November 10, 1999

Background Document for the Session

Issues Pertaining to Exposure Assessment and Estimating Cumulative Risk

(For Conducting Cumulative Risk Assessments on Pesticide Chemicals That Have a Common Mechanism of Toxicity)

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BACKGROUND

The Office of Pesticide Programs (OPP) presented a preliminary draft of proposed guidance on cumulative assessment of pesticide chemicals on September 23, 1999 for review by the FIFRA Scientific Advisory Panel (SAP) (see attached memorandum from S. DeVito, dated August 31, 1999). The purpose of that review was to seek comment from the SAP on the hazard and dose response analyses needed when accumulating risk from exposure to two or more chemicals that share a common mechanism of toxicity (The hazard and dose-response guidance is contained in Chapters 3 and 5 of the attached document dated August 27, 1999[1]) . The issues covered at the September 1999 SAP meeting included selection of a candidate group of chemicals, identification of a common end point, and selection of dose response metrics (e.g., no-observed-adverse-effect-levels or effective dose levels); appropriate methods (e.g., relative

[1]Chapters 1 and 2 of the August 27, 1999 cumulative guidance document contain introductory and background material.

potency factors) for normalizing the exposure to chemicals with different toxic potencies; and how to deal with uncertainty factors. A preliminary case study was presented on organophosphorus pesticides that illustrated the application of the hazard and dose-response guidance. When EPA receives the written comments from the September 1999 SAP meeting, revisions in the August 27, 1999 draft guidance document will be made to *Chapters 3 and 5*, as appropriate. The history of the document development for cumulative risk assessment guidance is shown in Table 1.

At the September 1999 SAP meeting, OPP indicated that it had not yet completed its guidance document and would return to the SAP in December 1999 for review of the exposure and risk characterization sections of the guidance. Toward that end, EPA now brings to the SAP the completed Chapter 4 (*Exposure Assessment and Characterization*) and Chapter 6 (*Estimation and Characterization of Cumulative Risk)* for review. In addition, the SAP had recommended to OPP that the case study presented in September be further developed by using actual data and including exposure information. Thus, this package also includes a revised case study on organophosphorous pesticides for the December SAP comment.

Figure 1 depicts the overall steps that will be followed in performing a cumulative risk assessment that are covered in the chapters of the guidance document entitled *Proposed Guidance on Cumulative Risk Assessment of Pesticide Chemical that Have a Common Mechanism of Toxicity (draft document dated August 27, 1999).* As illustrated in Figure 1, the first step in cumulative risk assessment is the identification of a candidate group of chemicals that share a common mechanism of toxicity. Single chemical aggregate exposure assessments should be conducted for each member of this initial common mechanism group (CMG) of chemicals. Individual chemicals initially identified as belonging to a group of chemicals with a common mechanism of toxicity may be eliminated from further consideration in the cumulative assessment if exposure information indicates there is no or little opportunity for overlapping exposure with other members of the group. A final decision to eliminate a chemical from a group of chemicals also involves integrating exposure information and toxicology data such as persistence of effects and presence of tissue residues following acute, short term, intermediate, or chronic exposure. At this point in the assessment, the final set of chemicals that should be included in the full cumulative risk assessment (called the cumulative assessment group or CAG) is made. The chemicals in the CAG are judged to have an exposure and hazard potential that could result in the expression of a cumulative risk.

The OPP December 1999 presentation to the SAP will provide a discussion of some of the exposure considerations for excluding or including chemicals in a final cumulative assessment, as well as the general framework of cumulative exposure assessment and characterization. The similarities and differences between cumulative and aggregate exposure analysis will also be emphasized. For example, in its aggregate risk assessment guidance (presented to the SAP, February 1999), OPP proposed that aggregate exposure will be based on reasonable exposure scenarios for each hypothetical individual in the population on a daily basis so that realistic risk estimates are developed to the extent that data permits. This will also be the basic approach for cumulative exposure assessment. However, there will be different linkages and co-variances in

cumulative risk assessment which may not have been considered in single chemical, aggregate analyses. In other words, one can not simply sum the aggregate risk estimates for the chemicals of interest in a cumulative assessment.

The final outputs of cumulative assessment will be multiple assessments (over different geographic areas and time frames for different subpopulations), and, given the uncertainty anticipated, the characterization of such outputs will be critical.

Table 1. Cumulative Assessment Guidance: Process of Document Development

Cumulative assessment guidance relies and builds on the two documents cited below:

Guidance for Grouping Pesticides by a Common Mechanism of Toxicity (Scientific Advisory Panel, March 1997; Public Review, August 1998; Final Document Published February 1999)
(The first step in cumulative risk assessment is to establish an initial candidate set of chemicals that act by a common mechanism of toxicity. This document defines what constitutes a mechanism of toxicity and provides guidance on what evidence is needed to group chemicals via common mechanism of toxicity.)

Guidance For Aggregate Exposure and Risk Assessment (Scientific Advisory Panel Review, February 1999; Public Comment October 1999)
(Guidance for cumulative assessments of exposure to multiple chemical by multiple pathways and route of exposure draws on many of the basic concepts outlined for conducting single chemical multi-pathway and route assessments, i.e., aggregate assessments).

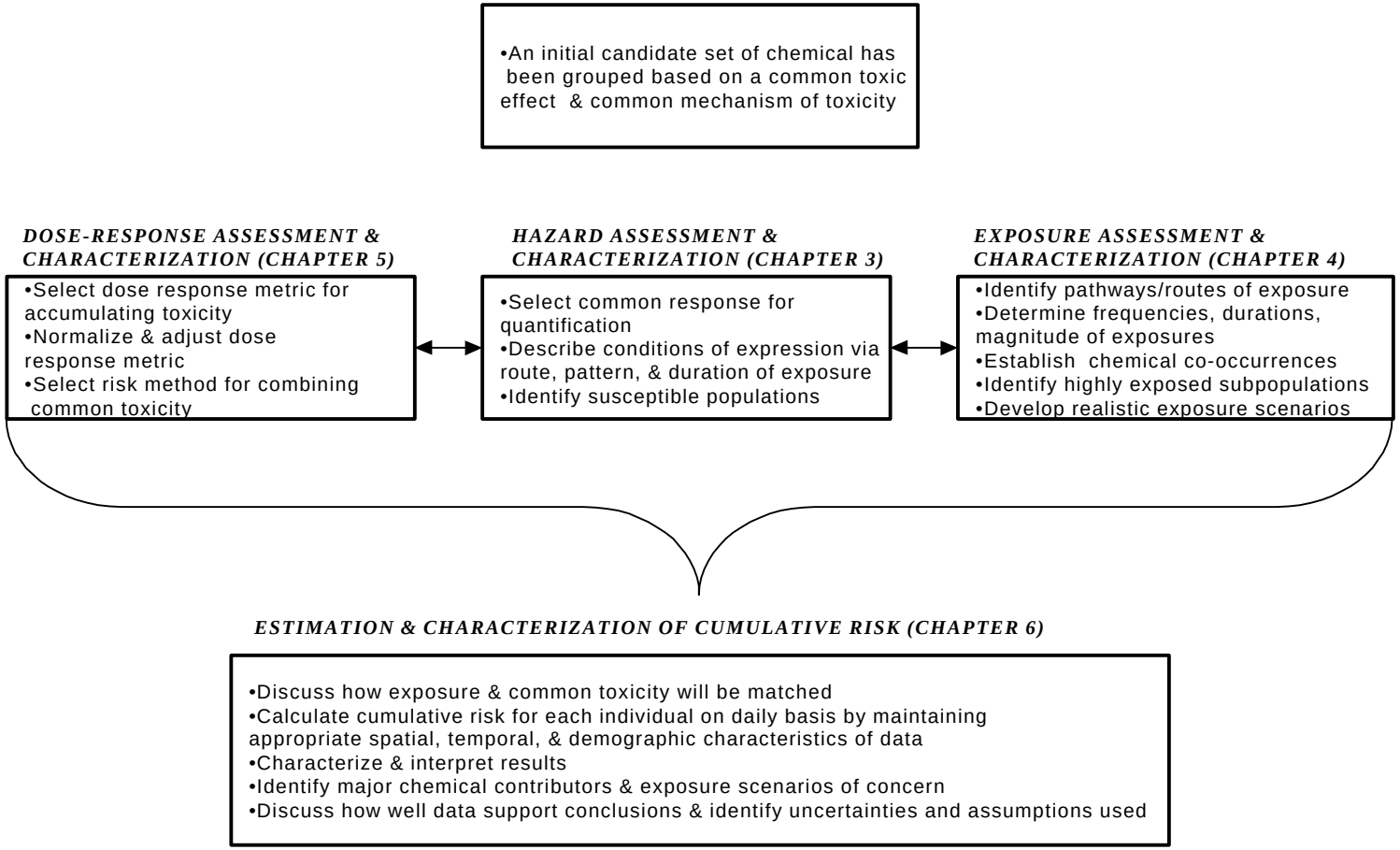
Guidance for Cumulative Risk Assessment
In September 1999, the Office of Pesticide Programs presented a preliminary draft of guidance for cumulative assessment to the Scientific Advisory Panel and the public. The review of the toxicological and exposure portions of this document is being carried out in two phases:

✓ **September 1999 Scientific Advisory Panel Review (Draft document dated August 27, 1999):**
Hazard Assessment and Characterization (Chapter 3)
Dose Response Assessment and Characterization (Chapter 5)

✓ **December 1999 Scientific Advisory Panel Review (Draft Chapters 4 and 6 dated November 10, 1999):**
Exposure Assessment and Characterization (Chapter 4)
Estimation and Characterization of Cumulative Risk (Chapter 6)

Chapters 1 and 2 of the cumulative guidance document contain introductory material.

Figure 1. Cumulative Risk Assessment: General Process



EXPOSURE ISSUES: QUESTIONS FOR THE SCIENTIFIC ADVISORY PANEL

Attached to this paper are *Chapters 4 and 6* and a Case Study (dated November 10, 1999) for SAP comment. Specifically, OPP seeks advice on the following issues:

Issue: Input Parameters

There are several types of data available for pesticide exposure assessment (e.g., field trial data, monitoring data, percent crop treated, label usage). For the dietary (food) pathway, monitoring data are available from the USDA Pesticide Data Program (PDP). OPP conducts the majority of its drinking water assessments by calculating a screening level value. Similarly, residential assessments are conducted using the draft residential SOPs which also provide a screening level assessment. Thus, given PDP, the assessment of the dietary (food) pathway will, in many cases, be based on higher quality data than for the residential and drinking water pathways where usually only screening values are available. Because of the different quality of data that will be encountered when conducting a cumulative exposure assessment, the concern is raised that the value and benefit of high quality monitoring data will be lost if combined with extrapolated exposure values from screening models.

> **Question 1a:** Please comment on how this concern could be addressed. For instance, should OPP at this time conduct separate pathway assessments for dietary (food), dietary (drinking water), and residential exposures so as to avoid combining higher quality monitoring data with more limited screening level data?
>
> **Question 1b:** The panel is asked to comment on whether there are other means of dealing with existing data to reduce the uncertainties about exposure values derived from screening approaches.

Issue: Exclusionary Criteria

OPP is proposing that exclusionary criteria be applied to defer consideration of "negligible" sources of risk in a full cumulative risk assessment. OPP believes that this approach will permit a better focus on the more important sources of risk. It will also assist the risk manager in understanding and evaluating sources of risk that may provide the greatest benefit with risk mitigation activities.

> **Question 2:** Please comment on whether the exclusionary criteria discussed in *Chapters 4* and 6 appear to be reasonable. Can the Panel suggest other exclusionary criteria that should be considered?

Issue: National and Regional Exposures

The potential for people to encounter overlapping exposures to different pesticides will be influenced by many factors. One important consideration is the geographic effects and seasonal uses of pesticides. Thus, a framework is proposed for assessing different pathways of exposure that are essentially driven by these considerations. OPP believes that the dietary (food) pathway should be approached on both a national and regional scale to account for both national and regional distribution of treated commodities. However, the Office believes that residential and dietary (drinking water) pathways are more appropriately dealt with on a regional or multi-state basis, since there is no single, national source of drinking water; and residential exposures may be driven by regional use patterns.

> **Question 3:** Please comment on whether the concept of developing a series of cumulative assessments on a geographic scale for different pathways is reasonable.

Issue: Case Study

Cumulative risk assessment is at an early stage of development. Furthermore, there is very limited experience in conducting such assessments. Thus, the development of case studies using actual data are critical to refining useful and practical guidance, and to identifying future research and testing needs. OPP is taking a step wise approach to the development of such case studies by starting with simple examples and moving toward more complex situations.

Attached is a case study that uses actual dietary (food) residue data on three pesticides and evaluates only a single pathway/route/duration of exposure. Certain assumptions were made in the case study. In single chemical exposure assessment, for example, nondetects are assumed to be one half the level of detection and composite samples are decomposited. In this case study, for illustrative purposes, nondetects were assumed to be zero, the samples were not decomposited, and surrogate data were not used.

> **Question 4:** Given that an important goal of the cumulative assessment is to reliably determine sources of concern from a multi chemical exposure, please comment on to what extent is it appropriate to apply standard practices and assumptions used in single chemical assessments.