

US EPA ARCHIVE DOCUMENT

*End Point Selection and Determination of Relative
Potency in Cumulative Hazard
and Dose-Response Assessment:
A Pilot Study of Organophosphorus Pesticide
Chemicals*

Presented by:

Dr. Kit Farwell, Dr. Anna Lowit, and Dr. Robert Fricke
Health Effects Division
Office of Pesticide Program
US Environmental Protection Agency
Washington DC

To the:

FIFRA Scientific Advisory Panel
Arlington, Virginia
September 27, 2000

BACKGROUND

The Food Quality Protection Act (FQPA) of 1996 directed EPA to conduct cumulative risk assessments on pesticides that share a common mechanism of toxicity. To solicit scientific peer review on the principles and approaches for conducting cumulative risk assessments, the Agency has submitted this pilot study to the Scientific Advisory Panel (SAP) for review.

The following case study demonstrates the application of the principles for conducting a cumulative hazard and dose-response assessment. It does not address the exposure component or risk characterization of cumulative risk assessment. In this case study, 24 organophosphorus pesticides that exert their toxic effects by a common mechanism of toxicity were evaluated. The selection of a common endpoint and determination of each chemical's relative potency are demonstrated. This project follows the general approaches and steps for determining the accumulation of common hazard set forth in the *Guidance on Cumulative Risk Assessment of Pesticide Chemicals That Have a Common Mechanism of Toxicity* (USEPA June 2000).

This analysis is not intended to represent a cumulative risk assessment of

organophosphorus pesticides for regulatory purposes. Although this pilot analysis is based on actual data, the organophosphorus pesticides have been given code names.

ATTACHMENTS

☐ Document for Review with Respect to Charge-

EPA September 5, 2000 Draft entitled: *End Point Selection and Determination of Relative Potency in Cumulative Hazard and Dose-Response Assessment: A Pilot Study of Organophosphorus Pesticide Chemicals*.

☐ Background Materials -

US EPA -Draft Cumulative Risk Assessment Policy. Summary: This proposed guidance was reviewed in September and December, 1999 by the FIFRA Scientific Advisory Panel (SAP) (See <http://www.epa.gov/scipoly/sap/1999/september/finalrpt.pdf>). On June 30, 2000, availability of the OPP draft guidance document for public comment was published in the *Federal Register* (<http://www.epa.gov/fedrgstr/EPA-PEST/2000/June/Day-30/6049.pdf>).

US EPA Guidance for Establishing a Common Mechanism of Toxicity for Use in Combined Risk Assessment. Summary: This document addresses a proposed approach to determining whether two or more pesticide chemicals are acting by a common mechanism of toxicity. The Food Quality Protection Act of 1996 stipulates that EPA perform a combined risk assessment for chemicals acting by a common mechanism of toxicity.
http://www.epa.gov/oppfead1/fqpa/SAP/criter_4.htm

CHARGE AND QUESTIONS FOR THE FIFRA SCIENTIFIC ADVISORY PANEL

Based on a review of the pilot analysis of 24 organophosphorus chemicals and the issues (Section V) described in the paper, *End Point Selection and Determination of Relative Potency in Cumulative Hazard and Dose-Response Assessment: A Pilot Study of Organophosphorus Pesticide Chemicals*, OPP seeks comment and advice from the FIFRA Scientific Advisory Panel on the following questions:

- Question 1** For most compartment and sex groupings, there were one or more chemicals for which multiple studies could be used to calculate an ED 50. (See Figures 2, 3, 5, 6, 8, and 9.) Please comment on the criteria OPP used to select the “representative study” from among the available studies available for a specific chemical to calculate the ED50 for that chemical, compartment, and sex.
- Question 2** There will be situations for some chemicals in which data are lacking for the critical measurements, in a certain species or sex, or for a certain route of exposure. The lack of data may be because critical measurement(s) simply were not measured or because data are considered to be of poor quality.
- Q2.1** We would like the panel’s view on the use of surrogate data as a substitute for the lack of appropriate data. To what extent should surrogate information be used to determine a chemical’s relative potency?
- Q2.2** How should situations be handled where an ED₅₀ can be determined for many of the chemical members but cannot be determined for a few members? We would like the Panel’s view on the use of NOAELs as substitutions for ED₅₀s for points of comparison.
- Question 3** We would like the Panel’s view on the relative importance of the factors discussed in the paper for selecting an index compound.
- Question 4** We would like the panel to comment on the log dose-probit analysis used to extrapolate the ED₅₀s for the chemicals evaluated in this pilot.

Question 5 For this group of chemicals, OPP has sufficient data to calculate relative potency factors by the oral route for six different compartment/sex groups. Relative potency factors could be calculated by use of a single compartment/sex or by compiling data across compartment/sex groups.

Q5.1 If the Panel favors a single compartment/sex, please comment on the criteria that should guide the choice of a compartment/sex group.

Q5.2 It is proposed in this pilot analysis, that data could be compiled across different studies to provide more confidence in the determination of relative potency. In establishing an effective dose (e.g., ED₅₀), to what extent should one compile data for each chemical of interest within or across different measures and/or studies? What are important criteria to consider when compiling data?

Question 6 Dose addition is considered an appropriate default approach to cumulative risk assessment. The mathematical definition of dose-addition requires a constant proportionality between the effectiveness of the chemicals being considered. It is anticipated that extensive dose-response data will not be available for many chemicals. Please comment on the approach taken to evaluate parallel dose-response curves. Please comment on how rigorous an analysis is needed to evaluate the assumption of parallel dose-response curves.

Question 7 How does one handle a response for a chemical that displays a different slope (i.e. an outlier)? Examples were demonstrated in this pilot analysis where one or a few chemicals of the common mechanism group exhibited pronounced species, sex, or compartment differences from the majority of chemicals.