Attachment to Staff Paper # 26

FRAMEWORK FOR REFINING FQPA SCIENCE POLICIES

Detailed Considerations

✯*Indicates a 'new' issue; that is, an issue that resulted from FQPA implementation*.

① **SCIENCE POLICY AREA** ①: Applying the FQPA 10-Fold Safety Factor

Definition of the Issue. FQPA requires EPA to use an extra 10-fold safety factor 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. A different safety factor may be used only if, on the basis of reliable data, such a factor will be safe for infants and children.

✯ The Science Policy Issue:

☞ Establishing Clear and Transparent Criteria for Retaining, Reducing or Removing the 10-fold Safety Factor ☜

Approach in Risk Assessment:

What We've Been Doing. In assessing risk, the Office of Pesticide Programs **R**etains the additional 10-fold safety factor unless reliable information in the toxicity and exposure database indicates that it can be **R**educed or **R**emoved. Our decisions are based on the available toxicity data, which include the inherent toxicity of the pesticide and potential for increased susceptibility to children, together with the exposure data such as who is exposed, for how long, and how often through the diet, drinking water, and/or residential exposures to the pesticides. The following briefly summarizes the current approach.

As the law requires, we begin with the assumption that the additional safety factor applies, but we examine all reliable data to determine if it can be reduced or removed while still assuring the safety of infants and children. In making this determination, EPA considers the entire toxicity and exposure database, with particular attention given to neurotoxicity, developmental and reproduction, and developmental neurotoxicity studies. EPA also considers the potential exposure from foods and other sources.

1. First, if there is little or no exposure to children or women of child-bearing age, the factor is removed.

2. If there are significant exposures for infants and children, we examine all of the data we have on the pesticide and weigh the evidence to determine whether there is adequate protection for infants and children.

    - If we lack fundamental information on whether infants or children are likely to be more susceptible to the pesticide, we retain the safety factor unless and until the data are generated.

    - When a full toxicology database is available and there is concern for either increased susceptibility or potential neurological effects, the safety factor would be retained or reduced depending upon the nature and severity of the effects, and the exposure data.

    - If we lack fundamental information on whether infants and children are likely to be exposed at levels that could exceed our levels of concern, we would retain the safety factor unless and until we can be confident that safety of children is assured.

3. In some instances when OPP concludes that more studies are required for either the individual pesticide or a category of pesticides, OPP will evaluate the available studies and recommend to retain, reduce, or remove the safety factor while waiting for the new studies to be submitted.

Decision-making on the 10X factor starts in an OPP interdivisional committee composed of staff from across the office. The committee examines all the data and makes a recommendation to OPP management, which makes the final decision. After a recommendation is made on the safety factor, a determination is made about applying the factor to specific population subgroup(s) (e.g., young children, women of child-bearing years) and to specific types of risk assessment (acute dietary, chronic dietary, etc).

EPA has sought the advice of the FIFRA Scientific Advisory Panel twice on the various aspects of the 10-fold provision. They have been generally supportive but suggested that we improve clarity.

Issues Related to the Current Approach. There are three major issues: (1) what are the appropriate criteria for deciding whether the safety factor should be retained, reduced, or removed; (2) the need for improved consultation outside of OPP in decision-making; and (3) the need for improved clarity and transparency of our policy and process.

What We Are Doing to Address the Issue. Three major efforts are underway to address these issues. (1) In July 1998, the Agency updated the SAP on its progress in responding to the issues raised by the SAP in March on the HED draft guidance on the FQPA safety factor. (2) An Intra-Agency workgroup is addressing general considerations regarding safety factor decisions such as

procedures for consistency and documentation, as well as ensuring the adequacy of the data set for decisionmaking. This workgroup includes representatives of the Office of Research and Development, the Office of Children's Health Protection, as well as the Office of Prevention, Pesticides, and Toxic Substances. (3) OPP has completed a draft SOP addressing safety factor determination issues at the working level.

☞ What We'll Be Doing in the Interim. While evaluating the SAP comments, including the criteria that trigger developmental neurotoxicity studies, the Agency will continue to make decisions regarding the safety factor consistent with the guidance provided by the SAP, and using the working level draft SOP guidance, which is consistent with SAP conclusions. See *"Standard Operating Procedures for FQPA Safety Factor Committee," Draft, April 6, 1998* and *Presentation for FIFRA Scientific Advisory Panel by Office of Pesticide Programs, Health Effects Division on FQPA Safety Factor for Infants and Children* (Tab 1).

Summary of Current Assumptions. The 10-fold safety factor is not simply a matter of uncertainty but is also a way of assuring an extra measure of protection for infants and children in cases where special sensitivity or exposure is identified. In assessing risk, OPP assumes retention of the 10-fold safety factor unless, based on a weight-of-the-evidence evaluation of all reliable, applicable information on toxicity and exposure, it can be reduced or removed.

Products/Timing

EPA is currently working on the three efforts mentioned above, and will complete two final guidance packages from this and other information:

- a general guidance document, which includes the scientific basis for the 10X policy, and
- a working level guidance document, which will provide the process to be used by those who are working on 10X recommendations.

Completion of these draft documents is expected in December 1998. We will hold a workshop to discuss them in addition to releasing them for written comment. The documents will become final in March 1999 after a 30-day Notice and Comment period, and 30 days for incorporation of comments.

② **SCIENCE POLICY AREA** ②: Dietary Exposure Assessment – Whether and How to Use Monte Carlo Analyses and the 99.9 percentile issue

Definition of the Issue. EPA assesses dietary exposure 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). Traditionally, EPA has used the Dietary Risk Evaluation System (DRES) to combine the residue and food consumption information with toxicity to calculate acute and chronic dietary risk. Over the last few years a new technique has been developed: the use of a statistical evaluation called Monte-Carlo analysis.

Monte Carlo analysis uses the entire range of data from controlled field residue studies. DRES analysis typically uses only the tolerance level which is the regulatory level, and is slightly higher than the highest level found in controlled field studies. In both cases the exposure data currently used are still likely to be higher than actual exposure since residues are measured at the field rather than the point of consumption where residues are typically much lower. Monte Carlo assessment has the capability to use more realistic data, which would be more representative of residues actually consumed.

The Science Policy Issues:

☞ Given that Monte-Carlo analysis provides more accurate (realistic) estimates of exposure than the previous DRES analyses, what percentile of exposure should the Agency use for regulation (e.g., 99.9th percentile)? ☜

Approach in Risk Assessment:

What We've Been Doing. The targets for regulation are the 99.9th percentile of exposure for Monte-Carlo assessments, where more realistic residue information is available, and the 95th percentile for DRES assessments for which actual (or proposed) tolerance levels are used during risk assessment. However, as discussed in the Agency's Risk Characterization Guidelines, the uncertainties and degree of refinement in the risk assessments are also considered before making risk management decisions regarding a pesticide use.

This is done to ensure that risk is assessed over the entire range of possible exposure levels and to increase confidence that we are considering the risk experienced by as many people as possible. In practice, risk assessments done at the 99.9th percentile using more refined data frequently result in lower estimated risk than risk assessments done at the 95th percentile using less refined data.

Issues Related to the Current Approach. There are three issues associated with the current approach: (1) Monte Carlo analyses may overestimate or underestimate risks at the extremes of the distribution. (2) Disagreement exists regarding the most appropriate percentile of exposure to use for regulatory decisions (e.g., 99.9th percentile?). (3) There is concern over the statistical treatment of data inputs into the Monte Carlo model and how these combine with using a 99.9 percentile output, including the accuracy of USDA's high-end consumption estimates.

What We Are Doing to Address the Issue. The following steps have been taken to address these issues: (1) The Agency has taken draft guidance regarding how to conduct Monte Carlo analysis to the SAP for comments and is presenting its response to those comments at the July 1998 SAP meeting. (2) USDA is addressing the issues of accuracy of the reported high-end consumption. (3) The issue of the appropriateness of using the 99.9th percentile was taken to SAP; SAP comments are being considered. (4) In a related effort, the Agency is working on statistical methods for effectively using composite data to estimate exposure from single-serving-sized food items. (In Monte Carlo analysis, there is a problem with using composite data.)

What We'll Be Doing in the Interim. In the interim we will continue using our current policy, i.e., use of the 99.9th percentile of exposure for Monte Carlo analyses and 95th percentile for DRES analyses as the baseline for risk management decisions. See *"Guidance for Submission of Probabilistic Exposure Assessments to the Office of Pesticide Programs' Health Effects Division," Draft, February 6, 1998 (Tab 2).*

Summary of Current Assumptions. (1) Methods and data must be publicly available and methods must be transparent to be used for regulatory decisions. (2) The Agency will consider using data from a multitude of sources to further refine its assessments.

Products/Timing

SAP comments and related policy issues will be incorporated into the Monte Carlo draft guidance in October 1998. Final guidance will be issued in January 1999 following a 60-day Notice and Comment period and 30 days for incorporation of comments.

Development of statistical methods for use of composite data to estimate exposure from single-serving-size food items: Complete draft for 60-day public comment period in November 1998. Publish final version in March 1999.

USDA is reviewing its food consumption data to ensure accuracy. This process will be complete in October 1998.

③ **SCIENCE POLICY AREA** ③: Exposure Assessment – Interpreting "No Residues Detected."

Definition of the Issue. Under the requirements at 40 CFR 158.240, the pesticide manufacturers (i.e., registrants) are required to submit data on the level of pesticide residues that remain on food. Quite often, no residues are seen above the 'limit of detection.' That is, the instrumentation in the laboratory is not able to detect any residue below a specified level, which is called the 'limit of detection' or LOD. A typical LOD would be 0.01 ppm. 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. The LOD is generally lower than the "Limit of Quantitation" (LOQ). The LOQ is the lowest level that can be measured by the method. When EPA sets a tolerance for residues that are below the LOD, the tolerance is set at the LOQ for enforcement and compliance purposes.

The Science Policy Issue:

☞How should the Agency interpret 'non-detects'? How should 'non-detects' be incorporated into risk assessments?☜

Approach in Risk Assessment:

What We've Been Doing. There are two possibilities when no detectable residues are found: either the residues are for all practical purposes zero, or the residues exist at some potentially significant level less than the limit of detection. Other data (e.g., metabolism data) are used to determine which of these conditions exists. If residues are expected to be insignificant, the use is assumed to present no risk. If residues are potentially significant, although not detectable, EPA factors these into the exposure assessment not as a zero but as '½ the limit of detection' or ½ LOD. The LOD is the lowest level of residue that the analytical instrument can 'see' or detect. Use of ½ LOD in these cases is standard throughout most of the risk assessment community.

For all registered pesticides used on foods, EPA requires a number of tests to evaluate whether and to what extent the pesticide leaves residue in and on food.

- When tests show that the pesticide does not leave residues (usually in meat and milk), EPA makes a finding of "reasonable certainty of no finite residues" and does not treat such foods as containing residues for risk analysis purposes.

- When the tests show evidence that the food products do have residues of pesticide, EPA proceeds to set a tolerance.

Evidence of residues below the limit of detection would include:

- Detection with more sensitive methods than can be used for routine sampling.
- Detection through radio-labeling process.
- Evidence of biological and chemical uptake and other chemical properties likely to lead to residues.
- Detection of residues when higher rates are applied.

When there is reason to believe that residues are found in and on the food, but cannot be quantified with current methods, EPA sets the tolerance at the limit of detection by available, replicable methods.

When we believe that there are residues and that they are properly quantified at some level below the limit of detection, we make the simplifying assumption that such residues would appear in a normal distribution and that it is adequately protective to use the value at ½ the limit of detection to represent the actual residues. Of course, as methods improve and we are able to measure such residues directly, we would use those measurements.

We are considering ways to expand the category of situations where we believe that it is appropriate to reach the conclusion that there is no likelihood of residues, regardless of the limit of detection. Under these circumstances, EPA could set a tolerance of zero to provide for continued enforcement monitoring and periodic review of the appropriateness of the tolerance.

Issues Related to the Current Approach. Issues in dealing with non-detectable residues include the following: (1) Common sense suggests that if no residues are detected, there are no residues (i.e., “zero is zero”); explaining the issue of non-detectable residues leading to unacceptable risk calculations is difficult. (2) There are potential trade and market impacts (e.g., to growers) if the Agency assumes that there is risk associated with a use based on non-detectable residues and the use is canceled, while other countries allow the same use, and these crops are imported into the U.S. legally because residues cannot be detected. (3) The Agency’s method for incorporating non-detectable residues into its risk assessment (½ LOD) may lead to inaccurate estimates of risk. (4) A use could pose a significant risk even though residues are not detected.

☆ Although this is not a new issue, FQPA requirements to add risks from all sources (i.e., food, drinking water, and residential) and from all chemicals with a common mechanism of toxicity greatly magnifies the problem, showing much higher risks even when residues are all below the level of detection.

What We Are Doing to Address the Issue. The Agency has two workgroups addressing the above issues. (1) An EPA workgroup is working on a paper to further refine and broaden the definition of "no reasonable expectation of finite residues" as discussed in 40 CFR 180.6(a)(3). With sufficient data and clearer guidelines, uses whose residues are insignificant could be assumed to have no risk associated with them. This would also improve international harmonization. (2) Another Agency workgroup is examining the availability of better statistical methods for assessing data sets that contain both detectable and nondetectable residues.

What We'll Be Doing in the Interim. Based on available data, the Agency will continue to use the old "no expectation of finite residues" criteria, and make decisions regarding appropriate residues to incorporate into risk assessments accordingly. Non-detectable residues that do not meet this criterion will be incorporated into risk assessments as ½ LOD until better statistical methods are available. See *Residue Chemistry Test Guidelines, OPPTS 860.1000 (see section (e), Food Use/Non-Food Use Determinations)* and *Determining the Need for Tolerances in Livestock Commodities, October 30, 1997* (Tab 3).

Summary of Current Assumptions. A treated commodity with non-detectable residues will be considered for purposes of exposure assessment to contain residues at ½ the level of detection.

Products/Timing

Products include:

- a paper to better define "no expectation of finite residues" (i.e., when is zero actually zero?)
- a paper describing appropriate statistical methods for incorporating non-detectable residues into risk assessments (i.e., where zero may not be zero, what is the appropriate method for incorporating a value in the risk assessment?)
- a paper describing use of limit of detection versus limit of quantitation in dietary exposure assessment

These three papers will be released for a 60-day public comment period in October 1998, with final guidance to be issued in February 1999.

④ **SCIENCE POLICY AREA** ④: Dietary Exposure Estimates

Definition of the Issue. EPA assesses dietary exposure using two distinct pieces of information: the amount of pesticide residue that is present in or on food (i.e., the residue levels) and the amount and proportion of food that we eat (i.e., food consumption). In assessing dietary risk, EPA starts out with 'worst-case' residues, which are the tolerance level residues that we obtain from the crop field trials. Tolerances are regulatory levels, which are set slightly higher than the highest residue found in crop field trials.

We start with 'worst-case' residues because of resource considerations – if the risks are acceptable at this level, then there's no point in refining the residues. If risks are found to be unacceptable, then EPA starts refining the tolerance-level residues, using what we know about the actual residues we eat in our food ('dinner plate' residues) and the percentage of the acreage that gets treated. When available and appropriate, EPA uses monitoring data that more adequately reflect residue data nearer the point of consumption.

The Science Policy Issue:

☞ Risk assessment can be further refined with information on actual agricultural and processing practices such as range of post-harvest intervals, cooking and commercial processing studies, actual versus maximum application rates, and other related information, as well as with more comprehensive monitoring data for food and water. In addition, the Agency needs accompanying residue data for typical use rates to show that typical rates really do yield lower residues. EPA also needs updated food consumption information. ☜

Approach in Risk Assessment:

What We've Been Doing. (1) The Agency has been meeting with the registrants early in the reregistration process to obtain comprehensive and updated use information (these are called SMART Meetings). We've been using this information, including percent crop treated data, in cases where the information is available. EPA and USDA have and will continue to ask for use information from growers. (2) EPA recently acquired the capability to perform exposure assessments using state-of-the-art software and the most recently available USDA food consumption data (1989-91). The Agency also has acquired the ability to do Monte Carlo assessments. (3) The Agency has been working to complete the National Pesticide Residue Database (NPRD), a comprehensive database that will contain information about actual pesticide residues in foods.

USDA is currently supplementing the existing food consumption data by increasing the number of children and infants surveyed but this data will not be

available for around two years. EPA welcomes this effort and believes it will improve our ability to refine decisions on dietary exposure.

Dietary exposure assessments can be improved with information on actual pesticide use, agricultural practices, and processing practices. This type of information includes data on pre-harvest intervals, actual application rates, application frequency, cooking and commercial processing studies, and other related information, as well as with more comprehensive monitoring data for food and water. To estimate actual residue levels, the Agency also needs certain supporting residue data or procedures to translate or model residue data for typical use practices.

Assuming that residues are present at tolerance level and that 100 percent 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 data or for the Agency to use resources to review additional data.

USDA provides the Agency with extensive information on pesticide use, food consumption data, and pesticide residues. The USDA information and information from other sources is key to the preparation of realistic risk assessments. USDA and EPA work to ensure that the needed information is identified, collected, and used appropriately in the risk assessment. USDA and EPA have and will continue to obtain use information from growers. When the Agency meets with the registrants early in the reregistration process, this information is reviewed and supplemented, as needed. EPA recently acquired the capability to perform exposure assessments using state-of-the-art software and the most recently available USDA food consumption data (1989-91). The Agency has been working to complete the National Pesticide Residue Database (NPRD), a comprehensive database that will contain information about actual pesticide residues in foods.
The Agency has confidence in the existing food consumption survey and our ability to make sound decisions using the data it provides. As appropriate, EPA will review earlier decisions once the supplemental data becomes available.

FQPA directs the Secretary of Agriculture to collect improved pesticide residue data on foods highly consumed by children and infants. This is being done, in part, through the Pesticide Data Program, and the data will become part of the National Pesticide Residue Database.

The law also requires EPA to use available and reliable data when making risk determinations. Where Pesticide Data Program information has been generated, it is used to refine dietary risk assessments. Pesticide Data Program data, where available, also are used during reregistration of older pesticides.

Issues Related to the Current Approach. (1) Dietary risk estimates may be unrealistically high when typical use practices have not been factored in; (2) Monitoring data are not available for all commodities, resulting in use of

significantly different quality data in risk assessments for different chemicals, and unrealistically high risk estimates for those pesticides and crops that lack monitoring data. (3) Information on actual pesticide use may be available but residue levels resulting from this use cannot be calculated without certain residue testing or monitoring efforts.

What We Are Doing to Address the Issue. (1) The Agency is compiling a matrix of use/usage data, defining what data are important in refining dietary risk assessments. These matrices will be provided to growers, with a schedule of the chemicals to be assessed, so growers can provide information in a timely manner. Accompanying residue data are needed to permit the incorporation of typical use/usage data in risk assessments. (2) USDA is looking into a new food consumption survey which focuses more on foods consumed by infants and children.

What We'll Be Doing in the Interim. (1) Continue SMART meetings. (2) Accept and use data from use/usage matrix where residue data on typical use rates are available. (3) Use data from the National Pesticide Residue Database as available. (4) Use the most up-to-date dietary exposure assessment software, which contains most recent USDA food consumption data. See *"Acute Dietary Exposure Assessment," Office Policy, June 1996, Draft OPP Policy for the Use of Anticipated Residues of Pesticides in Foods for Use in Chronic Dietary Exposure Assessments (presented to SAP in June 1997)–Appendices are not provided; they are available on request due to number of pages, and Comparison of the features of the DRES and DEEM dietary risk software systems* (Tab 4).

Summary of Current Assumptions. When data are lacking for actual (i.e., dinner plate) residues, percent crop treated, etc., we assume that residues are present at tolerance level and that 100 percent of the crop is treated. Making these assumptions allows cost-effective decisionmaking in many cases where risks are low and there is no need for registrants to spend the money to collect data or the Agency to use resources to review data.

Products/Timing

The following products are expected:

- Completed NPRD (data field have been established; data input underway; prototype version of the database available on the Internet in July 1998; final version in October 1998)
- Completed Use/Usage matrices September - December 1998
- Updated USDA food consumption survey information–available to EPA in mid-1999
- Guidance for growers, states, and others collecting use information on the need for the information

⑤ **SCIENCE POLICY AREA** ⑤: Drinking Water Exposures

Definition of the Issue. Under the requirements of FQPA, in setting tolerances EPA must now aggregate exposures from all sources for which there is reliable information – typically from food, drinking water, and residential exposures. Before FQPA, risks were not aggregated, but were considered separately for each of these sources. If data were not sufficient for one of the exposure sources (e.g., residential exposure), this lack of data would not typically affect a tolerance decision for oranges. The FQPA requirement for aggregation of exposures for tolerance setting requires EPA to consider all three sources of exposure. However, the pesticide program in some cases does not have an ideal database reflecting pesticide residues in drinking water. Available models generally are believed to overstate the drinking water exposure level, and when aggregated with exposures from food and residential uses, in some cases result in unacceptable estimated risks even though actual risks may in fact be acceptable.

☆ The Science Policy Issue:

☞ Obtaining drinking water data and developing models appropriate for dietary risk assessment. ☜

Approach in Risk Assessment:

What We've Been Doing. The Agency begins its assessment by evaluating studies required from registrants to define where the pesticide moves in the environment after it is applied, what compounds are formed as it breaks down, and how long it and its breakdown products stay in the environment. Data from these studies are used in simulation models that use conservative (health-protective) assumptions to estimate pesticide residues in vulnerable ground and surface water. (Vulnerable means shallow groundwater under sandy soils for groundwater and a small water body at the edge of a treated field for surface water.) The models used include GENEEC and PRZM/EXAMS for surface water residue estimates, respectively, and SCI-GROW to estimate ground water residues.

These estimates are then compared to human health levels of concern. The simulation models are screening tools. Pesticides that pass the screen do not require further drinking water evaluation. If the screening estimates are higher than human health levels of concern, EPA evaluates data from USGS, states, and other sources to try to provide a more realistic estimate. However, for many pesticides, EPA does not have data that fully characterize the nature and magnitude of drinking water contamination. Where data exist, EPA selects a value that is on the high end of the measured values, but not necessarily the

highest reported value. This selected value is then incorporated in the risk assessment.

We take into account the weight of all available evidence and we base any final regulatory decisions, whether for new or existing chemicals, only on a reasonable protective estimate of exposure from any source, not on worst-case or artificially high estimates which might be used for screening purpose. EPA has drafted an interim Standard Operating Procedure that describes this process.

Issues Related to the Current Approach. Current screening models may significantly overestimate residue levels in drinking water.

What We Are Doing to Address the Issue. EPA has several efforts underway: (1) The International Life Sciences Institute (ILSI) is organizing a workshop that will include participation from scientists with expertise in fate, transport, and occurrence of pesticides in ground and surface water. The workshop will be reviewing methods for estimating drinking water exposure and for data and model development for probabilistic aggregate exposure assessment; (2) EPA presented a proposed reservoir scenario as a replacement for the farm pond model and OPP's preliminary evaluation of watershed-scale models, including ACPA's regression approach at the July Scientific Advisory Panel (SAP) meeting. This new reservoir scenario uses an actual drinking water reservoir as part of the surface water modeling approach. At that point, the Agency will no longer use a farm pond even for its screening-level approach to drinking water. The farm pond "scenario" was used only for screening-level evaluations. (3) Continue to update the interim HED guidance as major milestones (e.g., SAP input) are met.

What We'll Be Doing in the Interim. Continue using our screening tools and available drinking water monitoring data. Move to use of newer models as soon as available. See *"HED SOP 97.1: Interim Guidance for Conducting Drinking Water Exposure and Risk Assessments," December 2, 1997* and *OPP's Interim Approach for Addressing Drinking Water Exposure in Tolerance Decisionmaking, November 1997* (Tab 5).

Summary of Current Assumptions. Assume risks are acceptable if pesticide passes conservative screen.

Products/Timing

Three products will be completed:

- Following resolution of SAP comments on the new water model methods, the policy will be published in November 1998 for a 60-day Notice and Comment

period, followed by 30 days for incorporation of comments and completion of the final document in February 1999

- Interim HED Standard Operating Procedure--update following receipt of SAP comments (March 1999) and later as needed.

- In addition, EPA plans to hold workshops in September 1998 and January 1999 to discuss issues related to drinking water and residential exposure assessment.

⑥ **SCIENCE POLICY AREA** ⑥: Assessing Residential Exposure

Definition of the Issue. Similar to drinking water. We must now include residential exposure in the aggregate risk assessments. Generally speaking, residential exposure monitoring data have not been routinely required. Thus, EPA has been depending on modeling data, including information on activity patterns, particularly for children.

☆ The Science Policy Issue:

☞Obtaining residential exposure data to refine exposure assessments and models ☜

Approach in Risk Assessment:

What We've Been Doing. EPA uses "scenarios" to model residential and other non-dietary, non-occupational exposures (referred to as residential for ease of discussion). The current guidances include exposure scenarios for 14 use sites (e.g., residential lawns, inhalation of residues from indoor treatments, and pet treatment) and 42 use scenarios (e.g., Handler Inhalation and Dermal Doses from Treating Pets with Dip, Shampoo, Dusts, and Flea Collar Pesticide Formulations).

Issues Related to the Current Approach. Like drinking water, residential exposure models may significantly overestimate exposure.

What We Are Doing to Address the Issue. There are several workgroups and task forces working on various efforts to generate data and improved methods for conducting residential exposure assessments: (1) Agency Standard Operating Procedures (SOPs) were completed and taken to the SAP for comment (November 1997). They are being revised based on the SAP comments and information in the published literature. (2) The Indoor Residential Exposure Joint Venture, an industry/Agency Task Force, is developing information on indoor pesticide treatments and pet uses. In Phase I, the Joint Venture will provide information to better characterize use patterns and practice. In Phase II, they will apply this information to exposure data, and will collect dislodgeable foliar residue data. The Task Force is generating these data to support their products; that is, these data will be used in lieu of the SOPs. (3) The Outdoor Residential Exposure Task Force (ORETF) is in the midst of generating lawn and turf data to support their products.

What We'll Be Doing in the Interim. We will continue to use the SOPs, using actual data instead of SOPs as the data become available. See *"Standard Operating Procedures for Residential Exposure Assessments," draft, December 18, 1997* (Tab 6).

Summary of Current Assumptions. Risks are considered to be of no concern if model estimates show insignificant risks. Risks are considered to be of potential concern if model estimates show significant risks.

Products/Timing

- Incorporation of SAP comments for the SOPs will be completed in December 1998. Following 60-day Notice and Comment period, comments will be incorporated and a final document completed in 30 days, March 1999.
- The Indoor Residential Joint Venture Task Force is expected to have a Phase 1 draft available March 1999; Phase 2 will be completed October 2000. The Agency will review the data generated by the task force and assess their applicability for use.
- Preliminary results from the Outdoor Residential Exposure Task Force are expected in August 1999. The Agency will review the data generated by the task force and explore their applicability for use.

⑦ **SCIENCE POLICY AREA** ⑦: Aggregating Exposures from all Non-Occupational Sources

Definition of the Issue. Under the requirements of FQPA, in setting tolerances EPA must now aggregate exposures from all sources for which there is reliable information - typically from food, water, and residential exposures. Specific issues related to each of these components to aggregate exposure were discussed separately. Methods for aggregating exposures to estimate risks accurately must be developed.

☆ The Science Policy Issue:

☞ Fully Developing the Methods for Aggregating Exposure ☜

Approach in Risk Assessment:

What We've Been Doing. OPP has been using an interim method, which calls for simple addition of risks across these sources of exposure. Exposure from a particular source is included in this assessment only if reliable quantitative information is available. If reliable data for quantification of exposure from a source is not available, upper bound modeling data are used to determine if risks from that source are likely to contribute minimally to the aggregate risk (conclusion: the risk is acceptable) or whether this cannot be determined.

Issues Related to the Current Approach. The current method for aggregating exposures using simple addition does not account for the distribution of risks across the population, but provides only point estimates. Methods that more clearly demonstrate the range of risks across the population and population subgroups (e.g., Monte Carlo analyses) would better characterize risk for risk management decisions regarding pesticide use. These methods generally use Monte Carlo analyses.

What We Are Doing to Address the Issue. In addition to Agency efforts to address these issues, the scientific community is examining comprehensive aggregate exposure assessment approaches. In February ILSI conducted a public workshop where six groups of experts presented proposed approaches. Workshop participants evaluated and commented on the approaches. Work to develop an OPP policy is underway.

What We'll Be Doing in the Interim. We will continue to use point estimates of exposure when adding components in an aggregate risk assessment. We will incorporate new methods, as developed, into these assessments. See *"Interim Guidance for Conducting Aggregate Exposure and Risk Assessments," HED SOP 97.2, 11/26/97* (Tab 7). (Note that this document is being revised.)

Summary of Current Assumptions. The entire population is exposed to pesticides at levels corresponding to the point estimates.

Products/Timing

Two products are planned:

EPA will be informed by independent scientific work by ISLI in their report, which will be completed in November 1998 plus other comments by the scientific community. The Agency will review these works and provide an Agency draft guidance document in March 1999. This guidance document will be published for a 60-day comment period, after which comments will be incorporated and a final document completed in 30 days (June 1999).

EPA will develop internal guidance on conducting aggregate exposure assessments, which will be released for public review and comment on the same schedule as above.

⑧ **SCIENCE POLICY AREA** ⑧: How to conduct a cumulative risk assessment for organophosphate or other pesticides with a common mechanism of toxicity

Definition of the Issue. Under FQPA, EPA is required to consider available information on the effects of cumulative exposure to the pesticide and other substances with common mechanisms of toxicity. EPA believes that the organophosphate pesticides, the first group examined, all operate via a common mechanism of cholinesterase inhibition.

☆ The Science Policy Issue:

☞ How to do cumulative risk assessment ☜

Approach in Risk Assessment:

What We've Been Doing. (1) Working with the scientific community to develop a framework for the hazard characterization and the exposure assessment components of a cumulative risk assessment. (2) The Agency is nearing completion of the revision of the Chemical Mixtures Risk Assessment Guidelines, which present methods for combining risks from multiple chemicals.

Issues Related to the Current Approach.

There is now no accepted method for doing cumulative risk assessment.

What We Are Doing to Address the Issue.

We are pursing an open, peer-reviewed process to develop cumulative risk assessment methods and approaches. For example, we expect a major ILSI workshop on this subject in September and a report from ILSI in January of 1999, which we will examine along with other sources in preparation of draft guidance.

What We'll Be Doing in the Interim.

During this interim period, we have considered combined exposures where two or more chemicals share common metabolites. With the exception of the triazines, we have not yet conducted any cumulative risk assessments. We have proceeded to evaluate all new chemicals and new uses for existing chemicals where there does not appear to be a common mechanism of toxicity by considering only the exposures to the individual pesticide. Until final methods are developed, the Agency will make decisions regarding pesticide uses with the condition that the cumulative risk will be addressed when adequate methods are available. See *"Guidance for Identifying Pesticide Chemicals That Have a*

Common Mechanism of Toxicity for Use in Assessing the Cumulative Toxic Effects of Pesticides, (undated) (Tab 8).

Summary of Current Assumptions. For the first group of pesticides examined, our working assumption is that the organophosphate pesticides all act by the same mechanism of toxicity.

Products/Timing

Draft report from ILSI is expected in January 1999, following the September workshop. The Agency will review the ILSI work and provide an Agency draft guidance document in May 1999. Sixty days will be allowed for notice and comment, followed by 30 days to finalize the guidance (August 1999).

Guidance for Identifying Pesticide Chemicals that have a Common Mechanism of Toxicity for Use in Assessing the Cumulative Toxic Effects of Pesticides has been released in August 1998 for a 60-day public comment period, which will be followed by 30 days for incorporation of comment, and will be completed in November 1998.

⑨ **SCIENCE POLICY AREA** ⑨: Selection of Appropriate Toxicity Endpoints (or critical effects) for Risk Assessments of Organophosphates

Definition of the Issue. Most organophosphate (OP) (and certain carbamate) insecticides exert their principal toxic effects on insects and mammals by the mechanism of cholinesterase inhibition. Communication between a large number of nerve cells in the peripheral and central nervous system is by means of acetylcholine, a neuro-transmitter. Acetylcholinesterase is the enzyme that breaks down acetylcholine after it has communicated the nerve signal between two nerve cells or the nerve cell and the muscle cell it stimulates. Inhibition of this enzyme prolongs the action of acetylcholine and results in the toxic effects known for these chemicals such as nausea, dizziness, confusion, diarrhea and myosis (pin-point pupils) and, more seriously, up to respiratory paralysis and death. 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 larger regulatory community about which measures of cholinesterase inhibition should be used for setting reference doses in risk assessments and more generally about how these data should be viewed along with the other types of data, such as clinical signs, in risk assessments. We focused on two issues: (1) the role of blood measures, since blood cholinesterases are not part of the nervous system, and so are only an indirect measure, and (2) whether plasma cholinesterases, which contain butyrylcholinesterase, a form similar to but not identical to acetylcholinesterase, the form found in the nerves, should be treated differently from red blood cell cholinesterase, which is all acetylcholinesterase.

The Science Policy Issue:

☞ How should we use measures of cholinesterase inhibition in plasma, red blood cells, and brain in the determination of critical effect levels and setting reference doses? ☜

Approach in Risk Assessment:

What We've Been Doing. For at least the last 10 years, EPA has used one or more of the effects of plasma, red blood cell, or brain cholinesterase inhibition as the basis for determining critical effect levels and setting reference doses. See *Office of Pesticide Programs Science Policy on the Use of Cholinesterase Inhibition for Risk Assessments of Organophosphate and Carbamate Pesticides, draft, April 30, 1997* (Tab 9).

Issues Related to the Current Approach. Over the past ten years EPA has consulted with the Agency's Science Advisory Board and the FIFRA Scientific

Advisory Panel (SAP) on several occasions. Also, other governmental bodies such as the Agency's Risk Assessment Forum, the Federal Coordinating Council for Science, Engineering, and Technology, the United Nations Environment Programme, the International Labour Organisation, the World Health Organization, and the California Department of Environmental Regulation have considered this issue.

What We Are Doing to Address the Issue. In June 1997, the Agency made a major presentation to the SAP including 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. 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 SAP generally agreed with EPA's proposal that a weight-of-the-evidence approach should be used in evaluating the overall significance of: clinical signs and overall behavioral or functional effects in humans and animals; symptoms in humans, central or peripheral nervous tissue measures of cholinesterase inhibition; and blood measures of cholinesterase inhibition. They also agreed that while blood cholinesterase inhibition is an imperfect mirror of nervous system inhibition, it was reasonable to use blood measures under some circumstances while awaiting further information on cholinesterase inhibition in peripheral tissues.

Since June 1997, ILSI has been addressing experimental techniques for measuring cholinesterase inhibition in peripheral tissues. A final report has been made available to EPA, which we expect will be helpful in preparation of our draft guidance.

What We Will Do in the Future. In evaluating cholinesterase inhibiting pesticides, the pesticide program will be evaluating the entire body of information on cholinesterase inhibition, which includes: cholinesterase inhibition in the red blood cells and plasma; cholinesterase inhibition in the central nervous system and the peripheral nervous system; human data such as headache, nausea, and dizziness; and signs and symptoms as can be observed in the animal studies. After looking at all these data and 'weighing the evidence,' OPP may select as critical effects:

- Clinical signs and other behavioral or neurophysiological effects in humans and animals;
- Symptoms in humans;

- Central (e.g., brain) or peripheral nervous tissue measures of cholinesterase inhibition; or
- Blood measures of cholinesterase inhibition.

Summary of Current Assumptions. In applying the weight-of-evidence approach to adequately evaluate a cholinesterase inhibitor, we assume that the essential elements of a critical study or a database are available. These essential elements are:

- Data on clinical signs (and symptoms in humans);
- Other functional effects (e.g., behavioral or neurophysiological effects) related to cholinesterase inhibition;
- Measurements of central nervous system and peripheral nervous system cholinesterase inhibition;
- Plasma and red blood cell cholinesterase inhibition;
- Data on the time of peak functional and biochemical effects; and
- Data on duration of effect for single or acute exposures.

Products/Timing. The guidance presented to SAP, Office of Pesticide Programs Science Policy on the Use of Cholinesterase Inhibition for Risk Assessments of Organophosphate and Carbamate Pesticides, draft, April 30, 1997, will be published for a 30-day comment period in October 1998, with 30 days for incorporation of comments and a final document to be available in December 1998.