GUIDANCE FOR PERFORMING AGGREGATE EXPOSURE AND RISK ASSESSMENTS

OFFICE OF PESTICIDE PROGRAMS

-DRAFT-

February 1, 1999

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I. Introduction and Regulatory Background

Pesticides are regulated under both the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) and the Federal Food, Drug and Cosmetics Act (FFDCA). In 1996, Congress passed the Food Quality Protection Act (FQPA) which amended both FIFRA and FFDCA. These laws mandated EPA to register pesticides and set tolerances based on a safety determination, a reasonable certainty that use of a given pesticide or consumption of raw agricultural commodity or processed foods that contain the pesticide and its residues will cause no harm to human health or the environment. EPA evaluates risks posed by the use and usage of each pesticide to make a determination of safety. Based upon this determination, EPA regulates pesticides to ensure that use of the chemical is not unsafe.

In the past, EPA evaluated safety of pesticides based on a single chemical, single exposure pathway scenario. However, FQPA requires that the Agency consider aggregate exposure in its decision making process. Section 408(a)(4)(b)(2)(ii) of FFDCA specifies with respect to a tolerance that there must be a determination "that there is a reasonable certainty that no harm will result from aggregate exposure to the pesticide chemical residue, including all anticipated dietary exposures and all other exposures for which there is reliable information." Section (b)(2)(C)(ii)(I) states that "there is a reasonable certainty that no harm will result to infants and children from aggregate exposure to the pesticide chemical residues..." This document sets out to explain the definition and implementation of aggregate exposure analysis at EPA.

To fulfill its mandate under FQPA, the Agency is developing science policies in new areas including cumulative risk and "common mechanism of toxicity" for two or more chemicals, the special susceptibility and sensitivity of infants and children, and aggregate exposure and risk assessment. The following guidelines are expressly for the performance of aggregate exposure and risk assessment. This document further expands upon the Interim Approach Paper for the March 1997 Science Advisory Panel (SAP) (US EPA, 1997c).

The U.S. EPA, Office of Pesticide Programs, considers aggregate exposure analysis to refer to single chemical exposure via the dietary (oral route), drinking water (oral route) and residential (inhalation, dermal and/or oral route) pathways. At this time, occupational exposure scenarios are not included in aggregate exposure and risk assessment although the same methods could be used to conduct such assessments. In the future, EPA may expand these guidelines to include the occupational exposure scenarios and other exposure pathways considered by other EPA offices.

In this document, it is assumed that aggregate exposure and risk will be estimated using probabilistic assessment techniques. EPA has already developed probabilistic risk assessment guidelines for acute dietary exposure assessments and routinely reviews such probabilistic assessments. EPA anticipates that aggregate exposure assessments will incorporate distributions of exposures for the residential and drinking water scenarios as well. Deterministic approaches will be considered as special case scenarios in the assessment. This document will provide guidance as to how the probabilistic distributions should be combined in an aggregate exposure

and risk assessment.

An aggregate exposure and risk assessment is distinct from a cumulative risk assessment. Cumulative risk is defined as "the measure or estimate of distributions of exposures (doses) for a set of chemicals that act by a common mechanism of toxicity" (USEPA, 1998b). Cumulative risk assessment evaluates risks from multiple chemicals via all routes and pathways of exposure. The cumulative risk assessment considers the combined toxicological effect of a group of chemicals with a common mechanism of toxicity. The definition of a common mechanism of toxicity is defined as "two or more pesticide chemicals that produce an adverse effect(s) to human health by the same, or essentially the same, sequence of major biochemical events. The underlying basis of the toxicity is the same, or essentially the same, for each chemical" (US EPA 1998b). Specific guidance concerning conducting a cumulative risk assessment is currently being developed.

Key Concepts and Definitions

Certain key concepts and definitions are important to understand in the discussion of aggregate exposure and risk assessments. This section briefly describes these concepts and definitions, with more detailed treatment appearing later in the document and in the glossary. For additional information about risk assessment concepts, the reader is referred to the following two documents: *Risk Assessment in the Federal Government: Managing the Process* (National Research Council, 1983) and *Science and Judgement in Risk Assessment* (National Research Council, 1994).

The most basic concept underlying all aggregate exposure assessments is that exposure occurs to an individual. The integrity of the data concerning this exposed individual must be maintained throughout the aggregate exposure assessment. In other words, each of the individual "sub-assessments" must be linked back to the same person. Because exposures are based on that received by a single individual, aggregate exposure assessments must agree in time, place, and demographic characteristics. Each of these parameters have imbedded attributes that must be matched to create a reasonable assessment. Some of these imbedded attributes include:

- Time (duration, daily, seasonally);
- Place (location and type of home, urbanization, watersheds, region); and
- Demographics (age, gender, reproductive status, ethnicity, personal preference).

To develop realistic aggregate exposure and risk assessments requires that the appropriate temporal, spatial, demographic exposure factors be correctly assigned. Examples of some of these factors include sex- and age- specific body weights, regional specific drinking water concentrations of the pesticide being considered, seasonally-based pesticide residues in food, and frequency of residential pest control representative of housing type. Once an aggregate exposure and risk assessment is completed for one individual, population and sub-population distributions of exposures and risk may be constructed by probabilistic techniques.

Marketplace forces must also be considered when developing realistic aggregate exposure and risk estimates. Many factors, such as registered uses of the active ingredient, permitted use sites, packaging, and market share will influence each assessment.

Another key concept is that all exposure events occur over a specific interval of time. An exposure event on one day may also produce exposures on subsequent days. One method of visualizing this is to consider exposures occurring on a calendar basis. For example, a homeowner uses an indoor fogger on Monday to treat a roach problem. Not only would the inhabitants of the home experience exposure to a pesticide on Monday, but they would also experience exposures on subsequent days as the pesticide is distributed in the house and the pesticide residues decay.

A final concept is that an individual's dose must be matched against relevant toxicological doses in terms of route, duration, and effect. For many compounds, the toxic effects are markedly different by one route and duration from those produced by a different route and duration. To produce a meaningful aggregate risk estimate, risk measures must be calculated separately for each route and duration for a given toxic effect and then combined. A separate aggregate assessment must be performed for each toxic effect of concern.

Some of the terms commonly used in this document are defined as follows:

Aggregate Dose - the amount of a single substance available for interaction with metabolic processes or biologically significant receptors from multiple routes of exposure.

Aggregate Risk - the likelihood of the occurrence of an adverse health effect resulting from all routes of exposure to a single substance.

Cumulative Risk - the likelihood of the occurrence of an adverse health effect resulting from all routes of exposure to a group of substances sharing a common mechanism of toxicity.

Dose -- the amount of a substance available for interaction with metabolic processes or biologically significant receptors after crossing the outer boundary of an organism.

Exposure -- the amount of a chemical available at the biological exchange boundaries (*e.g.*, respiratory tract, gastrointestinal tract, skin).

Exposure assessment -- the qualitative or quantitative determination or estimation of the magnitude, frequency, duration and rate of exposure of an individual or a population to a chemical.

Pathway -- the physical course a chemical or pollutant takes from the source to the organism exposed. Also called exposure pathway.

Route -- the way a chemical or pollutant enters an organism after contact, *e.g.*, by ingestion, inhalation, or dermal adsorption. Also called exposure route.

Organization of Document

This document provides guidance for performing aggregate exposure and risk assessments. Aggregate exposure and risk assessments are restricted to the analysis of the exposures and resulting risks from a single chemical by multiple routes. The routes considered at this time are oral (from dietary, drinking water, and residential pathways), inhalation (residential pathway), and dermal (residential pathway). It describes the overall framework and the necessary steps to performing an aggregate exposure and risk assessment. This guidance also includes a discussion of data sources (and their limitations) available for an assessment as well as guidance for integrating the three routes of exposure. It should be noted that the included discussion of these data sources does not fully investigate the inter-dependencies, co-variance and limitations of the data needed for evaluating multiple routes of exposure. EPA realizes that these investigations are on-going and that further work is needed in this area to produce a fully refined aggregate exposure analysis. Further, this document also includes suggestions for model validation, a discussion of reporting requirements, and provides the preferred format for an aggregate exposure and risk assessment.

OPP is developing a series of guidance documents addressing new facets of the risk assessment process as required by FQPA. Previous guidance documents will be referenced in this document as an additional source of guidance. In particular, this document relies heavily on the previously released Agency documents such as the Exposure Factors Handbook (USEPA, 1997b), the Residential SOPs (USEPA, 1997a), the Interim Guidance for the Conduct of Aggregate Risk Assessments (Stasikowski, 1997) and The Guidelines for Submitting Probabilistic Assessments (USEPA, 1998c). These documents serve as a source of information on default assumptions, discussions of the use of data in a probabilistic risk assessment environment, the identification of residential exposure scenarios, and the combining of deterministic and probabilistic sampling regimes. In all cases, where chemical specific or appropriate surrogate data are available, these data should be used in preference to default values.

II. Framework for Aggregate Exposure and Risk Assessment

Traditionally in performing risk assessments, OPP has treated exposures from different pathways as independent events, *i.e.*, one individual is exposed to one pesticide at a single point in time. In the real world, exposures to pesticides do not occur as single events but rather as a series of sequential or simultaneous events that are linked in time and place. In implementing the requirements of FQPA, EPA is required to perform aggregate risk assessments. The consideration of multiple exposure pathways from one chemical substance (dietary, drinking water and residential pesticide application) will move OPP's exposure and risk assessments closer that actually encountered in the real world.

An aggregate exposure and risk assessment focuses on the potential exposure by multiple routes to individuals in a population to a single chemical. In an aggregate exposure assessment, these exposures: 1) may occur by more than one route (i.e., oral, dermal and/or inhalation); 2) may originate from more than one source (i.e., dietary, residential, drinking water); 3) must occur within a time frame such that the chemical exposure overlaps the effective period of the adverse effect; and 4) must occur at a spatially relevant set of locations such that an individual will likely be exposed. In addition, the assessment must be linked to certain types of use scenarios. For example, in some cases, the use of one product may increase the likelihood of using another product. In other cases, the products may serve essentially the same purpose, such that the use of one will almost certainly preclude the use of the other. The process of conducting an aggregate exposure assessment is performed by developing a series of reasonable and rational scenarios which define the spatial and temporal characteristics of the likely exposures to the chemical based on the toxicological endpoints of significance. The scenarios also help to define populations of concern, and provide critical windows to time frames and routes of exposure that must be linked to toxicity endpoints.

A major goal of this guidance document is to describe a framework for linking routes and sources of exposure through scenario building. In most cases, dietary exposure to a chemical may be considered as a background upon which other pesticide episodic exposures are superimposed. In other words, the potential for dietary exposure can be considered to be relatively constant whereas potential pesticide exposures from residential and drinking water sources may be episodic in nature. To the extent possible, all sources of exposure should be combined in a probabilistic assessment allowing for the full range of variability in each source or use pattern. Information in the Guidance for Submission of Probabilistic Human Health Exposure Assessments to the Office of Pesticide Programs (US EPA, 1998c) should be consulted when preparing aggregate risk assessments.

An important premise underlying this guidance is that the preferred method for evaluating aggregate exposure is by including all routes and sources of exposure using probability distributions. However, OPP recognizes that, because of data limitations, major components of the aggregate assessment may still be presented as deterministic estimates or reflect defaults such as occur in the residential SOPs. Because of the historic emphasis placed upon dietary risk assessment, OPP anticipates that data will be available most frequently to permit the use of probabilistic techniques for the dietary component of the exposure. In the case of residential and drinking water exposure, the deterministic estimates or default values may be added as constants to any available acute dietary exposure distributions.

Note that this document does not address aggregating occupational exposures with other sources of pesticide exposure. This omission was a conscious decision because occupational assessments are explicitly exempted from FQPA considerations. However, the approaches that are discussed in this document are readily adaptable to inclusion of occupational exposures. The approach to simultaneously assessing potential exposure for workers who might be exposed to a pesticide through the food that they eat, the water that they drink and through residential uses can be

expanded by incorporating other occupational scenarios for exposure to estimate additional exposure from other sources of the same pesticides that they apply commercially.

III. Pathways for Integration

To aggregate exposure and risk, the magnitude of both exposure and risk for each route and exposure scenario must be calculated prior to combining exposures into one risk measure. Therefore, it is important to fully understand the data sources, model types and limitations, and robustness of data for each pathway. This section will describe general considerations in quantifying dietary, residential and drinking water exposures. Later in this document, the considerations and limitations of bringing all pathway/route specific exposure values together will be discussed.

Overview of Residential Exposure Assessments

Currently, OPP uses the *Draft Standard Operating Procedures (SOPs) for Residential Exposure Assessments* (USEPA 1997a) as guidance for conducting estimates of residential exposure. These SOPs identify approximately 15 common pesticide related activities / use sites (e.g., residential lawns, garden plants, etc.) that result in residential exposures. Each of these residential activities / use sites is further divided into handler and post-application categories. These are further divided by age group (i.e., adult, toddler), route (oral, inhalation, dermal), and specific activity (e.g., incidental ingestion of soil, incidental ingestion of treated turfgrass). These pathways and routes are illustrated for residential lawns in Figure 1. These SOPs produce a deterministic estimate of exposure for each assessed scenario.

Useful data for residential assessments are available from several sources. Data addressing non-dietary exposure have traditionally been required (under *Series 875 - Occupational and Residential Exposure Test Guidelines; Group A, Applicator Exposure, and Group B; Post Application Exposure*) when certain toxicity and exposure criteria were met. Acutely toxic compounds in Acute Dermal Toxicity Category I and Acute Toxicity Category II or greater were triggers for applicator exposure and post application exposure monitoring data requirements, respectively. Other adverse effects such as developmental or neurotoxicity were also considered, if results of adverse effects from those studies were available.

Other sources include proprietary data submitted to the Agency to support residential uses of pesticides, and in a few cases published studies. However, for most non-dietary exposure assessments, surrogate data and screening-level (Tier I) assessments presented in the Residential SOPs (US EPA, 1997a) must be used.

The basic steps in performing a residential assessment are as follows:

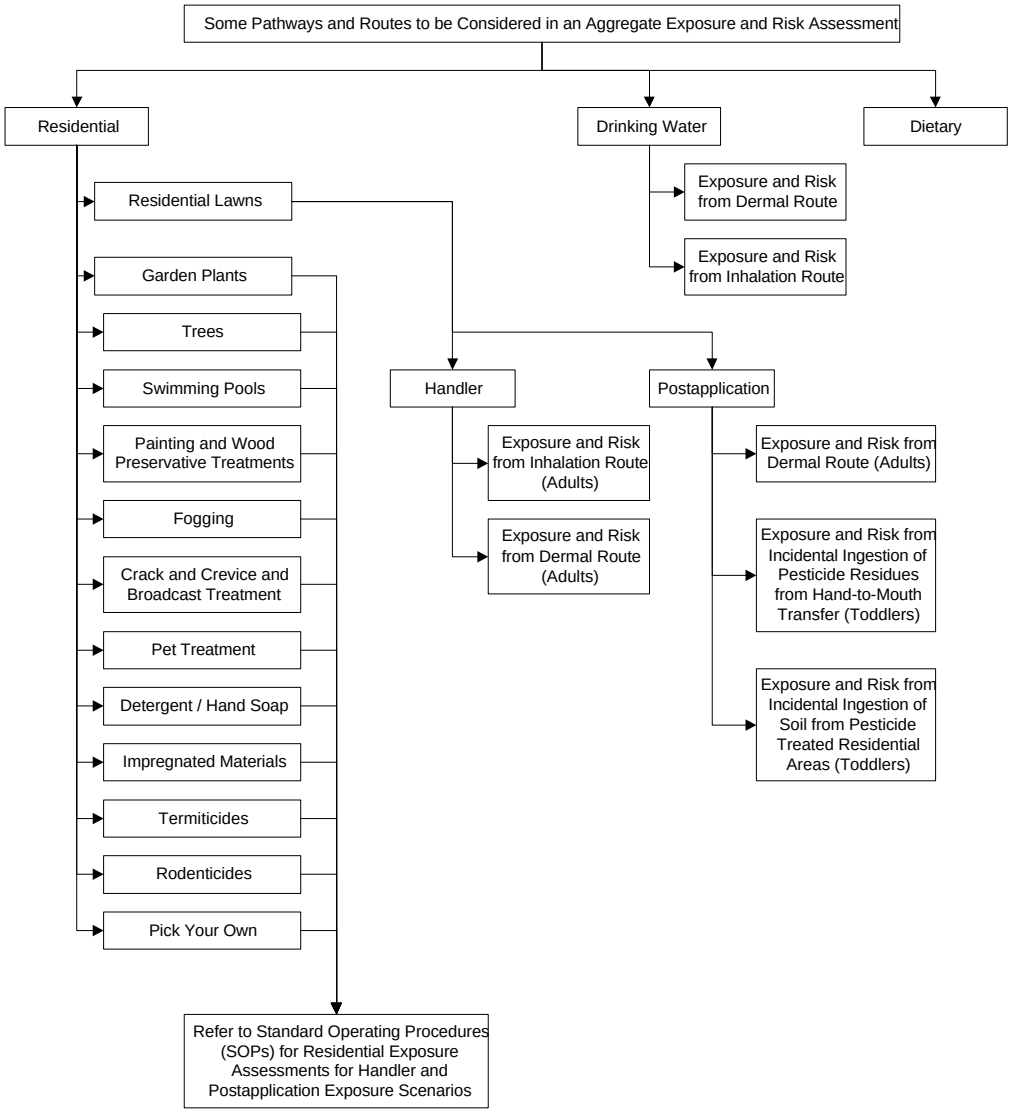
- identify formulations, application rates, and sites of application (from labels);
- identify method of application;

- determine magnitude of exposure by route for the applicator;
- identify post-application exposure scenarios;
- determine magnitude of post-application exposures (accounting for overall residues and dissipation);
- determine duration of exposure (short-term, intermediate-term, and long-term)

Additional details on the residential analytical methods, assumptions, and default values are included in the Residential SOPs (USEPA 1997a).

Currently the estimates of residential exposure (and the resulting risks) are aggregated in a deterministic fashion to produce a bounding estimate. EPA recommends that, where permitted by defensible data and assumptions, residential assessments be conducted in a probabilistic fashion.

Figure 1



Overview of Dietary Exposure Assessments

Dietary exposure scenarios are evaluated on an acute and chronic time frame of exposure. For both time frames, a tiered approach is used to introduce refinements to the assessment that reduce conservatism and to make the assessment more reflective of the actual exposure. Advancing through the tiered assessment process requires additional data describing use and usage of the pesticide on each commodity and the impact of processing (washing, peeling, cooking) or time after harvest on the residues in foods. In most cases, refinements may be possible for some proportion of the commodities undergoing evaluation, but not for others. OPP anticipates the occurrence of data of unequal quality depending upon commodity and pesticide combinations under review. In such cases, deterministic assessments may be conducted or more refined probabilistic data sets may be combined with other deterministic data.

Acute dietary exposure and risk assessments are conducted in a tiered approach. The criteria for the conduct of acute dietary risk assessments was outlined in a previously released policy document (Irene, 1996). OPP defines Tiers 1 and 2 as using residue input data of a deterministic nature and Tiers 3 and 4 using residue input data of a probabilistic nature. A Tier 1 dietary exposure assessment uses a single high end residue estimate and a distribution of consumption data. Tier 1 provides only an upper bound (worst-case) estimate of acute exposure. Tier 2 is the same as tier 1, except that it uses a single average residue data point for commodities which are typically mixed or blended. It provides a more realistic estimation of exposure by considering average anticipated residues for food forms that are typically mixed prior to consumption. Tier 3 uses a distribution of residue data points as well as a distribution of consumption data points. This provides a more realistic estimation of acute exposure than tier 2. And, Tier 4 requires more extensive data (*e.g.* single-serving market basket surveys, cooking studies, etc.) And provides the most representative exposure picture. However, it may not provide a lower exposure estimate than Tier 3. (Irene, 1996). As indicated above, Tier 3 and Tier 4 assessments will retain elements of Tier 1 and 2 for some portion of the commodities undergoing evaluation. The combining of distributional and deterministic data is acceptable to EPA.

Chronic dietary exposure and risk assessments are conducted by OPP also using a tiered approach, beginning with conservative assumptions and then proceeding through refinements to more closely reflect residue levels that might be eaten by the population of consumers. All iterations of the assessment produce estimates of dietary risk that are based on average consumption of foods (which may be categorized by population sub-groups) and a statistical evaluation of residues in specific foods (averages). Chronic assessments currently conducted by OPP will be deterministic in nature until appropriate methods are developed to estimate long term exposure from currently available consumption data. Tier 1 of a chronic dietary exposure and risk assessment uses tolerance level estimates of the magnitude of the residue and assumes that 100% of the crop is treated. Tier 2 is the same as a Tier 1 chronic dietary assessment, but data on the percent of the crop treated nationally is incorporated into the assessment. Tier 3 uses average residue from field trials or monitoring data for blended and single serving commodities,

incorporates the percent of the crop which is treated, incorporates processing factors and refined livestock burden and milk, meat, poultry and eggs (MMPE) residue values. And, Tier 4 of a chronic dietary exposure and risk assessment, uses market basket survey data (single serving sized samples) and incorporates cooking, residue decline, and residue degradation information.

The primary source of food consumption data used in dietary risk assessments is the Continuing Survey of Food Intakes by Individuals (CSFII) 1989-1991. The CSFII is particularly well suited to the conduct of national level dietary risk assessments because it is statistically designed to sample individuals of all ages and ethnicities to permit a reflection of the demographics resulting from the most recent census. It is also balanced regionally and seasonally so that all time of the year and parts of the country are represented. As subsequent surveys are translated to commodities for use in risk assessment, they will be used to update the dietary risk assessment process. Data on the residues of pesticides in foods are obtained from a variety of sources. The primary source of residue data in foods is field trial data that must be submitted in support of the registration of a pesticide. This data tends to overestimate the residues that are likely to occur in food as actually consumed because it reflects the maximum application rate and shortest pre-harvest interval. Residue data that are more reflective of foods as consumed are often available from monitoring data in which food samples further down the chain of commerce are sampled and analyzed. Monitoring data are more reflective of the residues likely to be consumed in foods as eaten. They come from federally funded surveys such as the Pesticide Data Program (PDP) conducted by USDA and the Total Diet Study conducted by FDA. These data are useful for refining chronic dietary assessments. Market basket surveys are the closest reflection of foods as eaten. However, these data are rarely available because of the high cost and complexity of conducting the surveys.

Overview of Drinking Water Exposure Assessments

To estimate aggregate pesticide residues in drinking water, OPP uses the general policy outlined in the "Standard Operating Procedures (SOP) for Drinking Water Exposure and Risk Assessments" (Stasikowski Memorandum, 1997) and the specific guidance outlined in "Interim Guidance for Conducting Drinking Water Exposure and Risk Assessments" (Stasikowski, 1998) to factor drinking water exposure into aggregate risk assessments. The registered uses and the potential for a pesticide to contaminate surface and ground waters are considered initially. If the use pattern and potential to contaminate water resources are such that there is no threat to surface or ground waters, OPP concludes the pesticide will not impact drinking water, and exposure to the pesticide in water is not included in the aggregate exposure assessment. This would be the case for pesticides exclusively registered as baits, seed treatments, or greenhouse uses, that is, uses unlikely to impact water resources because of the limited scope of the use pattern.

If the use pattern and potential to contaminate water resources are such that there is a potential threat to surface or ground waters, OPP uses water quality models that use conservative assumptions regarding the pesticide transport from the point of application to estimate the concentration of the pesticide in surface run-off and shallow ground water under worst-case

conditions. The concentration estimates generated from the models are considered to be upper bounds on pesticide concentrations in surface and ground waters. OPP considers the use of these models as a one-way screening-level exercise designed to eliminate from concern those pesticides unlikely to contaminate drinking water resources. OPP compares the model-generated concentration estimates of a pesticide in ground and surface water to levels of comparison in drinking water (calculated for acute and chronic toxic effects, respectively). A drinking water level of comparison (DWLOC) is the theoretical concentration of a pesticide in drinking water that would be an acceptable upper limit in light of the total aggregate exposure to that pesticide. If the model-estimated concentrations in ground and surface waters are less than the level of comparison in drinking water, OPP concludes with reasonable certainty that residues of the pesticide in drinking water will not contribute significantly to the aggregate exposure and resulting human health risk considering the present and proposed uses of the pesticide. In effect, OPP semi-quantitatively evaluates the potential exposure through drinking water as not contributing significantly to the risk estimate.

If the model estimates are greater than OPP's levels of comparison for drinking water (DWLOC), OPP refines its model estimates using more realistic assumptions and compares the estimates to levels of comparison for drinking water again. If, even after refinement, the model estimates exceed OPP's levels of comparison for the pesticide in drinking water, OPP obtains all available water quality monitoring data for the pesticide, and conducts an in-depth review of the data to determine if they are acceptable and reliable for use in quantitative drinking water exposure and risk assessment. In this sense, the models currently in use are one-way screening tools that effectively identify compounds not expected to impact drinking water resources. However, because of the conservative assumptions on which the models are based, it cannot be assumed that the pesticide concentration estimates from these models accurately reflect concentrations expected in drinking water.

If the monitoring data are suitable, they are used to calculate aggregate exposure for use in a human health risk assessment. Average annual and maximum (peak) concentration values from regional monitoring data for the pesticide are used in deterministic regional chronic and acute exposure assessments, respectively. The regional nature of the exposure assessments is dependent on the regional nature of the monitoring data used in the assessments. Because pesticide contamination of water is localized, drinking water exposure assessments are regional in scope, not national. Regional estimates of the exposure to the pesticide in drinking water are added to national estimates of exposure to the pesticide from food and residential uses (when applicable). There can be multiple aggregate exposure and risk assessments for a pesticide depending on the impacts of the pesticide on water resources regionally.

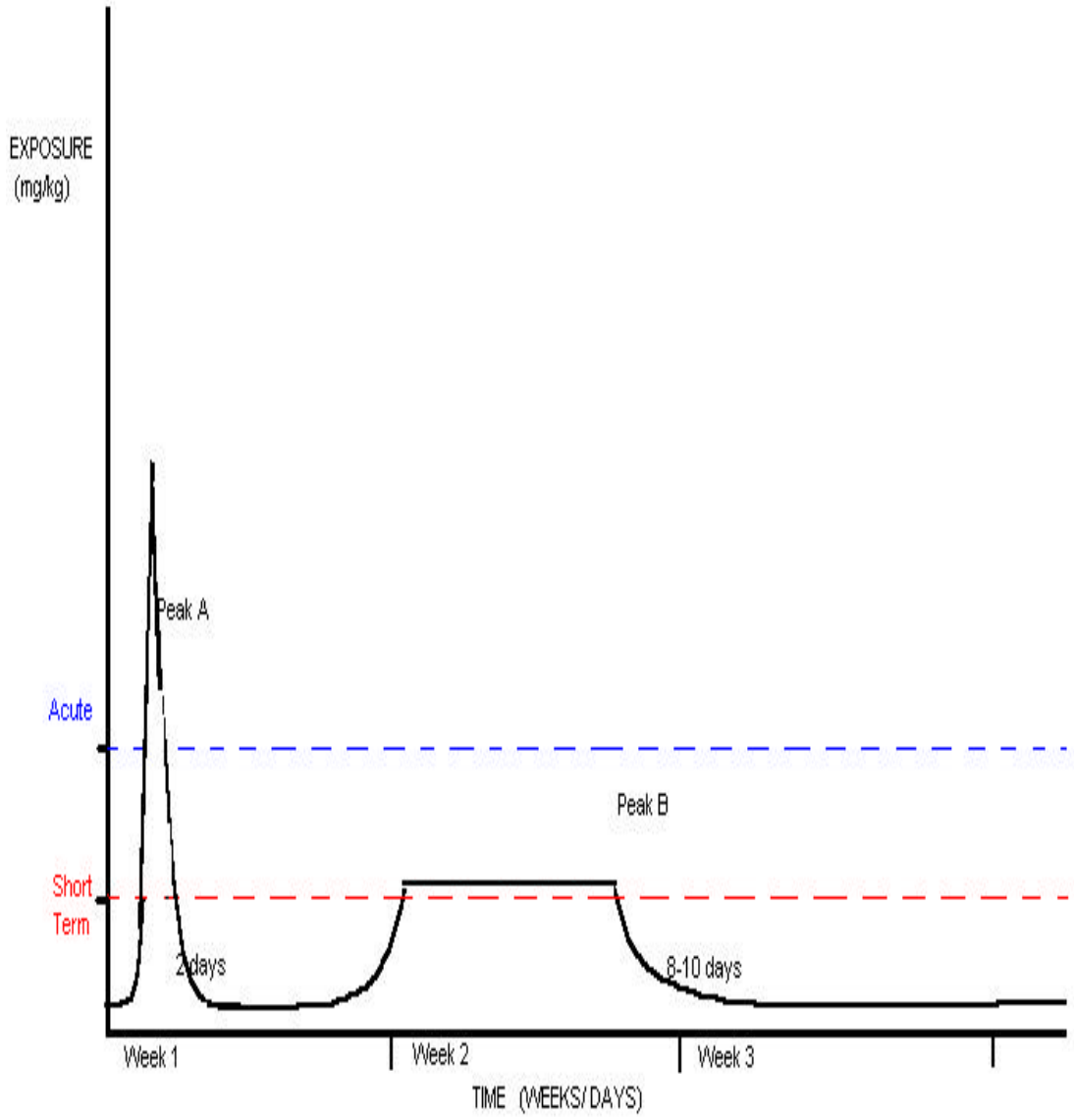
If the conservative water quality models' estimates exceed OPP's levels of comparison for the pesticide in drinking water, and no monitoring data are available, reliable and appropriate for use in a quantitative exposure and risk assessment, OPP considers the entire risk picture for the pesticide and determines the appropriate action. That is, if exposure to the pesticide is above levels of concern from food and residential exposures, and drinking water impacts are indicated

to be significant by the model estimates, a risk management decision may include a requirement for monitoring data to confirm the pesticide's presence in drinking water. Also, for those pesticides that fail the screening tiers and require detailed risk assessment, the preferred approach to the dietary (food plus water) portion of an aggregate exposure assessment is to combine a probabilistic drinking water exposure assessment with a probabilistic food exposure assessment performed by a Monte-Carlo analysis. EPA recommends that, where permitted by defensible data and assumptions, residential assessments be conducted in a probabilistic fashion.

IV. How to Perform Aggregate Exposure and Risk Assessments

OPP considers that aggregate exposure and risk will be assessed using probabilistic methods. OPP selects multiple toxicological endpoints for pesticides to reflect a variety of time frames (acute, short term, intermediate term and chronic) and routes of exposure (oral, dermal and inhalation). The endpoint selected for use in evaluating the risk from a variety of exposure scenarios must be consistent with respect to time frame with the exposure scenarios. When an aggregate assessment is conducted, peaks reflecting exposures above the background will occur. Comparison to multiple endpoints may be required to evaluate all possible resulting exposures of concern. Exposure peaks should be compared to the appropriate toxicity endpoint based upon evaluation of the mean exposure using an area under the curve approach. The mean daily exposure will be compared to the toxicity endpoint to determine if the exposure exceeds the critical effect level indicating an exposure of concern. In making the comparison, however, peak width must also be considered to ensure that the duration of exposure is consistent with the toxicity endpoint selected. The peak width will provide a measure of the duration of exposure predicted by the exposure. The concern for peak width as an important component in evaluating the appropriateness of the toxicity endpoint select can be demonstrated by Figure 2.

FIGURE 2



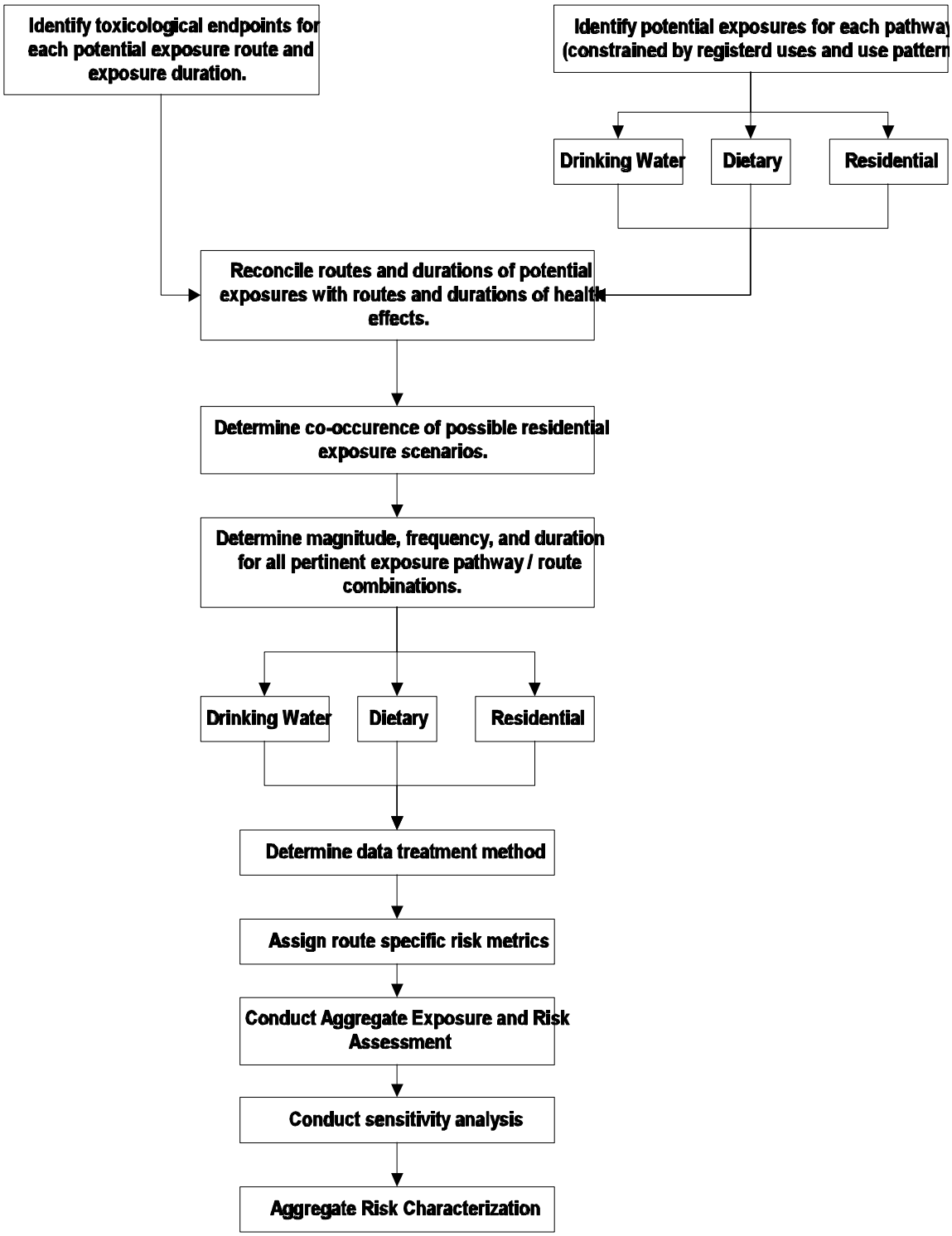
* FIGURE NOT TO SCALE

In the figure above, peak A results from a large flush of herbicide in drinking water resulting from a rain event occurring immediately after application. The duration of exposure (peak width) is about two days. Peak B reflects the indoor application of a broadcast insecticide due to a flea infestation. The duration of exposure is approximately 10 days. Both peaks have the same area under the curve and result in a mean daily exposure that exceeds a short term exposures limit (RfD). However, it would be inappropriate to compare peak A to the short term RfD because of the very short duration of the exposure. The peak width indicates that the more appropriate endpoint for evaluation would be the acute endpoint which is used for exposures of about 1 day duration.

The tails of the exposure distribution will contain individuals who reflect co-occurrence of a number of high exposures, probably from a variety of exposure pathways. The sources of exposure to these individuals should be evaluated to the extent possible to determine if a particular source of exposure is predominant and should be considered for mitigation. Consideration should also be given to whether or not these individuals reflect a particular sub-population who are particularly highly exposed. If so, the cause for the unusually high exposure should be evaluated. A qualitative evaluation of likely exposed sub-populations should also be made to determine if any subpopulation of concern is likely to experience unusually high exposure based upon lifestyle considerations. An example of such a subgroup would be farm children drinking from private wells and playing in areas treated with pesticides. Whether the indication of concern is based upon qualitative or quantitative assessment of potential risk, a separate assessment should be conducted for the subpopulation to determine the extent of the risk concern. Isolation of the subgroup may provide an indication of possible mitigation strategies to reduce exposure.

The following are guidelines for assessing aggregate exposure and risk, using both deterministic and probabilistic methods. See Figure 3 for an overview of the Aggregate Exposure and Risk assessment.

Figure 3: Steps in Performing Aggregate Exposure and Risk Assessment



1. Identify toxicological endpoints (i.e., effect, dose and duration) for each potential exposure route (i.e., oral, dermal, inhalation) and exposure duration (short term, intermediate term, and long term). The appropriate exposure duration will be selected and identified by consideration of the timing of health effects (day, week, chronic, or an intermediate interval), the duration of the health effect (i.e., the reversibility of the effect) and the time to onset of the health effect.

An initial step in performing an aggregate risk assessment is to identify the toxicological endpoints of concern for a particular pesticide active ingredient. Frequently, there may be more than one toxicological endpoint for a single chemical. If so, more than one aggregate exposure and risk assessment must be performed, evaluating each endpoint separately. If the toxicological effects via different routes of exposure are not the same, then those exposure scenarios should not be combined. Factors to be considered in evaluating a toxicological endpoint include the type of effect, the dose level, the duration of the effect, and the timing of the effect. All these considerations will be included in the identification of appropriate exposure scenarios via all pathways (*i.e.*, dietary, residential, drinking water) in the analysis of aggregate exposure and risk.

An additional complication is the potential difference between the toxicity of pesticides resulting from different routes of exposure. The differences may result from pharmacokinetic factors including rate and degree of absorption, distribution, and potential differences in metabolism. Materials absorbed through the skin may be partially metabolized as they enter the skin. Alternatively, some pesticides may require activation by the liver. The liver is bypassed when chemicals are absorbed through the lung and skin. The toxicity endpoint may also vary in treatment in the risk assessment depending upon the assumptions made about its interaction with the body. For instance, considerations of threshold may be important for non-cancer endpoints. Although low dose linearity is typically assumed for cancer and points increasing mechanistic research is providing support for non-linear dose response for curves certain cancer effects (*e.g.*, thyroid carcinogenicity via perturbation of thyroid-pituitary axis).

For example, if a particular pesticide active ingredient elicits an effect only following the oral administration, and no effects are seen via the inhalation or dermal routes, only those exposure scenarios which reflect the oral route of exposure will be included in the analysis of this toxicological endpoint. Specifically, the dietary pathway, any oral pathway residential exposure scenarios listed in the Residential SOPs, and the drinking water exposure scenarios will be evaluated in the assessment of aggregate exposure and risk. The timing of the health effect via oral route of exposure will depend upon the timing of the effect seen in the animal studies. If there is no effect seen at the acute dose level, but there is an effect in the long term (1-year dog study) only the long term scenario will be evaluated.

Toxicological effects which occur at different dose levels via different routes of exposure may be combined within an aggregate exposure and risk assessment. A conversion to a common risk metric may be required, however, to adequately combine the routes of exposure. Steps to combining pathways of exposure and things to consider while developing route specific exposure

scenarios, and combining exposure scenarios, are provided below.

The hazard identification step in the development of the aggregate risk assessment process must proceed in parallel with the development of appropriate exposure scenarios. The toxicity endpoint must match the temporal and spatial characteristics of the exposure scenarios selected as requiring inclusion in the assessment. However, the selection of exposure scenarios of concern will also be impacted by the toxicity profile of the pesticide, especially factors relating to the time of onset of effects and duration of effects or period of reversibility. Neither aspect of the assessment drives the other. Rather they must be evaluated in concert to ensure that all appropriate scenarios are accounted for and that all toxicity endpoints of concern are addressed.

2. Identify the potential exposures (including duration and route) for each pathway for each individual in the population. The universe of potential exposures should be constructed by first identifying the registered uses and the use patterns for the chemical.

In addition to considering the toxicological effect, dose level, duration of effect and timing of effect in developing logical aggregate exposure scenarios via all relevant routes of exposure, the analyst must also consider all registered uses and use patterns of the pesticide active ingredient. Evaluating all registered use patterns will enable the analyst to determine, for example, for the dietary pathway, which crops and crop groups should be included in the analysis; for the residential pathway, which uses are registered for the chemical and therefore which residential application scenarios should be included in the analysis; and, a review of registered uses and use patterns will allow the analyst not only to determine if a probability of drinking water contamination should be evaluated, but also allow the analyst to perform localized drinking water assessments, if necessary. Of the seemingly limitless combinations of dietary, residential and drinking water pathway scenarios to be developed in an aggregate exposure assessment, a review of the toxicologically appropriate constraints (*e.g.*, the duration of effect) and the registered uses and use patterns will likely, significantly limit the number of scenarios to be evaluated for each iteration of the aggregate exposure and risk assessment.

A key assumption underlying all aggregate exposure assessments is that exposure occurs at the level of an individual. During the construction of the aggregate exposure assessment, each of the "sub-assessments" (i.e., pathway and/or route specific assessments) must refer back to the same person. For instance, it would be inappropriate to utilize the consumption record of a 12-year old in the Northeast, in the winter, with the application of an outdoor lawn treatment, with regional drinking water assessment for an area other than the Northeast. In other words, the integrity of the exposed individual must be maintained throughout the aggregate exposure assessment.

Also, due to the complexity introduced into the risk assessment process, the identification of the potential exposure scenarios should be preceded by the bounding of all exposure scenarios. This is an important step in determining the scope of the assessment. This bounding process will greatly simplify the data preparation and calculation phases, but will also make the risk characterization process more transparent and useful by permitting the attention of the risk

manager to be focused on the more important aspects of the assessment. A first step in the bounding process is the evaluation of the relative contribution/importance of the various routes and pathways that may be of concern in the final risk estimate. Where a particular pathway will likely contribute less than 0.1% of thetotal risk, it should be noted in the risk assessment as extant but not included in the quantitative risk assessment. Similarly, if specific uses make negligible contributions to the risk assessment because of limited use or low consumption, or the toxicity by a particular route is low, the uses or routes should be noted in the risk assessment but not included in the quantitative risk assessment. The rationale for exclusion from the quantitative risk assessment should be explained in each case.

The negligible contribution from a pathway or route can be demonstrated by conducting a bounding estimate for a given pathway. A bounding estimate is one in which several conservative assumptions are combined to provide an estimate of exposure unlikely to be exceeded in actual occurrence. An example of a bounding estimate for dietary exposure is a Tier 2 acute assessment in which the entire crop is assumed to be treated and residues are assumed to be present at tolerance level. The actual exposure in the diet is unlikely to exceed this level and in most cases would be anticipated to be lower. For residential exposure assessments, use of the assumptions defined in the Draft Residential SOPs (US EPA, 1997a) with no adjustment for chemical specific data or other better data would provide a reasonable bounding estimate. The use of drinking water levels generated by existing models would provide a bounding estimate for the water portion of the assessment.

Where the contribution to exposure can be demonstrated to be negligible, these scenarios may be omitted from the assessment. Examples of negligible exposures may include the following: the absence of residential uses for residential assessments, registrations only for foods with low reported consumption values, use of child-proof packaging such as bait boxes, registrations only on minor use crops, low acreage applications, and for water, pesticides with low leaching or runoff potential or use patterns unlikely to impact drinking water resources. Arguments of negligible risk based upon toxicity considerations would include no evidence of adverse effect in adequately performed toxicity studies by a particular route or quantitatively different toxicity among routes such that one route would be likely to dominant the risk assessment. If other bases for arguing that a scenario represents negligible exposure or risk can be provided, they will be considered on a case by case basis. Unnecessary complexity (i.e., modeling parameters with little impact on the assessment) should be avoided. A sensitivity analysis will provide insight into the significance of any parameter in the risk assessment (See #9 of this section). In some instances, defaults or point estimates may be an adequate the level of refinement.

3. Reconcile the routes and duration of potential exposures with the routes and durations of the health effects. By matching exposures (by route and duration) with the toxicological endpoints (by route and duration) and then conducting an aggregate risk assessment on the matches only when the integrity of the individual relationship between the endpoint, route, and duration is maintained.

Determining which routes (e.g., ingestion, inhalation, and dermal) and pathways (e.g., diet, water, residential) to be aggregated is a key decision in the development of an aggregate exposure assessment. Two general factors control this decision process -- the biologically relevant dose and the potential exposure pattern of the active ingredient. The exposed individual's dose must be matched against a relevant toxicological dose in terms of route, duration, and effect. For example, evaluating the application of a lawn treatment in December in Maine may be allowable by the data, but defies the logic test. No such application is likely to take place and thus does not merit inclusion in the risk assessment. The careful evaluation of all route specific exposure scenarios based on timing of effect and other toxicologically relevant characteristics as well as the registered uses and use patterns, and then the matching of those scenarios based on data that support the combinations further assures the integrity of the aggregate exposure scenarios.

These assumptions for individuals may be extended to populations and sub-populations of concern by constructing distributions of individual doses. Assumptions must reflect time (duration, daily, seasonally); place (place and type of residence, urbanization, watersheds, region); and demographics (age, gender, reproductive status, ethnicity).

To illustrate this basic assumption, consider two individuals -- a man living in a single-family home in rural central Florida and a woman living in an apartment in Chicago. The individual in Florida depends on a private well for drinking water, performs his own lawn care, treats his home several times a year for roaches, has a private swimming pool, and eats locally produced food for nine months a year. The individual in Chicago depends on municipal drinking water, does not have a private lawn or swimming pool, lives in an apartment with monthly scheduled pest control service, and eats locally produced food only in the late summer. Based solely on time, place, and demographics it is likely that these two individuals have significantly different potential exposures to a given pesticide.

After defining the toxicological endpoint (effect) and route of concern, the assessor should decide upon the appropriate set of residential, dietary and drinking water exposure assumptions for combining these risk scenarios. The decisions concerning which residential scenarios should be considered in aggregate risk assessments should be made using the scenarios in the revised Residential SOPs as a basis for primary selection. Which scenarios should be used in combination in risk assessments are also discussed in the revised Residential SOPs. Furthermore, not all uses or scenarios can be considered as independent, that is, some types of products are likely to be used in combination if they are used at all.

4. Determine which of the possible residential exposure scenarios occur together (i.e., co-occur daily) and which occur independently.

Within the residential exposure pathway there are numerous exposure scenarios, via all routes of exposure. It is true that the use of one product may eliminate the use of another. For example, a homeowner is unlikely to use more than one type of roach repellant. However, the use of one home pesticide product may indeed guarantee the use of another. For example, conventional

treatment of flea infestation is to concomitantly treat the pet with a type of dog-dip and spray for the fleas in the home, so as to completely eliminate the problem and lessen the chance for reoccurrence. These types of co-dependencies and inter-relationships must be evaluated fully so as to eliminate unlikely combinations of residential exposure scenarios. There are standards being developed by EPA to identify co-dependencies and inter-relationships between events, and other data such as marketing data may be available to aid this task. It is vital all co-occurrences and co-variances be fully evaluated.

An example of a scenario in which multiple products are likely to be used is the flea infestation scenario. When a flea infestation occurs, a pet owner is likely to spray the pet, treat the carpet and bomb the residence in order to alleviate the problem and reduce the likelihood of recurrence. These three patterns of use would be viewed as linked for the purposes of aggregate risk assessment. Where adequate data are available, the residential component of the exposure should be included in the aggregate assessment through a series of probability distributions to combine the various scenarios with the dietary and water portions of the assessment. A presentation of OPP's guidance on preparation and submission of the residential portion of the exposure assessment can be found in the Guidelines for Submitting Probabilistic Analysis to the Office of Pesticide Programs. Information in this document is fully consistent with the preparation of aggregate risk assessments.

5. Determine magnitude (i.e., exposure concentration), frequency, and duration of exposure (i.e., contact) for all pertinent exposure combinations.

For all relevant exposure routes and pathways identified in the previous steps, the magnitude of exposure and risk must be calculated for each pathway/route separately, then brought together as a total risk value. The pathways/routes to be considered are dietary - oral; drinking water - oral; and, residential - oral, dermal, inhalation. Section III of this document describes the general considerations in determining the magnitude of exposure for these pathways. The magnitude of exposure may be determined through use of real data, such as for the dietary pathway, or, may be based heavily on modeled data and assumptions made in the absence of data, such as for the residential and drinking water pathways. The following section describes some of the specific points to consider when bringing together these three pathways/routes of exposure. Herein, the factors surrounding the appropriate matching of time and space, the matching of toxicological data with route specific scenarios, among other things, are discussed.

In order to bring together exposure pathways - dietary, residential, and drinking water exposure to chemicals used as pesticides - a number of steps must be taken. Of particular importance is the allowance for temporal and spatial considerations with regard to likely overlapping of exposures from a pesticide due to multiple sources of exposure. Temporal issues include those relating to seasonal variation within an exposure scenario. For example, certain types of behaviors such those relating to lawn care as stated earlier, may be unlikely to occur in the cold winter months. Similarly, contamination of water by corn herbicides is most likely to occur in the spring but less likely in the winter months. Another temporal aspect which must be

considered is the frequency of and time interval between exposure events. If a home owner fumigates a house today, it is unlikely that fumigation will be repeated tomorrow. However, residual exposure may continue for the next several days following fumigation although at a reduced level. Spatial considerations include at the grossest level the region of the country and climatic differences that may be anticipated. These include allowances for the seasonal differences in temperature that occur depending upon the region. In this example, the impact of region coincides with temporal considerations. For example, impacts of winter on use patterns for pesticides will be very different in Maine than in Florida. Another type of spatial consideration would be the identification of rural vs an urban setting. A private well as primary water source is much more likely to be associated with a rural setting than an urban setting. Similarly, regional production of fresh market produce may impact the need for a regional dietary assessment especially during peak harvest season. The following section describes in detail the types of steps one should consider when performing an aggregate exposure and risk assessment.

Specific Issues in Identifying the Potential Exposures from the Dietary Pathway for Aggregation

EPA anticipates that aggregate exposure scenarios will be developed around the dietary exposure pathway. That is, because the body of information is so great for this pathway compared to the other pathways, the development of the aggregate exposure scenarios will likely be driven by the information contained in the consumption database. As previously stated, aggregate analysis must be performed on an individual by individual basis in order to maintain the linkages and covariance between consumption data and demographic data. These data provide information on region of residence, season, and socio-economic status which may be useful in helping define likely related residential exposure scenarios. Similarly, regional differences in use rate and pesticide preference available from a variety of sources may also be related to region and permit development of more refined and focused risk assessments. These factors will also be important in selecting the appropriate drinking water data to combine in the assessment. An initial step in creating aggregate exposure scenarios is to identify the demographic profile of a sub-population upon which the assessment will focus. The age, sex and geographic location of this demographic would then be matched with exposure scenarios in the other two pathways of exposure, including appropriate assumptions concerning the likelihood and frequency of occurrence over time. The individual consumption records in the database matching the demographic descriptors will be used to simulate the consumption patterns of the sub-population of interest and the likelihood and frequency assumption for residential scenarios will be used to superimpose a pattern of residential exposures that would reasonably be expected to occur throughout the year. If a deterministic sampling regime is used, an average residue value would be used for a chronic assessment and an anticipated residue or tolerance value would be used for an acute analysis.

From the selection of an individual consumption record, other exposure scenarios are more easily defined. For example, if the consumption record selected was an infant 8 months old, female, in New England, this information would be used to select residential exposure scenarios that would

be feasible for different times of the year in New England. Also, this record would not be used in comparison with a pesticide applicator residential exposure scenario because an infant would not likely be a pesticide applicator. In addition, probabilities that drinking water source is well water or municipal would be assigned based on data on drinking water sources for that region of the country.

Specific Issues in Identifying the Potential Exposures from the Residential Pathway for Aggregation

Potential exposure to pesticides resulting from applications made in and around the home is influenced by temporal, spatial, and demographic considerations. In addition, age and gender characteristics also play a significant role when addressing aggregate exposure assessments.

In general, a decision to use a pesticide depends on a perceived need for control of a certain pest or group of pests. Those desiring a weed free lawn are inclined to use an herbicide at specified times of the year based on when weed seeds are germinating or shortly after they have emerged. A decision is made to make the treatment oneself or to hire a professional lawn care operator (LCO). Urban dwellers may live in housing in which chronic pests such as cockroaches are treated for on a routine basis. Exposure of young children, in these environments may be higher than adults due to their unique behavior (non-dietary ingestion, i.e., hand-to-mouth), increased activity or greater contact with the floor where pesticide applications may have been made.

Temporal considerations can be identified by focusing on the pest to be treated and if the application is to be made by the resident or a professional applicator. Weed control on lawns using broadcast applications is typically performed in the spring to control germinating or newly emerging weeds. Insects appear in lawns as the season progresses such as billbugs or sod webworms which occur in the summer. Summer weed control tends to be accomplished by the use of spot applications either made by the resident using a hand held sprayer to specific weeds or along patio borders. Professional applicators normally treat weeds during the summer on an as needed basis while making routine fertilizer treatments. Most LCO's have an additional trigger on their spray wands to activate the herbicide spray when they run into a weedy spot during the fertilizer treatment. Residents typically have poor knowledge of turf diseases thus less likely to use fungicides while professional lawn services are likely to anticipate disease conditions and make appropriate treatments. Temporal consideration regarding the use of LCO's regarding the time of the week an application is made. Treatments are likely to be made by a professional during the work week and by the resident on the weekend.

Spatial (geographic) considerations can also be identified by focusing on the site/pest considerations such as fire ants on lawns in the south. The use of a pesticide may be limited to cool season grasses which grow are primarily grown in the north and Midwest. Home gardens in the humid southeast may require more fungicide treatments than gardens in California. The periodic cicada is a problem in the northeast, yet does not occur in the Pacific Northwest.

Demographic considerations drive the use of a pesticide based on whether one lives in the city or the suburbs. Urban poor and rural poor may have different pesticide usage patterns based on likelihood of having a vegetable garden. Low income residents in suburban areas are less likely to hire lawn services while more affluent suburbanites may. Those who own homes may be more likely to hire lawn services than renters.

Age/gender/pathway considerations play a role in aggregate assessments due to the behavior of the individual. Young children may be exposed to more pesticide residues due to hand to mouth activity (non-dietary ingestion). Some national surveys of home and garden pesticide usage may suggest that more males than females treat lawns while females are more likely to treat the interior of the house. The combination of these types of considerations will aid in developing reasonable aggregate exposure and risk assessment scenarios.

Specific Issues in Identifying the Potential Exposures from the Drinking Water Pathway for Aggregation

Specific issues impacting potential exposure to pesticides through drinking water include: spatial, temporal, micro-environment, and treatment-related considerations. Exposure to pesticides in drinking water is usually a localized or regionalized phenomenon driven by pesticide use patterns and local hydrologic and climatological conditions. Because of this, it cannot be assumed that exposure to a pesticide in one region of the country will be the same for other regions. Drinking water exposures to pesticides should be incorporated into aggregate exposure assessments on a regional basis. This can be accomplished using distinct data sets collected in light of specific pesticide use patterns, i.e., drinking water concentrations of products used in the corn belt would not be assumed for all individuals across the entire country, but only for individuals in the region actually exposed. Multiple regional exposure assessments for drinking water will be performed and layered over the national exposure assessment determined for foods. Existing dietary exposure models can be used for different regions to incorporate both the regional distribution of pesticide concentrations in drinking water. And, regional drinking water consumption patterns. The quality of the regional exposure assessments for drinking water will be dependent on the quality and extent of the regional data sets available on pesticides in finished drinking water.

Because drinking water exposures to pesticides are regional in nature, regional drinking water data on pesticides should be matched as much as possible with other regionally-based sources of exposure for the same compound should be matched with any regionally-specific residential uses of the product, i.e., drinking data for a pesticide in the rice-growing regions of the Southeast and California should not be matched with exposure data for garden uses only in the Northeast. Food exposures will generally be assumed to be nationally distributed.

Pesticide impacts on drinking water are often seasonal in nature driven by time of application and the weather conditions shortly after application. Because of this, temporal variation in pesticide concentrations in drinking water must be considered in any aggregate exposure assessment for drinking water. Temporal variation should be considered in any monitoring study design. There

is general consensus that drinking water should be sampled more frequently during the pesticide use seasons (usually spring and summer) with sampling tapering off during the non-crop, non-use seasons (usually fall and winter). Any data set resulting from a monitoring scheme that incorporates temporal variability will have to be weighted appropriately such that the frequencies of sampling were represented in a valid manner before use in an aggregate exposure assessment.

Within a region, there may be "hot spots" where the impact of a pesticide(s) on drinking water is unique. Rural ground water wells sited in vulnerable areas frequently qualify for treatment as "hot spots" for drinking water in an aggregate exposure assessment. Data specific to the area and the drinking water wells in that area are used to estimate the exposure and risk for those wells only and are not extrapolated beyond the immediate area. Additional monitoring data may be required to establish the bounds of the "hot spot."

Recognizing the need to identify pesticide contamination on a localized or regional basis as directed by the pesticide's use pattern, and the types of monitoring data available and expected in the future, a general approach to incorporating drinking water concentration data into aggregate exposure and risk assessments has emerged. Ideally, data collected on the distribution of pesticide concentrations in drinking water from sites considered to represent most-vulnerable conditions is factored into the aggregate exposure in light of other exposure pathways (food, home-uses, swimming). Data from most-vulnerable sites could be combined for a regional assessment that provides an upper bound estimate of exposures in a region. If exposure and risk estimates resulting from incorporation of these concentration values are of concern, then monitoring data collected on a regional basis would be included to broaden the aggregate exposure and risk assessment beyond the most-vulnerable sites. Sites considered to be more typical and less vulnerable to contamination by pesticides would be included to assess exposure outside of the most-vulnerable setting.

Treatment related issues must be considered in any drinking water exposure assessment. Municipal drinking water facilities across the nation use a variety of treatment processes in delivering finished drinking water to the public. In addition, drinking water obtained from private wells is mostly untreated. Any aggregate exposure and risk assessment cannot be considered complete until the effects of treatment, if any, in whatever form (sedimentation, flocculation, chlorination, filtering through granular-activated carbon, etc.) have been included.

Situations may exist where isolated sub-populations have a different potential for exposure through drinking water to a pesticide than the vast majority of the population. Conditions for these situations exist where a pesticide's use pattern is very specific, *i.e.*, application to a specific ornamental plant in one county. Although the potential for exposure to the pesticide through drinking water may be low, it still exists. In this situation, only the population potentially affected, i.e., living in the county, should be considered in the risk assessment. The rest of the population would be considered unexposed and therefore not at risk. A pesticide with a broader use pattern can impact different drinking water sources to different degrees. A particularly vulnerable water source should not be the basis for an exposure assessment for individuals living

nearby, but drinking from another, less vulnerable, source. In these situations it is ideal to know the population associated with any drinking water source potentially impacted by a specific pesticide use pattern. Knowing the populations served by a drinking water source allows for population-weighted exposure assessments. Aggregate risk assessment procedures have to be flexible enough to accommodate these situations as they do exist.

6. Determine most appropriate technique (deterministic or probabilistic) for incorporating data into exposure algorithms.

Once input data are collected for exposure variables of interest, several techniques are available for representing these variables. EPA has traditionally used a deterministic approach to generate a single estimate of exposure and risk based on expressing all input variables in the exposure algorithm as single values. Alternatively, one could use probabilistic techniques to more fully incorporate available information taking into account the range of possible values that an input variable could take, and weighting these values by their probability of occurrence. Probabilistic techniques acceptable to EPA are discussed in a recently developed guidance (US EPA, 1998d).

Availability of data may determine the best sampling regime, either deterministic or probabilistic. The Aggregate Exposure and Risk Assessment Guidelines are written, however, assuming that a probabilistic sampling regime will be utilized. If both deterministic and probabilistic sampling regimes must be used for different pathways in the same aggregate assessment, consult the interim guidance on performing aggregate risk assessment (USEPA, 1997c).

7. Determine appropriate risk metric to be used in analysis and calculating aggregate exposure and risk.

There are several methods of measuring and aggregating risk for single chemical, multi-route, multi-source assessments. The following three methods are among those used by the Agency. Two aggregation methods were developed by HED – the Total MOE and the Aggregate Risk Index – which are easy to use and do not require route extrapolations (Whalan and Pettigrew 1998). A third method – The Hazard Index – is the reciprocal of the Aggregate Risk Index and is used for Superfund risk assessments (USEPA, 1989) and is being considered for use in HED. The selection among these methods depends, in part, on the required use of uncertainty factors.

Currently risk assessments in HED are based on the Margin-of-Exposure (MOE) concept. As a rule, risk increases as the MOE decreases. Each MOE is compared against an Uncertainty Factor (UF) which serves as a standard when ascertaining whether a given hazard is acceptable.

Total MOE (MOE_T) Method:

The following aggregation equation has been used since April 1996 to aggregate "unit-less" MOEs into a **Total MOE** (**MOE_T**). This concept was presented to, and endorsed by, OPP's

Science Advisory Panel (McConnell *et al.*, 1997):

Equation 1

$$MOE_T = \frac{1}{\frac{1}{MOE_1} + \frac{1}{MOE_2} + \ldots + \frac{1}{MOE_n}}$$

All MOEs must be compared against the same Uncertainty Factor (UF - typically 100 for interspecies extrapolation and intraspecies variability), as in this example:

Oral	MOE = **100**	UF = 100
Dermal	MOE = **200**	UF = 100
Inhalation	MOE = **70**	UF = 100

Equation 2

$$MOE_T = \frac{1}{\frac{1}{100_O} + \frac{1}{200_D} + \frac{1}{70_I}} = \mathbf{34.1}$$

The MOE_T is always lower than the lowest MOE. The MOE_T decreases with each additional MOE in the equation because each additional exposure increases the hazard. The lowest MOE (the inhalation MOE of 70 in this example) has the most influence on the MOE_T. The MOE_T of 34.1 is of concern because it is less than the acceptable UF of 100. A major deficiency of this method is that it cannot accommodate dissimilar UFs (i.e., UFs other than 100), such as when using human data

Ideally, route-specific MOEs for each route of exposure should be aggregated. When inadequate toxicity data make this impossible, data from another route can be substituted, although this introduces some degree of error. For example, an inhalation MOE can be calculated by using an oral NOAEL that has been extrapolated to an "equivalent" inhalation NOAEL. Error results from using an extrapolation method that does not account for pharmacokinetic differences between the routes, and from assuming that the route with no data will have the same toxic signs as the well characterized route.

Aggregate Risk Index (ARI) Method:

The Aggregate Risk Index (ARI) was devised as a way to aggregate MOEs that have dissimilar UFs. Because of its versatility, it supersedes the Total MOE method, and has been used in HED since February 1998. MOEs for each route of concern are compared against UFs which reflect the nature, source, and quality of the data, and the FQPA mandate to protect susceptible fetuses and children. This can result in a variety of UFs such as these:

	Oral	**Dermal**	**Inhalation**

MOE:	300	100	1000
	———	———	———
UF:	1000	100	300

MOEs can only be combined if they have a common UF. If the MOE/UF ratios for each route are treated as fractions (as shown above), they can be adjusted to a common denominator of 1. This is accomplished by dividing each MOE by its UF to yield a **Risk Index** (**RI**):

	Oral	**Dermal**	**Inhalation**
RI:	0.30	1.0	3.3

The RIs can then be combined to yield an **Aggregate Risk Index (ARI)**:

Equation 3

$$ARI = \frac{1}{\frac{1}{RI_1} + \frac{1}{RI_2} + \ldots + \frac{1}{RI_n}}$$

Equation 4

$$ARI = \frac{1}{\frac{1}{0.30_O} + \frac{1}{1.0_D} + \frac{1}{3.3_I}} = 0.22$$

RIs and ARIs are always compared against 1. This allows for direct comparisons between routes and between chemicals. As a general rule, an RI or ARI ≥ 1 is of little concern, but an RI or ARI <1 suggests a risk of concern. In this example, the ARI (0.22) suggests a risk of concern because it is <1. The oral exposure has the lowest RI (0.30), so it is the major route of concern.

The Aggregate Risk Index (ARI) is an extension of the MOE concept. As with the MOE, risk increases as the RI or ARI decreases. The ARI method automatically considers each route's potency when route-specific NOAELs are used. The following equation is a simplified way of calculating a chemical's ARI in a single step:

Equation 5

$$ARI = \frac{1}{\frac{UF_1}{MOE_1} + \frac{UF_2}{MOE_2} + \ldots + \frac{UF_n}{MOE_n}}$$

Oral hazards are usually expressed as the "Percent of RfD" rather than as an MOE. Because the UF for the oral route is used to define the oral RfD, the percent of RfD (expressed as a decimal) can be put directly into the equation (assume oral exposure is 80% of the RfD, i.e. 0.8):

Equation 6

$$ARI = \frac{1}{\%\ RfD_O + \frac{UF_D}{MOE_D} + \frac{UF_I}{MOE_I}}$$

Equation 7

$$ARI = \frac{1}{0.8_O + \frac{100_D}{100_D} + \frac{300_I}{1000_I}} = 0.48$$

Percentages of RfDs and RfCs for all routes may also be aggregated:

Equation 8

$$ARI = \frac{1}{\%\ RfD_O + \%\ RfD_D + \%\ RfC_I}$$

Hazard Index (HI) Method:

The **Hazard Index** (**HI**) is another aggregation method used by other parts of the Agency. The HI is an aggregation of individual **Hazard Quotients** (**HQ**) for each route of exposure. The HQ, which is a percent of RfD or percent of RfC, is calculated as follows:

Equation 9

$$HQ = \frac{Exposure\ (mg/kg)}{RfD\ (mg/kg)} \qquad HQ = \frac{Exposure\ (mg/L)}{RfC\ (mg/L)}$$

This method requires that an oral RfD, dermal RfD, and/or inhalation RfC be defined for each route of concern (the RfD and RfC are calculated by dividing a NOAEL by a summation of UFs). HQs (*i.e.*, percent of the reference dose (RfD) or reference concentration (RfC)) for each route of concern can be aggregated into an HI:

Equation 10

$$HI = HQ_O + HQ_D + HQ_I$$

Risk increases as the HQ or HI increases. As a general rule, an HQ or HI ≤ 1 is of little concern, but an HQ or HI >1 suggests a risk of concern. The ARI is the reciprocal of the HI (compare Equations 8 and 10).

8. Conduct analysis to determine the magnitude of exposure and risk for each pertinent exposure pathway. Aggregate as appropriate, exposure and risk by route, then by pathway, into a total exposure and risk from all routes and pathways. Several aggregate exposure and risk assessments may be required for a single active ingredient.

The basic concept underlying all aggregate exposure assessments is that exposure occurs to an individual. The integrity of the data concerning this exposed individual must be consistently

maintained throughout the aggregate exposure assessment. Each of the individual "sub-assessments" must be linked back to the same person and the aggregate intake must refer to dietary, drinking water, and residential intakes that are for the same individual at the same time, in the same place, and under the same demographic conditions. In other words, the aggregation must be *simultaneously* temporally, spatially, and demographically specific, i.e., they must agree in time, place, and demographic characteristics. It would be incorrect, for example, to simulate an individual's exposure by randomly selecting a dietary contribution from an entire population's distribution of dietary exposures, combining that contribution with an independently randomly selected drinking water contribution from an entire population's distribution of drinking water exposures and combining these two independently selected contributions with a third independently randomly selected residential contribution from an entire population's distribution of residential exposures.

To develop realistic aggregate exposure and risk assessments for these two individuals requires that the appropriate temporal, spatial, and demographic exposure factors be correctly assigned and consistently maintained. Specific considerations should include:

- Time (duration, frequency, and seasonality of exposure; seasonally-based pesticide residues in food; frequency of residential pest control which reflects housing location and type);

- Place (location and type of home; urbanization, watershed or aquifer characteristics; region; regionally specific drinking water concentrations of the pesticide being considered); and

- Demographics (age; sex; sex- and age-specific body weights; reproductive status; ethnicity; personal preferences, behaviors, and characteristics).

Aggregate exposure and risk assessment are first completed for individuals, who are then combined to develop distributions of exposure to subpopulations and populations.

Exposures and resulting risks must be combined for all routes that result in qualitatively similar toxic effects. If the effects of concern are not qualitatively the same, then the exposures should not be combined. Individual exposure and risk assessments should also be conducted for each potential route and source of exposure. Individual exposure assessments will provide the basis for developing risk mitigation strategies in the event that an unacceptable aggregate risk is indicated.

The choice of input distribution should always be based on all relevant information (both qualitative and quantitative) available for input. The selection of a distributional form should consider the quality and quantity of the information in the database, and should address broad questions such as the mechanistic basis for choosing a distributional family, the discrete or continuous nature of the variable, and whether the variable is bounded or unbounded. In all

cases, input values expressed as a distribution should be fully described. (US EPA, 1998c)

We note, however, that not all input values need, or should, be expressed as a mathematically-modeled distribution, and probabilistic techniques should be used only on those pathways and exposure patterns which significantly influence the final risk estimate. If an input variable does not significantly affect an exposure estimate regardless of its distribution, then its use in a probability distribution represents marginal value added. A sensitivity analysis should be performed to identify variables with significant effects on an assessment. (US EPA, 1998c)

9. Conduct sensitivity analysis to identify the driver or sources of risk for each route. Identify scenarios of concern, such as highly exposed sub-populations by sources.

After performing an aggregate exposure and risk assessment, it may be helpful to also conduct sensitivity analysis to ascertain the route, pathway, exposure scenario, commodity, or other element of the analysis, which contributes the highest amount to total exposure and risk. Those routes and pathways with the lowest risk index (RI) or the greatest hazard quotient (HQ) pose the greatest risk, and are the most likely candidates for risk mitigation. Sensitivity analyses are performed to learn how changes to input assumptions affect changes in the result. Sensitivity analysis in aggregate exposure and risk assessment are performed by examining areas of high exposure and defining the differences in total exposure and risk without those exposure contributors. For example, in dietary exposure assessment commodities with the most extensive use patterns, greatest consumption reported, and high magnitude of residue data are likely to contribute the largest overall exposure for the dietary pathway. The inclusion/exclusion of this type of commodity from the analysis could provide valuable information as to the relative importance of this commodity to total exposure and risk. A similar approach can be taken in examining the relative contribution of other routes of exposure or exposure pathways or other exposure scenarios within a pathway. For example, the analysis may focus upon which route of exposure contributes the largest portion of the total exposure, which residential scenario of the many that could be included in a single aggregate analysis is the greatest contributor to exposure, or for the dietary exposure pathway, which commodity or commodities are the greatest contributors to the total dietary exposure value. With this knowledge, an aggregate exposure and risk assessor may be able to delineate ways in which total exposure and risk could be reduced, state for risk management purposes the pathway of exposure which represents the greatest proportion of the total risk, or decide where future data gathering efforts should be focused. Sensitivity analyses are particularly useful in deciding whether or not to elevate a pathway specific analysis to the next level of data refinement.

V. Reporting Requirements

Format

The format for an aggregate risk assessment report should fully describe and document the 9 steps for conducting an aggregate risk assessment as detailed above in these guidelines. In addition, information should be provided on: purpose and scope; inputs and assumptions; data sources; exposure algorithms and scenarios; and, definition of defaults. These are described below.

Clearly state the purpose and scope of the assessment in a"problem formulation" section that includes a full discussion of any highly exposed or highly susceptible subpopulations evaluated (e.g., children, the elderly). The questions the assessment attempts to answer are to be discussed and the assessment endpoints are to be well defined. And, list all inputs and assumptions for exposure and hazard portion of the assessment. Information for each input and output distribution is to be provided in the report. This includes tabular and graphical representations of distributions (e.g., probability density function and cumulative distribution function plots) that indicate the location of any point estimate of interest (e.g., mean, median, high-end percentiles). The selection of distributions is to be explained and justified. Indicate whether distributions used for input parameters reflect re-sampling of empirical distribution functions or imputations.

The sources for data used in an assessment should be clearly identified. Where these are studies that have previously been submitted to OPP, and/or reviewed by the Agency, identifying information such as petition number, reregistration submission, document number (MRID), or Agency review number should be provided, so the data points may be readily confirmed. Where data points have been excluded from the probabilistic analysis, the exclusion should be identified and justified. Studies from which data are obtained should contain sufficient quality assurance/quality control of data to assure sample integrity during treatment, collection, transportation, storage, and analysis.

A discussion of the exposure algorithm and its appropriateness for the scenario and population under study is required. Names of models and software used to generate the analysis should be identified. Routes of exposure should be clearly defined. Sufficient information is to be provided to allow the results of the analysis to be independently reproduced. And, the analyst should define all defaults used and explain why they are reasonable. Assumptions that have a significant impact upon the results, are to be documented, explained and easily located in the report.

Discussion of Uncertainties

The uncertainties inherent in the evaluation of each of the pathways are described herein.

Residential Exposure

The ability to reconcile environmental measurements, human activity patterns that contribute to

potential exposure, and the biological factors that ultimately lead to absorbed dose is a challenge for all exposure assessors. Residential exposure offers unique challenges for exposure assessors attempting to estimate non-dietary, residential exposure, under the FQPA. Many of the current estimates (post application in particular) are made in the absence of formal guidance by the Agency. Although, the Agency's Office of Research and Development is conducting and designing studies to support post application and residential model development, the results of those studies are likely to be unavailable for the immediate future. Similar exposure studies to be generated by industry task forces are also in the design phase.

The current post-application residential exposure models addressing re-entry onto treated lawns and carpets are simple algorithms. Estimates (*e.g.*, Guranathan et al., 1998) need to be viewed in the context of available health surveillance data and studies in which biological monitoring was performed following structured activities. Biological monitoring studies such as those of young children living in the immediate vicinity of pesticide treated orchards (Loewenherz *et al.*, 1997, Simcox *et al.*, 1995) can also provide insight regarding the magnitude of residential exposure. While the models discussed above often predicted up to thousands of micrograms per kilogram body weight, the available biological monitoring data and health surveillance data suggest approximately 15 micrograms (or less) per kilogram body weight. The Agency is currently evaluating the default assumptions in the available model/algorithms which may inflate exposure estimates.

Methods of estimating residential exposure while applying pesticides is a more straightforward approach. To estimate residential handler exposure, Agency exposure assessors use surrogate data available in the Pesticide Handler's Exposure Database (PHED). These data are based on guideline studies, in which compensatory claims have been waived, and other published data. While these data consist of one or two studies, and may contain many non-detects, they do address activities that are reasonably well defined. Where uncertainty exists, is when exposure assessors estimate how much pesticides residents use to treat their homes, lawns and gardens, and how often are those applications made. These questions can be answered through the use of data available though marketing services, company data, or well designed surveys, when available.

Post application exposure following treatment of vegetables is also based on activities that are fairly well defined and based on models designed to estimate farm worker exposure. Often estimates of available residues can be estimated. However, chemical dissipation rates are often unavailable.

Post application inhalation exposure can be addressed using survey data from the National Human Activity Pattern Survey (NHAPS) and well defined ventilation rates available in the Agency's Exposure Factors Handbook (USEPA, 1997b). Surveys such as NHAPS can put individuals in a place for a period of time conducting an certain activity. Exposure is estimated by matching an activity, a duration and ventilation rate. What is often unknown is airborne concentrations of pesticides following applications and their subsequent dissipation.

Dietary Exposure

The dietary exposure pathway is perhaps the most thoroughly investigated pathway included in the aggregate exposure and risk rubric. Mainly due to the length of time in which EPA has assessed total exposure and risk to the general population and significant sub-populations, this exposure pathway is relatively well defined. There are uncertainties in the exposure analysis, however, the uncertainty decreases as higher tiers in dietary exposure analysis are reached. Uncertainties present in the dietary exposure and risk pathway may include the use of maximum use rates instead of "typical" pesticide use rates; this may overestimate exposures. Uncertainties may also be presented by the use of field trial data performed in past years which may not reflect current geographical distributions of pesticide uses and therefore not help capture the most accurate picture of residue values. And, although percent of crop treated information collected nationally are highly refined, even more accurate data may be available in the form of the individual company marketing information or data from growers or producers. These uncertainties should be considered as the dietary exposure pathway is investigated within an aggregate exposure and risk assessment.

Drinking Water

Whether using screening-level models to estimate pesticide concentrations in drinking water or the available monitoring data on water quality, there are various sources of uncertainties associated with incorporating data on exposure to pesticides in drinking water into an aggregate exposure and risk assessment. The following is a brief discussion of some of these uncertainties and levels of confidence associated with water quality models and monitoring data available for use in aggregate exposure assessments.

OPP believes the results provided by the computer simulation models currently used at the first tier 1 of analysis for pesticide concentrations in surface water do not accurately characterize either the effects of dilution and/or potential treatment at a drinking water facility. In addition, the small static pond scenario currently used does not accurately reflect the dynamics in a watershed which is large enough to support a drinking water facility.

Therefore, the models' limitations increase the uncertainty in the semi-quantitative exposure assessment which is based on their results. Consequently, OPP has low confidence in exposure assessments for drinking water based on current modeling results. Consideration by the International Life Sciences Institute (ILSI) panel and the FIFRA Scientific Advisory Panel (SAP) of the computer simulation models has prompted the OPP to develop a model scenario that more accurately reflects pesticide concentrations in reservoirs that are large enough to be used for drinking water.

Uncertainty is lower and confidence higher, respectively, for the results from the model for estimating pesticide concentrations in ground water because ground water concentrations estimated from the model have been shown to represent the upper 1% or less of measured

pesticide concentrations in ground water in the U.S. Therefore, although overestimates, they do represent the upper bound of distributions of pesticide concentrations actually monitored in ground water.

Data sets on pesticide concentrations in drinking water exist for very few compounds. Much of the currently available data, such as the USGS NAWQA program and data available in STORET, do not represent finished drinking water, and can only be used with low confidence and high uncertainty in aggregate exposure assessments for drinking water. These data do not incorporate the effects of dilution, distribution and treatment, if present. In addition, many of the available data sets on water quality were not conducted with a foreknowledge of documented pesticide use in the areas sampled. This introduces additional uncertainty into the data with respect to extent of pesticide contamination. In general, confidence in a data set increases if that data set represents finished drinking water sampled for specific pesticides from areas where specific pesticide use is known and well documented. Where these available data do represent finished drinking water and specific pesticide use can be correlated with any findings, they could be used with a moderate degree of confidence in an aggregate exposure assessment for drinking water.

The highest degree of confidence and lowest uncertainty is associated with data representing finished drinking water sampled for specific pesticides known to be highly to moderately used in areas surrounding the drinking water facility. A range of drinking water facilities stratified across those considered to be most vulnerable to contamination to those considered to be more typical would be included in a data set associated with a high level of confidence. For surface water, these vulnerable areas are represented by small to medium sized watersheds in agricultural areas that are heavily cropped. For ground water, agricultural areas with shallow depths to potable ground water, coarse or sandy soils, and high recharge rates are considered vulnerable to contamination from pesticides.

Data Needs

Drinking Water

There is consensus among the water quality modeling community that a basin-scale water quality model to estimate concentrations of pesticides in finished drinking water with a moderate to high level of confidence does not exist and would be many years in development.

Therefore, in the short term, OPP needs to improve the current screening level models used to estimate the concentration of pesticides in drinking water, particularly for surface water. Several approaches are being considered: 1) The use of a crop area factor to take into account that 100 percent of a basin supporting a drinking water facility may not be cropped, and 2) the small pond scenario currently incorporated into OPP's screening-level water quality models will be modified to simulate a small reservoir that is large enough to support a drinking water facility.

For pesticides that are not screened-out by models and/or available monitoring data representing

either drinking or non-drinking water supplies, data are needed on pesticide concentration distributions in finished drinking water for use in probabilistic aggregate exposure and risk assessments. Focused, targeted monitoring stratified across a variety of drinking water sources (vulnerable & typical) with known pesticide use for relevant pesticides are preferred. Data sets from most vulnerable drinking water sources (larger facilities serving large populations) could be used with high confidence to bound the upper end of the distribution of pesticide concentrations in drinking water. Data sets from more typical drinking water sources could be used with high confidence to bound the middle of the distribution of pesticide concentrations in drinking water. For incorporating drinking water into acute and chronic aggregate exposure and risk assessments these are the most critical portions of the pesticide concentration distribution.

Data for specific exposure and risk assessments associated with hot spots where drinking water is adversely impacted by pesticide use in specific vulnerable areas may be needed on a case-by-case basis.

Dietary

The development of probabilistic aggregate risk assessment tools has greatly expanded the level of detail with which risk assessment can evaluate the variability and impact of pesticide use and usage patterns on risk estimation. The importance of the rate of application of pesticides to foods and the distribution of pesticide use has been recognized as a potential area for refinement in estimating dietary exposure which has not be included in the assessment process. The Monte Carlo Guidance document includes a discussion of how use/usage data to date can be better included in the risk assessment. That document also describes acceptable sources of data and how the data will be used. Other possible modifications to dietary assessments might include adjustment for residue levels in foods based upon differences in use patterns on fresh market and processed commodities or information concerning domestic vs foreign production during different seasons.

Residential

The ability to determine the likelihood of coincidental dietary and non-dietary exposure requires access to detailed use information. Use information includes details regarding the amount of pesticide applied per use, the frequency of usage events and an estimate of the numbers and kinds of people making these applications. In addition, exposure assessors must be aware of applications made by consumers and applications made by professional for hire services such as, professional control operators (PCO's) and professional lawn care operators (LCO's). Usage information sources include inferences from pesticide product labels and information provided by BEAD taken from proprietary market research service firms such as Doane and Kline. States such as California have databases of usage information which may not represent other regions and associations representing professional for hire services may also have usage information helpful for assessors. Information from any of the above sources is not routinely provided.

Frequency of use information, on a national scale, is available in the Agency's National Home and Garden Pesticide Usage Survey (NHGPUS). However, this survey is 10 years old and focuses only on major use pesticides. In addition, this survey, tells us very little about post application activities.

Many firms, particularly firms that reformulate basic producers' products, have extensive consumer market share information. Unfortunately, these data are proprietary and considered very valuable from a business perspective. There are no regulatory tools in place making these marketing data, a data requirement, nor are there any mechanisms in place ensuring their confidentiality. That is, preventing marketing information being gleaned from one firm's database, and ending up in an exposure assessment for a product made by another firm.

Increasingly, as pesticide registrants form data generating Task Forces in response to the FQPA, longitudinal surveys are being considered. These surveys are being designed to address usage, frequency of use, and other key information needed in an aggregate assessments such as demographic, geographic and seasonal variation. These surveys are also considering information regarding post application activities. Careful consideration is required regarding the design of the study as well all parties having a clear idea as to how these data are going to be used in risk assessments. Once the survey data are available, confidentiality becomes an issue as discussed above, with respect to task force members and non-members.

Use of Biomonitoring Data for Validation of Aggregate Exposure and Risk Assessments

Biological monitoring, or biomonitoring, provides a basis for estimating an internal dose by measuring a pesticide and/or its metabolite concentrations in selected body tissues or fluids. When done quantitatively, the internal dose determined from biomonitoring reflects exposures (i.e., absorbed doses) from all possible routes. Since the internal dose calculated from biomonitoring represents that from all pathways by all routes, biomonitoring potentially provides a method of validation for aggregate exposure assessments.

The most appropriate methods for biological monitoring should be chosen based on a thorough knowledge and understanding of the pharmacokinetics of the specific pesticide in humans. Detailed guidance for the design and execution of biological monitoring studies are presented elsewhere (US EPA, 1998 and references therein). For certain pesticides, biological monitoring may not be an appropriate validation technique. Consider a particular pesticide that is extensively metabolized to a large number of minor metabolites. Each minor metabolite may be subject to inter-individual variability. The following example illustrates the degree of potential inaccuracy in predicting absorbed doses from minor metabolites. A minor metabolite may represent an average of 2 percent of the absorbed dose with reported values ranging from 0.5 percent to 5.0 percent in human volunteers. Using the average value would require the use of a 50-fold correction factor to calculate an absorbed dose. Conversely, if the 5 percent value is representative, a correction factor of 20-fold would be required. It is recommended that a suitable biological monitoring marker metabolite would represent at least 30 percent of the

administered dose, with a range of values not exceeding a factor of three in human volunteer studies.

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GLOSSARY

Absorbed dose: The amount of a substance penetrating across the absorption barriers (the exchange barriers) of an organism, via either physical or biological processes. Synonymous with internal dose. (US EPA, 1992).

Active ingredient (ai): The chemical component of a pesticide formulation or end-use product that is intended to act as a pest deterrent. The biologically active chemical agent in a pesticide product (US EPA, 1997a).

Aggregate dose: the amount of a single substance available for interaction with metabolic processes or biologically significant receptors from multiple routes of exposure.

Aggregate exposure assessment: A process for developing an estimate of the extent of a defined population to a given chemical by all relevant routes and from all relevant sources (ILSI, p. A-2).

Aggregate risk: the likelihood of the occurrence of an adverse health effect resulting from all routes of exposure to a single substance.

Biomonitoring: Measurement of a pesticide or its metabolites in body fluids of exposed persons, and conversion to an equivalent absorbed dose of the pesticide based on a knowledge of its human metabolism and pharmacokinetics (Woollen, 1993).

Cumulative Risk: the likelihood of the occurrence of an adverse health effect resulting from all routes of exposure to a group of substance sharing a common mechanism of toxicity.

Dislodgeable residue: The portion of a pesticide (which may or may not include its metabolites) that is available for transfer from a pesticide treated surface US EPA, 1997a).

Dose: The amount of a substance available for interaction with metabolic processes or biologically significant receptors after crossing the outer boundary of an organism (US EPA, 1992).

Dose rate: Dose per unit time (e.g., mg/day). Also called dosage. Dose rates are often expressed on a per-unit-body-weight basis (mg/kg/day). Dose rates may also be expressed as an average over a time period (i.e., lifetime) (US EPA, 1992).

Exposure: Contact of a chemical, physical, or biological agent with the outer boundary of an organism. Exposure is quantified as the concentration of the agent in the medium in contact integrated over the time duration of that contact (US EPA, 1992).

Exposure assessment: The qualitative or quantitative determination or estimation of the magnitude, frequency, duration, and rate of exposure of an individual or population to a chemical.

Exposure scenario: A combination of facts, assumptions, and inferences that define a discrete situation or activity where potential exposures may occur (US EPA, 1997a).

Intake: The process by which a substance crosses the outer boundary of an organism without passing an absorption barrier, e.g., through ingestion or inhalation. (See also potential dose). (US EPA, 1992)

Level of Comparison: A drinking water level of comparison is a theoretical upper limit on a pesticide's concentration in drinking water in light of total aggregate exposure to a pesticide in food, drinking water, and through residential uses.

Pathway: The physical course a chemical or pollutant takes from the source to the organism exposed. Also called **exposure pathway** (US EPA, 1992).

Potential dose: The amount of a chemical contained in material ingested, air breathed, or bulk material applied to the skin (US EPA, 1992).

Route: The way a chemical or pollutant enters an organism after contact, e.g., by ingestion, inhalation, or dermal absorption. Also called **exposure route** (US EPA, 1992).

Surrogate data: Substitute data or measurements on one substance (or population) used to estimate analogous or corresponding values for another substance (or population).

Transfer coefficient: Residue transfer rate to humans during the completion of specific activities (e.g., cm^2 per hour), calculated using concurrently collected environmental residue data (US EPA, 1998).

Unit exposure: The amount of a pesticide residues to which individuals are exposed, normalized by the amount of active ingredient used.

Uptake: The process by which a substance crosses and absorption barrier and is absorbed into the body (US EPA, 1992).