Part I.

Preliminary OP Cumulative Risk Assessment

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A. Introduction

The Food Quality Protection Act of 1996 significantly amended the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) and the Federal Food, Drug, and Cosmetic Act (FFDCA). One of the major changes is the requirement that EPA consider risk posed by pesticides acting by common mechanism of toxicity.[1] For such groups of pesticides, EPA's Office of Pesticide Programs has treated cumulative risk, under FQPA, as the risk of a common toxic effect associated with concurrent exposure by all relevant pathways and routes.

Since the enactment of the FQPA, the EPA Office of Pesticides Programs (OPP) has been working to develop new methodologies in a number of risk assessment areas. The several steps necessary to present this Preliminary Risk Assessment for Organophosphorus Pesticides were development of approaches for grouping chemicals by a common mechanism of toxicity (USEPA, 1999a), conducting aggregate (USEPA 1999c and 2001d) and cumulative risk assessments (USEPA 2000a and 2001a). At each major step in development OPP consulted with the FIFRA Science Advisory Panel (SAP) to seek expert review, advice and recommendations. We held several external review meetings with the SAP and asked for comment on our approaches to grouping chemicals based on common mechanism of toxicity, grouping chemicals for the purpose of cumulative assessment, improved methods for exposure assessment, approaches to aggregating food, drinking water and residential exposure and proposed models for combining these exposures. We also held several meetings with the FQPA Federal Advisory Committee Act (FACA) Groups of stakeholders (public interest groups, state agricultural agencies, pesticide industry representatives, growers, USDA and others) to present our methodologies as they were developed, and to seek comments and recommendations. All of the new science policies which are a foundation of this assessment were proposed for public comment. The work to develop the methodology was completed with the publication of the Revised Guidance Document for Cumulative Risk Assessment USEPA 2001a). The document was proposed for public comment on June 30, 2000 (65 FR127:40644-40650). The SAP and public comments were reconsidered and the Guidance was revised in December, 2001.

Organophosphorus pesticides were assigned priority for tolerance reassessment early during the process of FQPA implementation. OPP considered whether this group of pesticides caused common toxic effects by a common mechanism of

[1] For details see The Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), 7U.S.C. §§ 136 et seq., and Federal Food, Drug, and Cosmetic Act (FFDCA) 21 U.S.C. § 346a.

toxicity using EPA's *Guidance for Identifying Pesticide Chemicals and Other Substances That Have a Common Mechanism of Toxicity* (USEPA, 1999a). The inhibition of acetylcholinesterase was a focal point given that most organophosphorus pesticides cause this response as their critical and common effect. When acetylcholinesterase is inhibited, acetylcholine accumulates and cholinergic toxicity results due to continuous stimulation of cholinergic receptors throughout the central and peripheral nervous systems which innervate virtually every organ in the body. Cholinergic effects associated with exposures to OP pesticides have been found in both humans and animals.

Office of Pesticides Programs asked the ILSI Risk Sciences Institute (RSI) to convene a workgroup of expert scientists to examine whether the organophosphorus compounds act by a common mechanism of toxicity (Mileson et al., 1998). The workgroup concluded that the cholinesterase inhibiting OP pesticides should be considered to act by a common mechanism of toxicity. OPP presented its draft document on a common mechanism of toxicity for OP pesticides to the SAP in March 1998. SAP agreed that acetylcholinesterase inhibition provides a sufficient basis for determining that a common mechanism exists for the purpose of grouping these pesticides.

OPP proceeded with the methodology and risk assessment development in a step by step process. The approach to the risk assessment was evaluated using a case study of three organophosphorus pesticides. That assessment was reviewed by the SAP (September and December 1999 see FIFRA SAP 2000a,b), who recommended that OPP proceed with a more comprehensive case study. OPP developed the hazard, dose-response and exposure assessment for twenty four OP pesticides and brought it to the SAP for comment in September and December of 2000 (FIFRA SAP 2001a,b). Based on the comments, the hazard and dose-response assessment was revised and again reviewed by the SAP in September of 2001(FIFRA SAP 2001c). The SAP was very supportive of the approach, calling it both 'skillful' and 'creative.' The recommendations made by the September 2001 SAP have been addressed in this Preliminary Risk Assessment.

The exposure assessment of the OP pesticides presented here incorporates probabilistic approaches in all pathways considered: food, drinking water and residential/ non-occupational. The methods and the models used were reviewed by the SAP and their recommendations for changes incorporated.

The hazard and dose-response, drinking water, food and residential exposure assessments for the organophosphorus pesticides were presented at three separate technical briefings to the public; in August, October and November of 2001. A technical briefing is planned for the entire Preliminary Risk Assessment in January of 2002. The Science Advisory Panel will review the Preliminary Assessment at a four day meeting, starting February 5th, 2002.

The Preliminary Risk Assessment for the organophosphorus pesticides presented here is a first time that the Agency has assessed risk combining multiple sources of exposure for multiple chemicals acting via a common mechanism of toxicity. The general methodology and the specific approach have been under development for five years and have been subject to extensive peer review and public comment. The assessment is a state of the art approach. As the science of risk assessment develops, future cumulative risk assessments will be further refined to take advantage of advancements such as biological and pharmacokinetic modeling, and two dimensional Monte Carlo analysis.

Cumulative Risk Assessment is a complex analysis and OPP needs to emphasize that the results are not a collection of numbers or bright lines. Quantitative methods have been used throughout the analysis but the results need to be interpreted with a full understanding of the assumptions made and the uncertainties introduced by making these assumptions. As the regulatory managers and the stakeholders look for guidance in reading the document, it is especially important to consider the Risk Characterization Chapter of the Risk Assessment. It is that risk characterization that will form the starting point in discussions between the risk assessors and risk managers. Between the time of the release of this Preliminary Assessment and the technical briefing in January and the SAP review in February, OPP will continue to conduct uncertainty and sensitivity analysis to provide additional information to the risk managers and the stakeholders.

Following the release of the Preliminary OP Cumulative Risk Assessment on December 3rd, 2001 the Agency will open a public comment period that will run until March 8, 2002. For information on submitting comments, contact: Karen Angulo at 703/308-8004 or angulo.karen@epa.gov.