October 8, 1999

EPA's Risk Assessment Process For Tolerance Reassessment

Staff Paper #44

Note To Reader:

The attached paper represents the revised version of TRAC Staff Paper #25. It describes in plain language the process EPA's Office of Pesticide Programs follows in conducting human health risk assessments in support of tolerance reassessment.

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EPA'S RISK ASSESSMENT PROCESS for TOLERANCE REASSESSMENT[1]

Pesticides are widely used in producing food. The term pesticide includes ingredients used in products, such as insecticides, fungicides, rodenticides, insect repellants, weed killers, antimicrobials, and swimming pool chemicals, which are designed to prevent, destroy, repel, or reduce pests. Before a pesticide may be sold in the United States, EPA evaluates the proposed pesticide thoroughly to ensure that it will not harm human health or the environment. Pesticides that pass this evaluation are granted a license or "registration" that permits their sale and use according to requirements set by EPA to protect human health and the environment under the Federal Insecticide, Fungicide, and Rodenticide Act and the Federal Food, Drug, and Cosmetic Act, both of which were amended by the Food Quality Protection Act of 1996.

INTRODUCTION

The Office of Pesticide Programs (OPP) evaluates the safety of pesticides to people through a process that is known as a human health risk assessment. This process involves assessing the toxicity or hazard potential of a chemical and determining how much exposure is likely to occur. The result of this analysis is used to ensure that when a pesticide is used, people are adequately protected. This paper focuses on the risk assessment process underlying tolerance reassessment, which follows the same principles as the process used to assess proposed new tolerances. Although ecological and occupational risk are analyzed for both new and existing pesticides, this paper only describes the human health risk assessment process for food, drinking water, and indoor/outdoor residential exposures.

What is a Tolerance?
A tolerance is the maximum amount of a pesticide residue that may lawfully remain on a food commodity that has been treated with a pesticide.

Although the process can be described in a step-by-step fashion, it often is not conducted sequentially. In fact, there are many opportunities to resolve issues and refine the assessment by obtaining better information about exposure (e.g., how pesticides are used in real-world conditions) or performing more sophisticated analyses (e.g., probabilistic assessments).

Food Quality Protection Act Tightens Pesticide Regulatory Standards

In setting tolerances under the Food Quality Protection Act of 1996, EPA is now considering:

- *A new safety standard*--"reasonable certainty of no harm" (previously was "no unreasonable risk of adverse effects")
- *Exposure from all routes*--oral (e.g., from food and drinking water), dermal and inhalation (from the use of household pesticides)
- *Cumulative effects* of exposure to the pesticide and other substances with "common mechanism of toxicity." When two or more substances have a common mechanism of toxicity it means that they act in the body in a similar manner.
- *Special sensitivity of children to pesticides*. EPA must include an extra safety factor in addition to the traditional 10- to 100-fold safety factor unless, on the basis of reliable data, a different factor is determined to be safe for children.

Under FQPA, EPA must reassess all tolerances established before August 3, 1996 within 10 years. In doing so, EPA must give highest priority to pesticides that appear to pose the greatest risk.

EPA also is developing a screening and testing program for chemicals with the potential to disrupt endocrine (hormone) function.

MANAGING THE PROCESS

OPP is required by law to re-evaluate all pesticides first approved before November 1984 and reassess all tolerances established before August 1996. Within OPP, the Special Review and Reregistration Division (SRRD) manages the assessment of most conventional chemical pesticides for both reregistration and tolerance reassessment. SRRD starts the risk assessment process by submitting studies and any other relevant information to the Health Effects Division (HED) for an evaluation of human health risks and to the Environmental Fate and Effects Division (EFED) for an evaluation of drinking water exposure (as well as environmental effects). Throughout the process, SRRD is responsible for requesting, receiving, and managing the review of information necessary for reassessing food safety.

DEVELOPING SCIENCE POLICIES RELATED TO RISK ASSESSMENT

EPA is committed to public participation in implementing FQPA. For example, EPA has worked with a group of stakeholders convened by the Agency in cooperation with the U.S. Department of Agriculture [the Tolerance Reassessment Advisory Committee (TRAC)] to identify key areas where science policies that affect risk assessment would benefit from further development or better definition.[2] This paper includes references to certain of those issues, to indicate where policies may change or be clarified in the future based on the planned process of public notice and comment.

On October 29, 1998, EPA published "Framework for Addressing Key Science Issues Presented by the Food Quality Protection Act (FQPA) as Developed Through the Tolerance Reassessment Advisory Committee (TRAC)" in the Federal Register (Volume 63, Page 53038). It describes the plan for publication of future notices of availability for the guidance documents that will be subject to comment as described in the Framework. These documents will be available in the OPP Docket and on OPP's web site as they are released. See *For More Information* at the end of this paper.

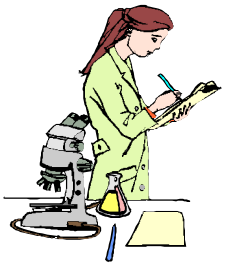
What are the nine science policies?

1. Applying the FQPA 10-Fold Factor
2. Dietary Exposure Assessment - Whether and How to Use "Monte Carlo" Analyses
3. Exposure Assessment - Interpreting "No Residues Detected"
4. Dietary (Food) Exposure Estimates
5. Dietary (Drinking Water) Exposure Estimates
6. Assessing Residential Exposure
7. Aggregating Exposures from all Non-occupational Sources
8. How to Conduct a Cumulative Risk Assessment for Organophosphate Insecticides or Other Pesticides With a Common Mechanism of Toxicity
9. Selection of Appropriate Toxicity Endpoints for Risk Assessments of Organophosphates

The list of papers associated with these issues is attached to this paper.

DATA FOR RISK ASSESSMENT

To perform a risk assessment, OPP needs data. Generally, pesticide manufacturers (i.e., registrants) are required to submit a full and comprehensive battery of toxicity, residue chemistry, and other data for food use chemicals. As part of implementing the 1988 amendments to the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), OPP required and received the basic toxicity and residue chemistry data for pesticides registered before November 1984. Since November 1984, OPP has routinely required these data before registration for any new pesticide chemical used on food crops.



Toxicity data are used to identify the hazard potential of a pesticide. Residue chemistry data are used to determine the identity and amounts of pesticide residues in and on all foods and food products, including milk and meats. Agency scientists review all data to ensure they were developed according to standard practices within the discipline and Agency Test Guidelines (available at www.epa.gov/OPPTS_Harmonized/)

In addition to toxicity and residue chemistry data, OPP may also use other data when refining and making more realistic exposure assessments for residues on food. As with the base toxicity and residue chemistry data, OPP reviews these data to assure their reliability and accuracy before they are used to refine the exposure assessments. Additional data may include:

- ✔ Residue measurements from the U.S. Department of Agriculture (USDA), the Food and Drug Administration (FDA), and state monitoring programs;
- ✔ Market basket or grocery store surveys conducted by registrants or users;
- ✔ Information on the percentage of a crop treated with the pesticide, and;
- ✔ Field-level information about how a pesticide is used, including application rates, and timing and frequency of pesticide application.

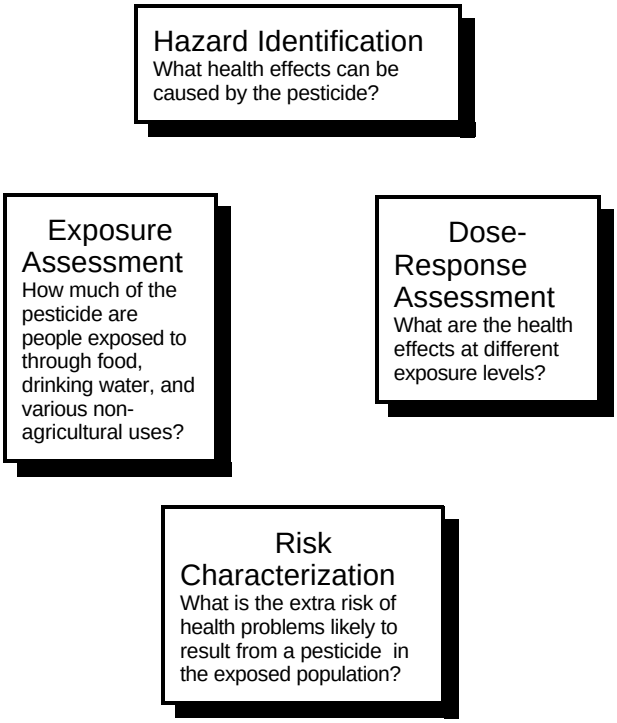
USDA provides data from several sources. These include the National Agricultural Statistics Service (NASS) surveys of pesticide use and Integrated Pest Management practices, Agricultural Research Service food consumption surveys, and Agricultural Marketing Service surveys of pesticide residue data (the Pesticide Data Program).

FDA provides data from its regulatory monitoring and its Total Diet Study, which is a market basket study. Foods are prepared as a consumer would prepare them and analyzed for various components, including pesticide residues. These results and residue data from sources such as field tests, the Pesticide Data Program, and monitoring programs are used with USDA consumption studies to estimate dietary intakes of pesticide residues for various age groups, ranging from infants to senior citizens, for both males and females.

The scientific literature also contains a great deal of information related to pesticides, some of which is relevant to pesticide regulation. While data from the scientific literature do not always meet EPA's strict standards (known as Good Laboratory Practices), some do and are directly used for regulatory purposes when appropriate. EPA may seek additional data from the registrant when such studies suggest a potential concern with a pesticide. Studies that do not meet the standard for use in a risk assessment can serve as additional supporting evidence for a decision that is based primarily on other data that do meet Agency standards.[3]

CONDUCTING THE RISK ASSESSMENT

Risk assessment follows a four-part process, which is described in the sections that follow.



The Health Effects Division (HED) evaluates toxicity data, residue chemistry data, information on use, exposure measurements, and percent crop treated to establish health effects of concern and to characterize food and residential exposure. These analyses, along with the drinking water exposure evaluation are the basic elements of a human health risk assessment.

Hazard Identification

Pesticide registrants conduct toxicity tests on animals, which are exposed to the test chemical by different routes, including oral, dermal, and inhalation. The toxicity tests are designed to explore a wide spectrum of effects that may occur (e.g., birth defects, cancer, changes in fertility or ability to reproduce, neurotoxicity, harmful effects to the kidney or liver, etc.) and to determine if the pesticide is causing such effects. Other sources of toxicity data include the open literature, epidemiology information, and additional, voluntary submissions by the registrants.

During hazard identification, all available toxicology data are reviewed to see what harm the pesticide might cause. Unless there is some reason to believe otherwise, OPP assumes that animal test results are relevant to identifying hazards in humans. Some effects may appear quickly (e.g., unsteady walk). Other effects generally appear only after years of exposure (e.g, liver damage). Knowing whether the effects are acute, chronic, or both is important in dietary exposure assessment.

Health effects identified in the hazard identification portion of a risk assessment are referred to as *toxicological endpoints*. Effects appearing quickly are known as *acute;* longer term effects are called *chronic*.

Dose-Response Assessment

In evaluating a toxicity test, the HED science review team determines at what dose level the effects occurred and what population group, if any, is most likely to exhibit the effects. The science review team also looks for the critical effect that occurs at the lowest dose. In some cases, there will be no response in the test animals until a certain dose level is reached. This type of effect–no harmful response until a certain dose level is reached–is called a threshold effect (for example, weight loss). An effect that is observed even to the smallest degree at every dose level is called a non-threshold effect. Cancer is the classic example of a non-threshold effect. The distinction between threshold and non-threshold effects is important in the application of the extra 10-fold safety factor provision of FQPA because, according to the statute, this provision only

applies to threshold effects.

A threshold effect is evaluated by looking at all the doses given to the animals in a specific study and across the entire set of toxicology data for that chemical and identifying the highest dose where no harmful effect is observed. This level is called the No-Observed-Adverse-Effect-Level (NOAEL).[4]

Non-threshold effects are evaluated differently. All the doses and their corresponding effects are fed into a computer model that calculates a statistical number called a q_1* ("Q Star"). The q_1* indicates the relative potency of the chemical as a carcinogen–the higher the number, the more potent the chemical.

Peer Review Validates Results

When an HED science review team has completed its primary assessment of endpoints or effects of concern, an internal peer review committee known as the Hazard Identification Assessment Review Committee evaluates the science review team's work to ensure that all reviews are consistent with EPA procedures. The committee also looks at the relationship between chemical doses and the response they provoke in animals and sets a numerical value based on that relationship.

Depending on the type of effects associated with a pesticide and the outcome of the peer review done by the Hazard Identification Assessment Review Committee, other internal Science Assessment Review Committees (SARCs) also may evaluate the science review team's work for specific issues. These committees include the Cancer Assessment Review Committee and the Mechanism of Toxicity Assessment Review Committee.

Setting the Reference Dose

The process of putting a number on (i.e., quantifying) the toxicity portion of risk is called dose-response assessment. For threshold effects, dose-response is quantified by a reference dose. The pesticide program calculates a reference dose by dividing the no-observed-adverse-effect level from an animal study by at least two uncertainty factors–a 10-fold factor to account for uncertainty in extrapolating from animals to humans (i.e., interspecies) and a 10-fold factor to account for the variation within the human population (i.e., intraspecies).

A *chronic reference dose* (RfD) is an estimate of the level of exposure to a pesticide residue that is believed to have no significant harmful effects if consumed daily over a 70-year life span. It is generally expressed as milligrams of the chemical per kilogram of body weight per day (mg/kg/day).

An *acute reference dose* (aRFD) is an estimate of the pesticide residue to which one could be exposed in a single day without harmful acute effects.

A *population-adjusted dose* is an RfD (either acute or chronic) that has the FQPA factor included. (PAD=RfD/FQPA factor)

FQPA Factor Yields Population-Adjusted Dose

In addition to these two 10-fold uncertainty factors, the FQPA factor addresses special sensitivities of infants and children and uncertainties about the toxicity and exposure dose. The decision on the FQPA factor occurs at a later stage in the risk assessment process. EPA calls a reference dose that has been adjusted to incorporate the FQPA factor a population-adjusted dose.

Exposure Assessment

Pesticide exposure can occur through three routes of exposure–oral, dermal, and inhalation–depending on where the person is and what the person is doing. The FQPA provision on aggregate exposure means that in addition to the pesticide exposure that occurs through food, OPP also must include exposure that occurs from other non-occupational sources, which include drinking water and residential exposures. HED evaluates exposure through food and in residential activities; the Environmental Fate and Effects Division (EFED) evaluates the drinking water exposure level. HED aggregates or combines exposures from all these sources.[5]

Exposure through Food

As with toxicity data, an HED science review team evaluates a battery of exposure data to estimate the amount of pesticide residue that may be in foods. Actual pesticide residue measurements are taken from specific grains, fruits, and vegetables (raw agricultural commodities) that are grown in treated fields. To estimate the amount of pesticide residue that would be found in other food forms such as apple juice and raisins (processed commodities), OPP may gather additional data or perform calculations, extrapolating from data on how pesticide levels change during processing.

What pesticide residues are present?
Metabolism studies in plants and animals show whether the pesticide or any breakdown products are present.

How much residue is present?
Crop field trials (pesticide applied at maximum label rate and crop harvested at minimum pre-harvest interval) show the highest likely residue.

OPP's analysis of exposure includes looking at food consumption for all ages and both males and females. The USDA consumption data described earlier in this paper form the basis for this analysis.

Developing More Realistic Exposure Assessments

It is important to note the nature of actual crop field trials, the studies conducted to help determine the legal maximum amount of pesticide (the "tolerance") that may remain in or on food. In these studies the pesticide is applied at the highest rate allowed and with the shortest pre-harvest interval, according to the label instructions. When the crop is harvested, sampling is done at the 'farm gate,' which means that sampling occurs before the crop has gone through any sort of processing such as washing or has entered the channels of trade. This represents the highest level of pesticide that might occur on that fruit or vegetable from legal use.

In reality, consumers generally are not exposed to pesticide residues in food at the tolerance level. So, in refining or developing more realistic dietary exposure assessments, OPP often uses pesticide residue measurements that were taken from foods sampled under more 'real-life' situations, such as at the grocery store or through FDA or USDA monitoring. OPP also may use information on typical use rates to compare both typical and maximum exposure. For example, information on typical use rates may come from registrants, growers, or other sources. However, OPP also must receive data (such as from *bridging studies*) showing what

Data Come from Various Sources
The USDA Pesticide Data Program develops statistically reliable, national data for pesticide residues in foods most likely to be eaten by infants and children.

residues can be expected if pesticides are used at lower rates than allowed by the pesticide label. OPP cannot assume that residues are present in direct, linear proportion to the amount of pesticide applied. If studies have been done to document the effects of food processing on residues, this information also can be used.[6]

A final piece of information that can be used in assessing dietary exposure and risk is the percentage of a given crop that is actually treated with the pesticide. HED obtains national estimates of percent crop treated from the Biological and Economic Analysis Division in OPP and also can consider regional variations where needed. The typical use of this information is shown in the table, Tiered Approach to Exposure Assessment. Without percent crop treated data, OPP will assume that 100 percent of the crop is treated. Such an assumption can lead to an overestimate of the actual exposure level, especially for chronic exposure estimates.

USDA Provides Data

The U.S. Department of Agriculture is developing crop profiles, which include information on how much of a crop is treated for various pests in each state. Other data that come from USDA include field trial results showing residue values, actual use data, and residue information from the Pesticide Data Program.

EPA is considering how to handle situations where no residues are detected. In some cases, there actually is no residue present. In others, there is a residue, but it is present at levels too low for current analytical instruments or methods to detect. This is referred to as being below the level of detection. A related possibility is that the residue can be detected but is lower than the lowest level that can be accurately measured, called the limit of quantitation. EPA is developing policy on how such residues will be treated in the risk assessment.[7]

EPA looks at information such as plant metabolism, environmental fate, and crop field trial data in deciding whether residues might be present below the limit of detection. Studies of plant metabolism using radioactively labeled pesticides often are used because they usually involve a lower limit of detection or limit of quantitation than other residue measurement techniques. Another way to show that the pesticide truly is not present is to conduct studies using a larger amount of the pesticide than allowed by the label, which would ensure that any residue would be measurable.

Agricultural Use/Usage Data Help in Refining Risk Estimates

In addition to actual grower use (what pesticide is used and how, e.g. foliar application) and usage (how much, e.g., pounds per acre) practices or shipping/storage practices, EPA needs data from special trials or studies that form mathematical relationships that allow the information to be used in risk assessments.

Bridging Studies allow estimation of residues that might result from pesticide applications at less than the maximum label rate.

Residue Decline Studies show the relationship between pre-harvest interval and pesticide residues (i.e., at what rate the residues naturally decline before the commodity is harvested).

Residue Degradation Studies account for reduction in pesticide residues while products are stored before consumption (e.g., potatoes and apples) or in cases where produce is harvested before maturity (e.g., bananas, tomatoes).

Processing Studies show the effects of industry and consumer cooking practices on residues; processing can alter the identity of residues and reduce or concentrate residues.

A Tiered Approach Allows Risk Assessment Refinements Where Needed

All this information is put to use in exposure assessment through a tiered approach. At the first level or tier, OPP assumes that residues are present at the level of the tolerance and that 100% of the crop is treated. These assumptions result in the highest potential level of exposure. If the risk is unacceptable with this screening approach, more refined data are used where available. The tiered approach is used to conserve resources, since in many cases there is no need to go to higher levels of refinement. The table, Tiered Approach for Exposure Assessment, shows the assumptions for the four tiers for both acute and chronic exposure estimates.

Exposure through Residential Activities

Reliable residential and other non-occupational exposure estimates are needed to understand aggregate exposure. However, EPA has not routinely required specific data to measure these exposures. HED uses available data, including:

- ✔ data generated for pesticide handler and post-application exposures
- ✔ data from generic databases, such as the Pesticide Handlers Exposure Database, which relies on measured residue values
- ✔ results derived from models and data included in EPA's Standard Operating Procedures (SOPs) for Residential Exposure Assessment

The SOPs include 14 categories of exposure (e.g., residential lawns, crack and crevice and broadcast treatment) and 42 scenarios within the categories. These SOPs were presented to the Scientific Advisory Panel in 1997 and published in draft the same year. A revision to the SOPs is planned for late 1999, based on the review of science policies described elsewhere in this paper. Exposure of children to pesticides is included in these scenarios. For example, there is a scenario that estimates the pesticide ingested by toddlers who touch pets that have been treated, then put their hands in their mouths.

Two categories of non-occupational exposures are not included in the scenarios but are modeled based on existing scenarios: schools/playgrounds/parks and public health sprays. For example, OPP uses the residential lawn scenario to estimate exposures in outdoor areas of schools, playgrounds, and parks. Indoor exposures in schools are estimated based on appropriate residential scenarios, such as crack and crevice treatment. Public health applications, such as mosquito abatement, are estimated based on deposition rates derived from models of aerial, ultra-low volume sprays together with residential turf scenarios and data on the breakdown rate of the pesticide.[8]

Tiered Approach for Exposure Assessment

	Acute Exposure	Chronic Exposure	Result
Tier 1	▸Tolerance-level residues ▸Assume 100% crop treated	▸Tolerance-level residues ▸Assume 100% crop treated	▸Tolerance value used in risk assessment
Tier 2	▸Tolerance-level residues (or highest residue found in a field trial) for items consumed as single-servings ▸Average field trial residues for blended commodities (e.g., wheat) ▸Assume 100% crop treated	▸Tolerance-level residues ▸Incorporate % crop treated information	▸For acute assessment, tolerance or field trial value used in risk assessment ▸For chronic assessment, multiply residue level by % crop treated (e.g., 20 ppm x 20%CT = 4 ppm)
Tier 3	▸Use probabilistic techniques ▸Use distribution of crop field trial residues for items consumed as single-servings ▸Use average of crop field trial residues or 95th percentile from monitoring data for blended commodities ▸Use % crop treated information (as part of probabilistic techniques) ▸Use processing factors	▸Use average of crop field trial residues or monitoring data for blended commodities ▸Use % crop treated information ▸Use processing factors ▸Use refined livestock dietary burdens for meat, milk, poultry, and eggs residue values	▸For acute assessments, use a distribution of residues, incorporating % crop treated data (e.g., if 20% of the crop is treated, there will be an 80% chance of choosing zero residue) ▸For chronic assessments, multiply the field trial or monitoring residue value by the % crop treated (e.g., 8 ppm x 20% CT = 1.6 ppm)
Tier 4	▸Market basket surveys (single-serving-sized samples) ▸Use processing factors or other studies	▸Special studies (market basket surveys, consumer processing studies, residue degradation studies, etc.)	▸Allows additional refinement; produces more realistic exposure estimates.

Exposure through Drinking Water

The Agency generally begins its assessment by evaluating laboratory and field studies submitted by 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. The extent to which a particular pesticide moves down into groundwater or moves across land to contaminate surface water such as rivers, lakes, streams and reservoirs depends in large part on the physical and chemical properties of the pesticide combined with factors such as the type of soil and the amount of rainfall in the use areas.

Pesticide manufacturers are required to conduct many different kinds of tests that help us to understand whether a particular pesticide will move down easily into groundwater or move readily across land into surface water and whether it will persist. These tests show how quickly a pesticide breaks down in water, how quickly sunlight degrades a pesticide, how quickly microbes in soil degrade a pesticide, how readily the pesticide binds to certain types of soil and whether the pesticide readily dissolves in water. Some tests are done in the laboratory and some tests are done outside, in fields where the pesticide is used.

EPA's predictions of whether a pesticide will move into groundwater or surface water are

based on the tests described above, informed by decades of experience EPA has accumulated in understanding what makes a pesticide more or less likely to move to groundwater or surface water and stay there at concentrations of concern. EPA has developed mathematical models based on this experience along with pesticide-specific data and uses them to estimate pesticide concentrations in groundwater and surface water under various pesticide use conditions.

A pesticide can be used in many different locations, involving many different soil types, amounts of rainfall, depths to groundwater, and proximity to surface water. Therefore, when EPA develops its initial estimate of potential pesticide concentrations in groundwater and surface water, EPA assumes conditions and circumstances that are more likely to result in movement. In this way, EPA can quickly see whether there is any likelihood whatsoever that pesticide concentrations in groundwater or surface water could be above levels of concern to human health. For example, for purposes of estimating surface water concentrations, EPA assumes that the soil is of a type that would result in more movement off-site, that the reservoir or pond is at the edge of the treated field, and that there is significant rainfall within a few days of application.

If initial predictions of pesticide concentrations in surface water or groundwater appear to exceed levels of concern to human health, EPA attempts to refine its estimates using more pesticide-specific information on how and where the particular pesticide is used. Monitoring data representing actual measurements of the pesticide in groundwater and surface water are reviewed as well. If adequate monitoring data exist and these data confirm the estimates of levels in surface water or groundwater, EPA then uses all of the available data and information to produce an estimate of the concentration of the pesticide in drinking water for use in the aggregate human health risk assessment.

USDA Provides Water Consumption Data
The USDA Agricultural Research Service surveys of food consumption include data on water consumption by various population groups, which are used in the EPA models.

It is important to understand that monitoring data are highly variable. EPA must, therefore, exercise a substantial amount of judgment in the selection of a single value for use in the human health risk assessment. In general, EPA selects a concentration that it believes a significant subpopulation of Americans may be exposed to in the water they drink.[9]

Risk Characterization

The final step in risk assessment is risk characterization, which is the process of combining hazard, dose-response, and exposure information to describe the overall magnitude of the public health impact. OPP uses the 1996 EPA Risk Characterization Guidelines in conducting this process.

Setting Acceptable Risk Levels

Simply put, RISK = toxicity × exposure. Risk characterization quantifies and describes risk to human populations.

When assessing risk, one of the goals can be to identify the exposure level that represents an acceptable level of risk. This is done by comparing the expected or estimated exposure to the toxicity of the pesticide.

For threshold effects, if exposure is less than the toxicity, the risk is presumed to be acceptable. For acute and chronic threshold effects, EPA expresses risk as a percentage of the acute or chronic reference dose (% aRfD or %RFD).

Acute and Chronic Threshold Effects

% aRfD (or %RfD)= Aggregate Exposure (in milligrams per kilogram per day) ÷ Reference Dose x 100

For non-threshold effects, the risk number represents the likelihood or probability that someone will experience the toxic effect. For example, a $1x10^{-6}$ cancer risk means that the person has a one in a million chance of developing a tumor from exposure to the pesticide.

Nonthreshold Effects (Cancer)

Probability (of Developing Cancer) = q_1 × Aggregate Exposure (in milligrams per kilogram per day)*

Aggregate Exposure is the combination of dietary exposure from food residues, nonoccupational exposure from indoor and outdoor residential pesticide applications, and drinking water exposure. Exposure from food is based on measured residues in foods and on what we know about food consumption in the United States. This food consumption data is supplied by the USDA. Food consumption data and dietary exposure estimation models such as DEEM™ (Dietary Exposure Evaluation Model) allow EPA to estimate dietary risks from food for the U.S. population as a whole, as well as 26 different population subgroups, including eight that are specific to infants and children, such as non-nursing infants.[10]

OPP replaced its former acute and chronic dietary risk assessment software, Dietary Risk Evaluation System (DRES), with the Dietary Exposure Evaluation Model (DEEM). This newer model has the capability to conduct both chronic and acute risk assessments, as well as both probabilistic and non-probabilistic risk assessments. It also includes more recent food consumption data (1989-91 and 94-96) than DRES used. These assessments will use the range or distribution of residue levels from field trials and percent crop treated or monitoring data to estimate exposure more accurately.[11]

Peer Review Ensures Risk Assessment Quality and Consistency

The various Science Assessment Review Committees (SARCs) provide internal peer review of the risk assessment components. For example, the Cancer Assessment Review Committee evaluates any cancer concerns, as appropriate. The Mechanism of Toxicity Assessment Review Committee considers whether a common mechanism of toxicity may exist with other pesticides.

Finally, the overall risk assessment for the pesticide is developed. The risk assessment presents a comprehensive picture of any risk concerns associated with uses of the pesticide. The last SARC, the Risk Assessment Review Committee, reviews all risk assessments for consistency.

FQPA Safety Factor Evaluation

To make a recommendation on the appropriate application of the FQPA factor, OPP has created the FQPA Safety Factor Committee, composed of both risk assessors (including toxicologists and exposure experts) from its science divisions and risk managers from the

What is a Probabilistic Risk Assessment?
Probabilistic risk assessments are done to develop more refined risk estimates. They use statistical techniques to more accurately quantify both the range of exposures to pesticide residues and the probability or chance of exposure to any particular level.

EPA uses survey data from USDA and other sources regarding the amounts of various foods real people report they have eaten. These individual consumption values are then randomly combined with data from crop field trials, USDA, and FDA on pesticide residue levels in the specified food (e.g., milligrams of pesticide in an apple).

Say, for example, EPA is doing a risk assessment for women of child-bearing age. There are data on food consumption for thousands of such women. For each woman's daily consumption of apples, the computer program randomly selects a measured residue value on apples for the pesticide being studied and multiplies the daily consumption by the pesticide residue value to obtain a daily pesticide exposure. (For that fraction of the commodity that is not treated, a zero value for pesticide residue is used.) This process is repeated many times to develop the probabilistic risk assessment.

conventional chemical regulatory divisions (SRRD and Registration Division). When HED completes the risk characterization, this committee reviews all risk characterization information (food, residential, and drinking water exposure as well as toxicity endpoint selection) and recommends retaining, increasing, reducing, or removing the FQPA factor in line with the approach presented to the FIFRA Scientific Advisory Panel in January 1998. The committee considers completeness of the toxicity database, type and severity of effects observed, and nature and quality of available exposure data.[12]

External Review

In the past, once a risk assessment, such as a "chapter" for a Reregistration Eligibility Decision, had been approved by HED management, it could be shared by SRRD with affected registrants in an effort to see if they had additional data or analysis that may significantly add to the quality of the assessment. It was often at this stage that registrants developed or gathered additional data or conducted probabilistic or other analyses of existing data if the initial risk assessment did not include them.

Based on discussions of the Tolerance Reassessment Advisory Committee, OPP has begun a pilot project to enhance public review and access to the preliminary risk assessments for the organophosphates. Once a preliminary risk assessment has had a 30-day review by the registrant for error-checking only, the risk assessment is made available to the public. It is placed in the OPP docket, and a notice of availability is published in the Federal Register. They also are available on OPP's web site.

Following the public review period, all comments are considered in any revisions to the risk assessment, as well as in the resulting risk mitigation and management process. Revision of the risk assessment also includes consultation with USDA and FDA.

CONCLUSION

OPP's risk assessment process is evolving and improving as better data and improved models and other tools become available. More realistic risk assessments benefit both the pesticide registrants and the public.

This paper has not addressed cumulative risk assessment because this process is still under development. However, the basic risk assessment must be done for each individual pesticide in any case, to have data to use in more complex risk assessments.[13]

For More Information

Please see the EPA Office of Pesticide Programs' home page, **http://www.epa.gov/pesticides** for further information on EPA's pesticide regulatory program, as well as periodic updates on EPA's progress in implementing the tolerance reassessment schedule and other provisions of the FQPA.

Information on pesticides and their toxicity is available from the National Pesticide Telecommunications Network at 1-800-858-7378 or through their website (**http://ace.orst.edu/info/nptn/**).

USDA and FDA have web sites, too: **www.usda.gov** and **www.fda.gov**, where you will find additional information on their programs and data.

To reach the OPP Docket:

- ✔ *By mail*: Write to Public Information and Records Integrity Branch (7502C), Office of Pesticide Programs, Environmental Protection Agency, 401 M St., SW, Washington, DC 20460.
- ✔ *In person*: Visit the Public Information and Records Integrity Branch, Room 119, Crystal Mall #2, 1921 Jefferson Davis Highway, Arlington, VA from 8:30 a..m. to 4:00 p.m., Monday through Friday.

1. This paper is a revision of Staff Paper 25, which was prepared for the Tolerance Reassessment Advisory Committee meeting held September 15-16, 1998.

2. These issues are described fully in papers prepared for the TRAC, for example, Staff Paper 26, prepared for the September 15-16, 1998 TRAC meeting, available on OPP's web site.

3. The process of refining dietary exposure assessments based on data from various sources is discussed in Science Policy Area 4, Dietary (Food) Exposure Estimates (see the Federal Register notice described on page 2 of this paper).

4. A threshold effect that is of particular concern in evaluating the organophosphate pesticides is cholinesterase inhibition. See Science Policy #9, "Selection of Appropriate Toxicity Endpoints (or critical effects) for Risk Assessments of Organophosphates." The policy paper, "OPP's Science Policy on the Use of Cholinesterase Inhibition for Risk Assessments of Organophosphate and Carbamate Pesticides" was published for comment on November 5, 1998.

5. "A User's Guide to Available EPA Information on Assessing Dietary (Food) Exposure to Pesticides" was published for comment on January 4, 1999.

6. See "Data for Refining Anticipated Residue Estimate Used in Dietary Risk Assessments for Organophosphate Pesticides," published for comment April 7, 1999 for more information.

7.See Science Policy #3, Exposure Assessment–Interpreting "No Residues Detected." Three papers on this issue were published for comment on December 4, 1998.

8.Science Policy #6, Assessing Residential Exposure, includes discussion of use of these SOPs and the process and schedule for developing additional data. The Standard Operating Procedures for Residential Exposure Assessment were published for comment on January 4, 1999.

9.Science Policy #5, Dietary (Drinking Water) Exposures, describes the current situation with regard to review of new models and plans for further development. A science policy paper, "Dietary (Drinking Water) Exposure Assessments," was published for comment on January 4, 1999. Two related papers will be published later.

10.See Science Policy #7, Aggregating Exposures from All Non-occupational Sources for further discussion of this issue in the Federal Register notice described on page 2 of this paper.

11.Science Policy #2, Dietary Exposure Assessment– Whether and How to Use "Monte Carlo" Analyses," is represented in the paper titled "Choosing a Percentile of Acute Dietary Exposure as a Threshold of Regulatory Concern," published for comment on April 7, 1999. On November 5, 1998, EPA published "Guidance for the Submission of Probabilistic Human Health Exposure Assessments to the Office of Pesticide Programs" for comment.

12.See Science Policy #1, Applying the FQPA 10-Fold Factor in the Federal Register notice described on page 2 of this paper.

13.See Science Policy #8, How to Conduct a Cumulative Risk Assessment for Organophosphates or Other Pesticides with a Common Mechanism of Toxicity in the Federal Register notice described on page 2 of this paper.