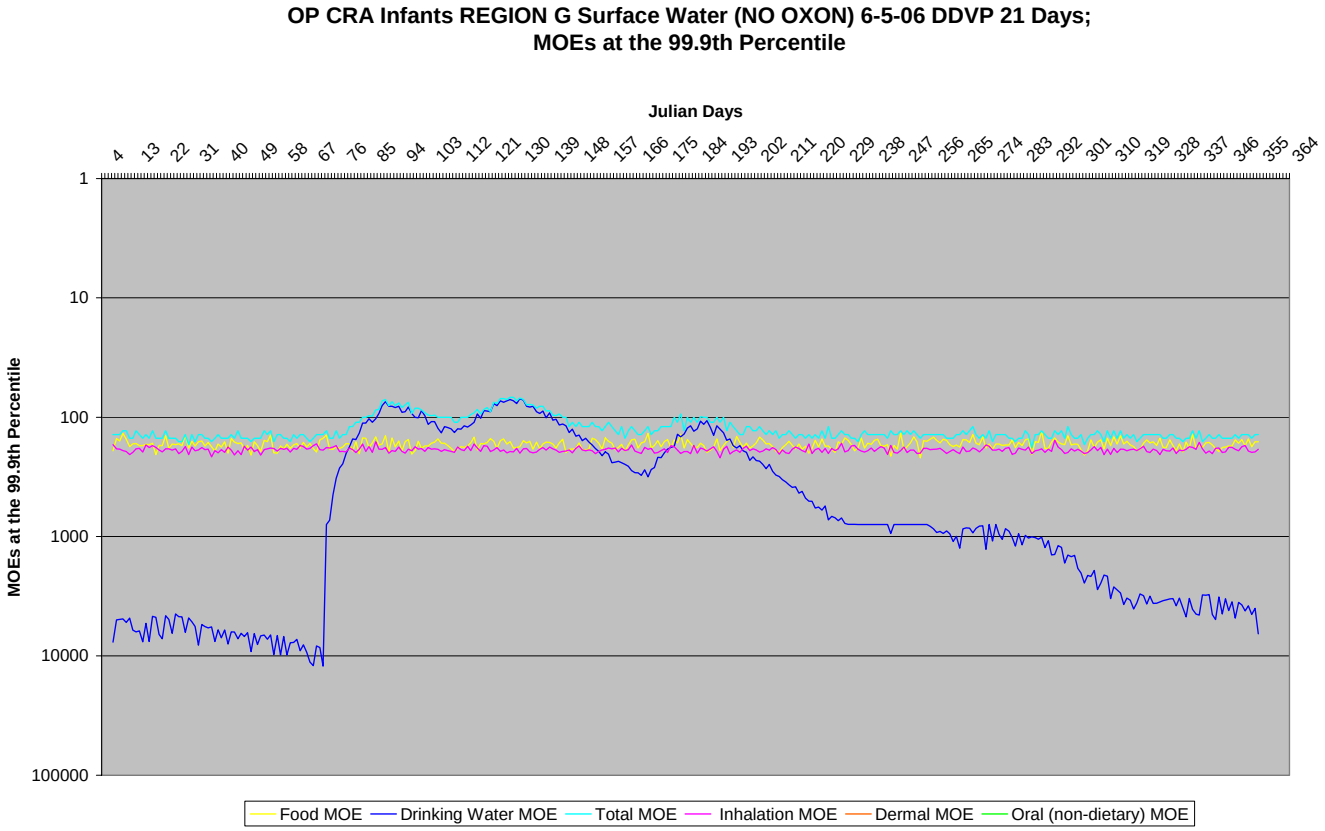


Figure 1c. Example of the probabilistic output from Calendex which provides a calendar-based approach for evaluating Margins of Exposure across various percentiles of exposure: 99.9th Percentile Exposure for Infants from the Mid South Region.



Attachment B

Use of Probabilistic Risk Assessment in the Office of Solid Waste and Emergency Response

EPA supports the development and use of probabilistic techniques in human health and ecological risk assessments where the results of the probabilistic analysis will add value to the risk management decision. The use of probabilistic risk assessment across the Agency varies among several program offices, with some offices using the techniques with greater frequency than others. The differences in application of these techniques may reflect regulatory requirements, nature of decisions (i.e., national decisions compared to site-specific decisions), and knowledge regarding the limitations and benefits of these techniques.

The Office of Solid Waste and Emergency Response (OSWER) initiated probabilistic techniques in risk assessments in the early 1990's to support a number of program office activities, for example, national waste management regulatory and policy decisions. The purpose of this short paper is to briefly mention a few key Agency documents on probabilistic risk assessment (PRA) and to summarize some uses of PRA in the Office of Solid Waste (OSW) and in the Office of Superfund Remediation and Technology Innovation (OSRTI) or the Superfund program.

Probabilistic Risk Assessment (PRA) uses probability distributions to characterize variability or uncertainty in risk assessments. For example in PRA, one or more exposure variables in the risk equation are defined as probability distributions rather than a single number. Similarly, the output of a PRA is a range or probability distribution of risks experienced by receptors. The evaluation of variability and uncertainty in the risk assessment, either quantitatively or qualitatively, is an important component of the risk characterization of all risk assessments. Two key policy statements have informed this work. In the 1995 Risk Characterization memorandum, Administrator Carol Browner (U.S. EPA, 1995) stated,

> *…we must fully, openly, and clearly characterize risks. In doing so, we will disclose the scientific analyses, uncertainties, assumptions, and science policies which underlie our decisions…There is value in sharing with others the complexities and challenges we face in making decisions in the face of uncertainty.*

In addition, the 1997 EPA Policy for Use of Probabilistic Analysis in Risk Assessment (U.S. EPA, 1997) stated that PRA techniques, given adequate supporting data and credible assumptions, can help to analyze variability and uncertainty in risk assessments. *Guiding Principles for Monte Carlo Analysis* (EPA, 1997) describes the Agency's general use of a "tiered approach" that sequentially employs more sophisticated analysis (e.g., sensitivity analysis to full probabilistic analysis). This document highlighted several questions to consider in developing a PRA including:

- Does the project warrant this level of effort?

- Will the quantitative estimate of uncertainty improve the decision?
- Is adequate information available to fully characterize variability and uncertainty?
- Are the skills and experience needed to perform the analysis available?
- Can the costs of a PRA analysis be met within the budget limitations?
- Have issues associated with communication of the results to the public and decision makers been considered?

With consideration of the above factors, OSWER agrees that PRA can be useful in risk management decisions, although a deterministic risk assessment must also be done in accordance with Superfund PRA guidance.

One of the earliest probabilistic applications in the Office of Solid Waste (OSW) was in support of the Toxicity Characteristic rule, a national rule which identifies wastes as hazardous if they contain certain constituents at or above listed levels due to their leaching potential and health threat if consumed in drinking water. Other national assessments where probabilistic techniques have been applied include several Resource Conservation and Recovery Act (RCRA) hazardous waste listing determinations (e.g., chlorinated aliphatics production, dyes and pigments production, inorganic chemicals manufacturing), support for the Maximum Achievable Control Technology (MACT) standards for hazardous waste combustors, and the Surface Impoundment Study, in which OSW developed national assessments of exposures and potential risks associated with managing decharacterized wastes in surface impoundments, resulting in a report submitted to Congress in 2001.

EPA Regions typically use the DRAS (Delisting Risk Assessment Software) model, which is based in part on probabilistic modeling, to support RCRA hazardous waste delisting decisions. These assessments have used the Monte Carlo probabilistic technique, specifically in the prediction of a constituent's release, fate, transport and exposure components of an assessment to account for both variability and uncertainty. The probabilistic analyses not only capture the variability in waste management units properties, but also they capture the differences in environmental settings (e.g., hydrology, meteorology) where wastes may be managed, the chemical-specific parameters related to fate and transport, and the variability of human exposure factors and receptor locations.

To date, OSWER has not characterized the variability or uncertainty in human health toxicity values (reference doses, cancer slope factors) in regulatory decision making by using PRA.

Assessments incorporating PRA can be costly and resource intensive in the development and review stage and pose challenges in communicating results of the analysis to the public. Tools that OSW has developed include: (1) an integrated multimedia risk assessment model (3MRA), components of which have been used in a probabilistic mode to support regulatory decision-making, (2) a groundwater model, EPA's Composite Model for leachate Migration and Transformation in Products (EPACMTP), which is a simulation model for subsurface fate and transport of contaminants released from land

disposal sites designed to predict the groundwater exposure in domestic drinking water receptor wells, and (3) a ground water modeling tool, Industrial Waste Management Evaluation Model (IWEM), which is designed to assist a user in determining the most appropriate waste management unit design to minimize or avoid groundwater impacts.

The Office of Superfund Remediation and Technology Innovation (OSRTI) makes risk management decisions ranging from removal decisions where there is an imminent threat of release to site-specific decisions at sites, ranging in size from less than a quarter acre to thousands of acres. Typically, site-specific risk assessments include assessment of the Reasonably Maximally Exposed (RME) individual and Central Tendency (CT) or average exposed individual and a qualitative discussion of uncertainty. In addition to the risk assessment, risk managers must also consider the nine National Contingency Plan criteria (e.g., protection of human health and the environment, federal and state regulations or ARARS, long term effectiveness and permanence, reduction in toxicity, mobility and volume, short-term effectiveness, implementability and cost, and state and community acceptance.

OSRTI developed a guidance document for the use of PRA in site-specific risk assessments, which can be used for characterizing risks at Superfund and RCRA Corrective Action sites. *Risk Assessment Guidance for Superfund (RAGS) Volume III: Part A* (2001) is an externally peer-reviewed technical guidance on the application of PRA methods to human health and ecological risk assessment in EPA's Superfund program. It focuses on Monte Carlo analysis (MCA) as a method of quantifying variability and uncertainty in risk and is geared toward risk assessors, but it includes an overview of concepts, policies, and guiding principles directed at risk managers who serve as decision makers at hazardous waste sites. This guidance document provides a description of the potential benefits and limitations of probabilistic techniques. The guidance document highlights a tiered approach that relies first on a deterministic estimate of risk. Then it provides decision criteria for determining whether probabilistic techniques, ranging from sensitivity analysis to two dimensional MCA, may be appropriate based on site considerations. The document also provides generalized and detailed guidance on how to perform probabilistic assessments, both for human and ecological receptors.

In addition, OSWER is developing a workbook to assist risk assessors interested in applying the techniques by providing case examples. However, since some case studies involve inhalation exposure and the Superfund inhalation guidance is currently being revised, the completion of the case studies is dependent on the finalization and peer review of the Superfund inhalation guidance.

Some Offices and Regions have begun applying probabilistic techniques to a range of site-specific risk assessment within OSWER. In keeping with the guidelines discussed in RAGS III Part A, site-specific determinations based on a deterministic risk assessment results, cost, resources for conduct and review, and value added were made regarding where to apply PRA. To date, PRA has been applied primarily at larger sites, where the additional information derived by PRA techniques was determined to add value to the

risk management decision. Some simple forms of PRA have also been used at some small-medium sites, when the level of effort in providing the additional information was not large. Sensitivity analyses have been valuable in identifying sensitive parameters in the risk assessment where additional analyses may be warranted.

In general, the most common type of PRA application in Superfund has been in the characterization of variability and/or uncertainty in human exposure. This includes PRA-based evaluations of variability and/or uncertainty in various fate and transport processes, as well as variability and/or uncertainty in human contact (intake rates, frequencies, durations) with one or more environmental media (soil, drinking water, surface water, air, dietary items, etc).

OSWER relies primarily on the Integrated Risk Information System and EPA's National Center for Environmental Assessment to provide toxicity values for use at sites. This approach provides consistency in the application of toxicity values at sites and avoids duplication of efforts in the development of toxicity values. Some ecological risk assessments have begun to take simple steps to address variability and/or uncertainty in ecological risk assessments. For example, when evaluating risks to a population of small home-range receptors (e.g., benthic macro invertebrates in the sediment of a stream), variability in sediment concentrations may be expressed as a probability density function (PDF). This can be used to help estimate the fraction of the population that is exposed to contaminant levels above a level of potential concern. Likewise, data on between-individual variability in exposure parameters (sometimes available in EPA's Wildlife Exposure Factors Handbook) can be used to help characterize between-individual variability in exposures of species with large home ranges.

In addition, some ecological risk assessments have begun to take early steps to address variability and uncertainty in ecological toxicity reference values (TRVs). For example, when the assessment is intended to evaluate risks to a feeding guild rather than a particular species, the species sensitivity distribution (SSD) may be assembled for the member species of the guild, and the toxicity reference value (TRV) selected to represent the group is taken from the low end of the SSD, thereby accounting for variability in toxicity between species. To address uncertainty in TRVs, some ecological risk assessments use the range between the No Observed Adverse Effect Level (NOAEL) and the Lowest Observed Adverse Effect level (LOAEL) to serve as a rough index of the uncertainty in the Hazard Quotient (HQ) values based on that TRV.

In conclusion, OSWER will continue to evaluate the value-added by the use of PRA in the development of national waste management regulatory and policy decisions, as well as in site-specific risk assessments. The Superfund Program is also evaluating whether additional guidance, modification of our existing guidance, or training might be useful to promote more meaningful uses of PRA in the Superfund Program.

OSWER is currently working with the rest of the Agency through the Risk Assessment Forum to evaluate how the PRA techniques are being used through a "Risk Assessors/ Risk Managers" dialogue. The plan is to develop case studies to further inform other risk

managers regarding the lessons learned in the application of this technique in specific decisions.

References

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Attachment C

Presentation Title: Innovation in IRIS Health Assessments - the Last Five Years

Presenter: Dr. Lynn Flowers, Toxic Effects Characterization Team Leader, IRIS Program, National Center for Environmental Assessment

Description: The Integrated Risk Information System (IRIS) Program develops Agency-wide scientific positions on potential adverse human health effects from exposure to various chemical substances found in the environment. The program follows EPA guidelines for health risk assessment and fosters consistent risk assessments across EPA program offices and regions. The IRIS database contains over 540 chemical-specific IRIS summaries, many with complete toxicological reviews or similar background documents. Currently, there are 77 chemicals undergoing IRIS assessment. The assessments provide qualitative hazard identification, cancer weight of evidence characterizations, and quantitative toxicity values, i.e., oral reference doses and inhalation reference concentrations for noncancer effects and oral slope factors and inhalation unit risks for carcinogenic effects. IRIS users include EPA program and regional offices, other federal agencies, international, state and local agencies, and the public - including academia, regulated industries, environmental organizations and individuals. The IRIS web site receives over 21,000 hits per day.

The current process for developing an IRIS assessment consists of a public nomination process including announcement of substance selections, development of a draft assessment, internal Agency review, interagency review by interested federal agencies, external peer review with public comment period, final EPA approval and posting on the IRIS database.

EPA is incorporating advances in the field of risk assessment in its IRIS assessment development process. Examples from EPA's IRIS assessments from the past 5 years and several on-going assessments will be discussed. The examples illustrate a range of advances in risk assessment, including greater use of mode-of-action data to inform hazard identification and cancer characterization and to identify appropriate low-dose extrapolation methods in cancer assessments, quantitative methods for expressing uncertainty, PBPK modeling, approaches to mixtures, and weighting of epidemiological data.

As a specific example, USEPA's *Guidelines for Carcinogen Risk Assessment* and *Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure* make greater use of the increased scientific understanding of the biological mechanisms leading to cancer following environmental exposures. The IRIS Program is considering mode of action (MOA) data in evaluating the carcinogenicity of environmental chemicals. Due to significant scientific advances in the field of both cancer and non-cancer effects, elucidation of a MOA for a particular response in animals or humans can inform human health risk assessments in a number of ways. The *Guidelines* suggest that MOA data, when available and of sufficient quality, can be useful for understanding whether findings in animals are relevant to humans, the potency of a chemical, its potential effects at low

doses, and which populations or lifestages may be particularly susceptible. However, the increasing availability of MOA data raises several questions as to its application to risk assessment. For example, how can qualitative biological information on a MOA for chemical-induced carcinogenesis be linked with appropriate mathematical and statistical considerations for quantitative risk evaluations? What data are needed to determine whether a MOA supports particular approaches to low dose extrapolation? Other key implementation issues include a focus on the weight of evidence for a hypothesized MOA, lifestage issues related to carcinogenesis, and data needs for determining a MOA.