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Background and Issue Paper for the Thursday, September 23, 1999, Session 4

Proposed Guidance on Cumulative Risk Assessment of Pesticide Chemicals: Issues Pertaining to Hazard and Dose-Response Assessment

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BACKGROUND

The passage of the Food Quality Protection Act (FQPA) in 1996, which amended the Federal Insecticide Fungicide and Rodenticide Act and the Federal Food Drug and Cosmetic Act as they apply to the regulation of pesticides in the U.S., has prompted many changes in the way risk assessment for pesticides is to be conducted. Among the mandated changes is the necessity to consider "...available information concerning the effects of cumulative exposure to pesticides and other substances sharing a common mechanism of toxicity..." Cumulative risk has been defined in a number of ways. For purposes of implementation of FQPA, cumulative risk assessment encompasses the integration of the hazard potential of non-occupational exposures in the aggregate (i.e., multi-pathway and route) and focused only on those pesticide and other substances which share a common mechanism of toxicity.

The Office of Pesticide Programs (OPP) of the U.S. Environmental Protection Agency is developing a technical guidance document entitled *Proposed Guidance on Cumulative Risk Assessment of Pesticide Chemicals.* Because cumulative risk assessment is in its infancy, OPP views cumulative risk assessment and the articulation of guidance for conducting such assessments as a developing area and a work-in-progress that will require continued method and tool building as well as policy development. Thus, any guidance develop must be flexible in order

to accommodate a variety of situations including the acquisition of new knowledge.

The presentation to the FIFRA Scientific Advisory Panel (SAP) will provide an overview of the hazard and dose response components, Chapters 3 and 5, of the OPP's proposed technical document, as well as a case study illustrating the elements of this part of the guidance. OPP considers the hazard and dose-response chapters sufficiently developed for comment. The exposure component of this document (i.e., Chapters 4 and 6) is still under preparation, and thus not ready for comment at this time. It is planned that the exposure portion of the guidance document will be presented to the SAP for review in December 1999. The focus of the December 1999 meeting will be on the exposure elements of the guidance. When completed, this guidance will be used by OPP for conducting cumulative risk assessments for those chemicals that are toxic by a common mechanism.

The cumulative risk assessment guidance will build on other guidance documents (already completed or ongoing) which articulate relevant approaches and methodologies for the cumulative risk assessment process. Two key documents have been to the SAP for comment and include:

- *Guidance for Identifying Pesticide Chemicals and Other Substances Which Have a Common Mechanism of Toxicity*: final document issued February 1999. This document describes the approach that OPP will use for identifying and initially grouping pesticides and other substances that cause common toxic effects by common mechanisms of toxicity. This document presents: An interpretation of common mechanism of toxicity with respect to making a determination of safety under FFDCA, as amended by FQPA; the specific steps that will be taken for identifying mechanisms of toxicity of pesticides and other substances that cause a common toxic effect; the types of data and their sources that are needed to make such judgments; how these data are to be used in reaching conclusions regarding commonality of mechanism(s) of toxicity; and, the criteria for initially categorizing pesticides and other substances for the purpose of conducting cumulative risk assessments. <u>It is important to note that after grouping chemicals by a common mechanism, additional hazard analyses and exposure analyses are needed to determine which chemicals from the common mechanism group should be included in the final cumulative risk assessment.</u>

- *Guidance for Performing Aggregate Exposure and Risk Assessments*: draft document was presented to the SAP for review February 1999. This document describes the approach that OPP will use to determine risk resulting from all pathways and routes of exposure to a single pesticide chemical. The cumulative risk guidance document will refer to the relevant methods and tools from the aggregate guidance document and focus on the unique aspects of cumulative exposure assessment. <u>It is important to note that one cannot simply sum the aggregate risks of individual chemical to obtain the cumulative risk for a group of chemicals because of different linkages between or among multiple chemical</u>

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exposures.

In general, OPP's cumulative risk guidance document is organized in a manner consistent with the National Academy of Sciences' risk assessment paradigm: Hazard Identification, Dose-response Assessment, Exposure Assessment and Risk Characterization (NAS, 1983& 1994). Cumulative risk assessment will be iterative in nature with the hazard (toxicity) assessment and exposure analyses (those multi-pathway, multi-route exposures from food, drinking and non-occupational exposures (e.g., those which might occur around the home) being interactive processes. Also, some modifications will be needed which reflect the shift from single chemical assessment to multiple chemical assessment. It is the shifts in the traditional hazard assessment paradigm as well as other issues for which OPP seek input from the SAP at this time:

ISSUES FOR THE SCIENTIFIC ADVISORY PANEL

[Please note that the relevant chapters of the technical guidance document, which OPP is seeking comment on at this time, are referenced for the below issues and questions]

Issue 1. Selection of Chemicals for a Cumulative Risk Assessment

Chapter 3 of the technical document emphasizes that all chemicals which have been initially grouped by a common mechanism of toxicity are not necessarily appropriate for inclusion in a final cumulative risk assessment. There are both hazard and exposure considerations.

> **Question 1-1:** Does *Chapter 3* clearly present additional hazard considerations that are needed to determine those chemical members which should be included in the final cumulative risk assessment?

Issue 2. Selection, Normalization, and Adjustment of the Point of Departure (POD) for Cumulating the Common Toxicity

As discuss in *Chapter 5.1-5.2*, a point of departure (i.e., a dose or exposure metric corresponding to some fixed marker of toxicity) must be selected to sum the combined exposure for the chemical group. To the extent possible, the PoDs should reflect a uniform measure of the common toxic effect, which is produced by a common mechanism of toxicity, across the chemical members. A benchmark dose approach is preferred to derive the PoDs for each chemical member.

> **Question 2.1:** In single chemical assessments, the Agency uses the upper bound estimates (i.e., the lower confidence limit on dose) for both cancer (called LED) and noncancer benchmark dose assessment. The concern has been raised, however, that summing upper bounds of multiple compounds may result in a exaggerated risk.
>
> Does the SAP agree that it is more appropriate to sum the central estimates (i.e., ED) rather than combining upper bounds in the cumulative risk assessment of multiple chemicals?

Issue 3. Incorporation of Group Uncertainty Factors

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As discussed in *Chapter 5.3*, traditionally one or more of the uncertainty factors are used to derive a Reference Dose (RfD) for a single chemical. There are five uncertainty factors that are considered to account for the following extrapolations: LOAEL to NOAEL (UF_L), subchronic NOAEL to chronic NOAEL (UF_S), experimental animal to humans (UF_A), interhuman variation (UF_H), and incomplete database to complete database (UF_D). It is proposed that the extrapolations of LOAELs to NOAELs or subchronic NOAELs to chronic NOAELs be applied as adjustments of a chemical's PoD before estimating the cumulative risk. These adjustments are meant to be based on some scientific data that permits a reasonable extrapolation or interpolation rather than applied solely as a science policy default decision. It is further proposed that other traditional uncertainty factors be treated as a composite "group uncertainty factor" that pertains to the chemical members as a whole. Thus, the intra- and inter-species UFs and the database completeness UF are applied as a composite group factor after cumulative risk is estimated (i.e., not before on each chemical's PoD). The rationale of the group UF is based on the premise that these factors should be viewed for the group as a whole given that all the chemicals are anchored by a common toxic effect produced by a common mechanism. Additionally, one is not simply evaluating risk in the context of a single chemical data base but the database for all the chemicals in the assessment. The advantage of a group uncertainty factor is that if allows one to separate the resulting risk that is based on scientific adjustments from judgmental policy decisions to account for uncertainty. It is also further proposed that an FQPA Safety Factor decision be applied for the group rather than on individual pesticides.

> **Question 3.1:** Does the SAP agree with this approach?, and does the technical document clearly describe the rationale and guidance for the implementation of chemical specific adjustment factors and of a group UF for the cumulative risk assessment? Has the document clearly presented the limitations and strengths of the group UF approach?

Issue 4. Methods for Estimating the Cumulative Toxicity

As discussed in *Chapter 5.6*, one of the steps in the cumulative risk assessment process will be to select a method to cumulate dose or exposures. This method will serve to normalize differences in the toxic potencies among the chemicals in the cumulative assessment. Precedence in the Agency's 1986 and revised 1999 *Guidance for Conducting Health Risk Assessment of Chemical Mixtures* describes several techniques for estimating risk to multiple chemicals. The cumulative guidance focuses on the component-based dose addition methods used in the EPA's chemical mixture assessment guidance document. Two methods, a margin-of-exposure approach and an approach using relative potency factors, are presented.

> **Question 4.1:** Does the SAP agree that both methods are valid to consider for estimating cumulative risk associated with exposures to chemical that cause a common toxic effect by a common mechanism? Has the document clearly described these two approaches and their strengths and limitations? Are there other methods that OPP should consider?

> **Question 4.2:** It is anticipated that most mechanisms of toxicity encountered currently will be nonlinear dose-response relationships. Nevertheless, for mechanisms of toxicity consistent with linear dose-response relationships, does the SAP agree that using the

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relative potency factor approach by summing the slopes of the dose-response curves is an appropriate method? If not, what methods would the SAP recommend for low-dose linear extrapolations of risk?

Issue 5. Case Study

In *Appendix A* of the technical guidance document is a case study on organophosphorus pesticides.

Question 5.1: Does this case study provide a clear example of the application of the hazard and dose-response elements of the draft guidance?

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