October 30, 1998

A FRAMEWORK FOR ADDRESSING THE NINE KEY SCIENCE POLICY ISSUES

Introduction

Although the Agency has always sought independent review and public participation on a wide variety of issues related to the implementation of the Food Quality Protection Act of 1996 (FQPA), last summer EPA decided that the implementation would benefit from a more thorough process of notice and comment on major science policy issues. As directed by Vice President Albert Gore, EPA has been working with the U.S. Department of Agriculture (USDA) and a new subcommittee of NACEPT, the Tolerance Reassessment Advisory Committee (TRAC), chaired the by EPA Deputy Administrator and USDA Deputy Secretary, to address FQPA issues and implementation. Over the course of its five meetings last summer, TRAC identified nine science policy issues it believed were key to the implementation of FQPA and tolerance reassessment. These issues are provided below along with the corresponding documents that will address them. Each of these documents will be announced in the *Federal Register* for public comment. On October 29, 1998 this Framework with more detailed discussion and general information on the process for addressing addressing the policy issues was announced in the *Federal Register* (63 FR 58038-58045).

The Nine Science Policy Issues

Science Policy Area	Discussion of the Science Policy Area and Associated Issues	Guidance to Be Issued	Timing for Revised Product
① Applying the FQPA 10-Fold Factor	FQPA requires EPA to use an additional 10-fold factor when assessing a pesticide's dietary risk to take into account potential pre- and post-natal developmental toxicity and completeness of the data with respect to exposure and toxicity to infants and children. The additional FQPA factor may be reduced or removed only if, on the basis of reliable data, the factor used will be safe for children. In asessing risk, the Office of Pesticide Programs (OPP) applies the 10-fold factor unless it determines, based on a weight-of-the-evidence evaluation of all reliable, available information on toxicity and exposure, that it should be modified. The main science policy issue is the establishment of appropriate, clear, and transparent criteria for retaining or modifying the 10-fold factor. Another closely related issue is determining what constitutes a complete and reliable database for toxicology and exposure data to assess risks to children. In part, to address these issues, an intra-agency workgroup is looking at general considerations regarding the FQPA factor decisions such as: establishing procedures for consistency and and documentation; ensuring the adequacy of the data set for decision-making; and establishing criteria for retaining or modifying the FQPA factor. Two documents will be produced.	The Intra-agency workgroup is drafting guidance that will be completed and available for comment in February 1999. This document is intended to provide broad-based guidance regarding FQPA factor decisions.	July 1999
		A working level “Standard Operating Procedure” has been drafted and will be issued for public comment in February 1999. This document is intended to be guidance for Agency scientists.	July 1999

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② Dietary Exposure Assessment – Whether and How to Use "Monte-Carlo" Analyses	EPA assesses dietary exposure to pesticides in raw and processed foods using two distinct pieces of information: the amount of pesticide residue that is present in and on food (i.e., the residue level) and the types and amounts of food that we eat (i.e., food consumption). The residue information comes from the numerous crop field trials and other sources (such as monitoring data) where the amount of pesticide on a given commodity is measured. Consumption information comes from USDA surveys of what people eat. In the past, EPA has used the Dietary Risk Evaluation System (DRES) to combine the residue and food consumption information with data on a pesticide's toxicity to calculate acute and chronic dietary risk. This deterministic model calculates a single value (sometimes referred to as a point estimate) for all the residues for a given commodity. Over the last few years, a different technique has been applied to estimating acute dietary exposure - a probabilistic evaluation called Monte-Carlo analysis. A probabilistic analysis uses the entire range of data from the numerous crop field trial studies or other sources to estimate the distribution of exposure to the residues for the population of concern. This technique allows for a more realistic estimate of exposure. There are three issues associated with the use of probabilistic techniques: (1) Probabilistic analyses often exhibit a level of uncertainty at the extremes of the distribution. This uncertainty makes it difficult to judge if the results reflect an accurate estimate of risk, or an overestimate or underestimate of risk. (2) EPA needs to make decisions that are appropriately protective of larger numbers of people, especially children, necessitating estimates of 'high-end' exposures (e.g., 99.9th percentile). (3) There is a concern over statistical treatment of data that are inputted into the Monte-Carlo model. For example, how USDA's high-end consumption estimates combine with the use of a 99.9 percentile output needs to be resolved. To resolve these issues, EPA has (among other things) been working with USDA and has sought the advice of the FIFRA Scientific Advisory Panel. As a result, three documents will be issued.	A draft document entitled "Guidance for Submission of Probabilistic Exposure Assessments to the Office of Pesticides Programs' Health Effects Division" will be issued in October 1998. This document is intended to be used chiefly by persons conducting probabilistic human health exposure assessments for purposes of registration or reregistration of pesticides.	March 1999
		A draft policy paper exploring probabilistic techniques and the 99.9th percentile will be issued in December 1998. This paper will provide the rationale for selection of the regulatory percentile.	May 1999
		A paper is being drafted on using composite residue data (e.g., monitoring data) to estimate exposure that would occur from single serving food items. A draft will be issued in April 1999. This piece is intended to help address a technical statistical issue.	September 1999

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<tr><td rowspan="3">③ Exposure Assessment - Interpreting "No Residues Detected"</td><td rowspan="3">Pesticide manufacturers (i.e., registrants) seeking to have a tolerance established are required to submit data on the level of pesticide residues that remain in or on food. Often, instrumentation in the laboratory is not able to detect any residue below a specified level, which is called the 'limit of detection' or LOD. However, even though the laboratory instrumentation cannot detect a residue, a residue may be present, at some level below the LOD, which may still present a potential concern to human health. Current EPA policy is to assume that non-detectable residues remain on treated commodities at ½ LOD.

How the Agency should interpret non-detectable residues and how they should be incorporated into risk assessments presents two issues: (1) The Agency's method for incorporating non-detectable residues into its risk assessment (½ LOD) may either overestimate or underestimate risk depending on the actual distribution of data below the LOD. (2) There are potential trade and public health impacts if the Agency cancels a use, and subsequently revokes the corresponding tolerance in the U.S., based upon apparent unacceptable risks attributable in significant part to non-detectable residues, while other countries allow that use.

To address these issues, one EPA workgroup is examining approaches that could allow EPA to determine that there is "no reasonable expectation of finite residues" while another is looking at the availability of better statistical methods for assessing data sets that contain both detectable and nondetectable residues. Three papers will be issued.</td><td colspan="2">A paper entitled "Threshold of Regulation" will be issued in November 1998.

This paper will delineate when a non-detectable residue is truly insignificant; it will allow the Agency to focus its resources on evaluating exposures to pesticides at levels below the LOD for which there is potential risk of concern.</td><td>April 1999</td></tr>
<tr><td>A paper that will describe the rationale surrounding the use of ½ LOD. A draft will be issued in November 1998.</td><td rowspan="2">Both papers will will more closely examine the treatment of non-detectable residues. This will allow the Agency to better estimate dietary exposure.

Most likely, these will be combined into a single paper during the Agency's comment response period.</td><td rowspan="2">April 1999</td></tr>
<tr><td>A paper that will describe the use of statistical methods that can be used in situations where some of the residues are non-detectable. A draft will be issued in November 1998.</td></tr>
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④ Dietary (Food) Exposure Estimates	In assessing dietary exposure from pesticide residues in food, EPA starts out with the "worst-case" residue level, which is the tolerance. Tolerances are regulatory levels and are set to accommodate the highest residue level that may be found in crops at the farm gate. Crop field trials are used to determine the highest residue level that can result from maximum legal use of a pesticide. The actual residues on food are likely to be much lower, and may be virtually non-existent. Assuming that residues are present at tolerance level and that 100% of the crop is treated allows cost-effective decision-making in many cases where risks are low. In these cases, there may be no need for registrants to collect additional data or for the Agency to use resources to review additional data. Food exposure assessments can be improved with information on actual pesticide use, agricultural practices, processing practices, and actual or anticipated residues. There are several issues associated with the need for data to estimate food exposure more realistically: (1) Dietary risk estimates may be unrealistically high when such typical use practices have not been factored in. (2) Information on actual pesticide use may be available, but residue levels resulting from such use cannot be calculated without certain residue testing, modeling efforts, or bridging data to meld the guideline studies with actual usage information. (3) Monitoring data are not available for all commodities, resulting in use of significantly different data in risk assessments for different chemicals and/or foods, and high risk estimates for those pesticides and crops that lack monitoring data. EPA is working to resolve these issues. The National Pesticide Residue Database (NPRD) will be on-line soon and clarifying information is being developed. Two documents will be released along with use and usage matrices and better food consumption information for the general U.S. population and children.	A brief description of the NPRD and an 'umbrella' paper that will describe how OPP assesses acute and chronic exposure to pesticides in food and more importantly, where in the existing guidance one can find methods for doing such exposure assessments. Also, the umbrella paper will provide guidance on the residue data needed to go with the usage information. The NPRD description and a draft of the umbrella paper will be made available in December 1998. Both of these items are intended to provide the regulated and environmental communities with clarifying information on how the Agency assesses pesticide exposure from food.	April 1999
		EPA will complete matrices describing organophosphate use and usage on individual crops. These matrices present real-world information on pesticide usage and the pests which drive the usage, and are developed with support from USDA and the grower community.	December 1998
		Recently gathered USDA food consumption information for the general U.S. population is being 'translated' into a form EPA can use for dietary risk assessment. A peer review draft will be ready in April 1999. USDA is collecting supplementary food consumption data for children which EPA will translate.	June 1999 for the general U.S. population data and December 1999 for the child data.

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⑤ Dietary (Drinking Water) Exposure Estimates	EPA must aggregate exposures to a pesticide from both dietary sources (food and drinking water) and all non-occupational sources for which there is reliable information. There are two complementary methods for estimating concentrations of pesticides in drinking water: (1) Using direct measurements for pesticides in drinking water; and (2) Using model-based approaches for predicting potential drinking water exposure levels are based on screening models that predict pesticide levels in vulnerable groundwater and surface water. The latter approaches are generally believed to overestimate the concentration of pesticides in most drinking water sources, and hence, in some cases drinking water exposure may appear to present an unacceptable dietary risk even though actual risks to most people may in fact be lower. Several efforts are underway to address the problem that current screening models, particularly surface water screening models, do not well represent drinking water systems and may significantly overestimate residue levels in most drinking water sources. Three documents are under development – two will address some of the technical issues associated with developing drinking water models and one will provide guidance to reviewers who assess pesticide exposure from drinking water.	A draft policy on using the "reservoir scenario" instead of the "small field pond" scenario; and a change in the "drinking water level of concern" terminology. This will be issued in December 1998.	May 1999
		A revised policy on an approach to factoring the percentage of land surrounding a reservoir that is "cropped" into the screening level assessments. This will be issued in May 1999.	October 1999
		Procedural guidance for Agency scientists who assess drinking water exposure. The first iteration of this will be released in June 1999 and the second in December 1999.	1st iteration: November 1999 2nd iteration: May 2000
⑥ Assessing Residential Exposure	EPA must now include residential and other non-occupational exposures in the aggregate exposure assessments for pesticides. Generally speaking, residential exposure monitoring data have not been routinely required. Thus, EPA has been relying on existing monitoring, survey, and modeling data, including information on activity patterns, particularly for children, to estimate residential exposure to pesticides. Because highly specific residential exposure data are generally lacking and there is not wide undertstanding and acceptance of existing models and assumptions, several workgroups and task forces are working to generate data and improve methods for conducting residential exposure assessments. Two documents are being produced.	Residential Standard Operating Procedures, which provide standard methods for developing residential exposure assessments when data are limited. A draft document will be issued in December 1998.	May 1999
		A "plain english" paper on how the Agency assesses residential exposure. The purpose of this document is to provide the regulated and environmental communities with a description of how the Agency assesses exposure to pesticides that found in residential and public areas. A draft will be issued in December 1998.	May 1999
⑦ Aggregating Exposures from all Non-Occupational Sources	EPA must now aggregate exposures from all sources where there is available information. The current method for aggregating exposures uses simple addition; it does not account for the distribution of risks across the population, but provides only point estimates. Better methods that more accurately estimate aggregate exposure by looking at the range of risks across the population and population subgroups are being developed. Two documents are being developed.	A draft aggregate exposure guidance document will be issued in April 1999.	September 1999
		A Standard Operating Procedure for Agency scientists who assess aggregate exposure will be issued in April 1999.	September 1999

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⑧ How to Conduct a Cumulative Risk Assessment for Organophosphate Insecticides or Other Pesticides with a Common Mechanism of Toxicity	EPA is required to consider available information on the effects of cumulative exposure to the pesticide and other substances with common mechanisms of toxicity. To address the first part of this policy area – identifying chemicals with a common mechanism – the Agency has drafted guidance that describes the approach EPA proposes to use for identifying and categorizing pesticide chemicals that have common mechanisms of toxicity for purposes of assessing the cumulative toxic effects of such pesticides. With respect to cumulative risk, since there are currently no standard methods for doing cumulative risk assessment, EPA is pursuing an open, peer-reviewed process to develop approaches to cumulative risk assessment.	A document entitled, "Guidance for Identifying Pesticide Chemicals that Have a Common Mechanism of Toxicity for Use in Assessing the Cumulative Toxic Effects of Pesticides" was issued in the *Federal Register* last August.	January 1999
		Cumulative Risk Assessment guidance is being developed and will be issued in June 1999	November 1999
⑨ Selection of Appropriate Toxicity Endpoints for Risk Assessments of Organophosphates	Most organophosphate (OP) and certain carbamate insecticides exert their principal toxic effects by the mechanism of cholinesterase inhibition, which may lead to neurotoxicity. Measurement of cholinesterase levels in the blood or nervous system after exposure to OPs has become the most common endpoint used in risk assessments of this chemical class. Over the last several years, the Agency has engaged outside scientists and the regulatory community about how measures of cholinesterase inhibition should be used in risk assessments. EPA has also discussed more generally how these data should be viewed along with the other types of data in risk assessments. Two issues focused on were: (1) The role of blood measures in risk assessment since plasma and red blood cell cholinesterases are not part of the nervous system but they may be an indirect measure of what is occurring in the central and peripheral nervous systems; and (2) Whether plasma cholinesterase should be treated differently from red blood cell cholinesterase. In June 1997, OPP made a comprehensive presentation to the SAP on cholinesterase inhibition. The presentation included a literature review, a series of case studies, a summary of activities related to methods of cholinesterase measurement, and a proposed policy to use a weight-of-evidence approach considering all of the data that might result in the use of cholinesterase measures in plasma, red blood cells, or brain for defining critical effects and no-adverse-effects levels. In addition, EPA also asked the SAP about the feasibility of using measures of peripheral nervous system tissue to replace blood measures, which largely serve as indirect estimators of cholinesterase inhibition in the peripheral nervous system in animals. The positions contained in the paper presented to the SAP entitled, "Office of Pesticide Programs Science Policy on the Use of Cholinesterase Inhibition for Risk Assessments of Organophosphate and Carbamate Pesticides."	Guidance on the selection of appropriate toxicity endpoints for risk assessment of organophosphates is being developed. The SAP paper will be issued in October 1998 and the SAP's comments (with the Agency's response) will be available in the public docket.	March 1999