Guidance on Cumulative Risk Assessment of Pesticide Chemicals That Have a Common Mechanism of Toxicity

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EXECUTIVE SUMMARY

In assessing the potential health risks associated with exposure to pesticides, attention has historically focused on single pathways of exposure (e.g., from pesticide residues in food, water, or residential/nonoccupational uses) for individual chemicals, and not on the potential for individuals to be exposed to multiple pesticides by all pathways concurrently. In 1996, the Food Quality Protection Act (FQPA) imposed upon the Office of Pesticide Programs (OPP) the requirement to consider potential human health risks from all pathways of dietary and nondietary exposures to more than one pesticide acting through a common mechanism of toxicity. This document provides guidance to OPP scientists for evaluating and estimating the potential human risks associated with such multichemical and multipathway exposures to pesticides. This process is referred to as cumulative risk assessment.

The current guidance has been revised in light of review and comment offered by the public on an earlier draft version during the public comment period of June to September 2000 (USEPA, 2000a; 65 FR 40644), by the FIFRA Scientific Advisory Panel (SAP) in September and December 1999 (USEPA, 1999j and 2000g), and by comments offered by other external parties at the SAP meetings. Furthermore, OPP has gained experience in implementing the draft guidance itself with actual datasets on pesticides that share a common mechanism of toxicity. A pilot analysis was presented to the SAP on 24 organophosphorus pesticides illustrating the hazard and dose-response guidance in September 2000, and on the exposure assessment and risk characterization process in December 2000. The SAP comments on this pilot analysis have also led to refinements in the process of conducting cumulative risk assessments.

Cumulative risk assessments may play a significant role in the evaluation of risks posed by pesticides, and will enable OPP to make regulatory decisions that more fully protect public health and sensitive subpopulations, including infants and children. The cumulative assessment of risks posed by exposure to multiple chemicals by multiple pathways (including food, drinking water, and residential/nonoccupational exposure to air, soil, grass, and indoor surfaces) presents a formidable challenge for OPP. This guidance takes into account the knowledge and methods available now for assessing cumulative risk, and provides flexibility for addressing a variety of data situations. Because methods and knowledge are expected to continue to evolve in this area, OPP will update specific procedures with peer-reviewed supplementary technical documentation as needed. Further revision of the guidance itself will take place when extensive changes are necessary.

Before undertaking a cumulative risk assessment on pesticides sharing a common mechanism of toxicity, OPP will typically perform an aggregate risk assessment for each chemical in the common mechanism group. When conducting aggregate assessments, OPP uses the guidance described in the document entitled *General Principles For Performing Aggregate Exposure And Risk Assessments* (USEPA, 2001h). The aggregate guidance recommends that the risk assessor simultaneously consider the exposures from food, drinking water, and residential/nonoccupational uses of a pesticide. When the aggregate risk assessments are completed for individual chemicals that share a common mechanism of toxicity, OPP will consider a cumulative risk assessment in the steps summarized below.

A cumulative risk assessment begins with the identification of a group of chemicals, a common mechanism group (CMG), that induce a common toxic effect by a common mechanism of toxicity. OPP has developed a general framework for identifying the chemicals that belong in that group (see *Guidance for Identifying Pesticide Chemicals and Other Substances That Have a Common Mechanism of Toxicity*, USEPA, 1999a). Once a CMG has been established, the next step is to evaluate registered and proposed uses for each CMG member in order to identify potential exposure pathways (i.e., food, drinking water, residential) and routes (i.e., oral, inhalation, dermal). During the hazard characterization phase, the various endpoints associated with the common mechanism of toxicity are identified, as well as the test species/sex that might serve as a uniform basis for determining relative potencies among the chemicals of interest. The common effect is also evaluated to determine if it is expressed across all exposure routes and durations of interest for each CMG member. The temporal aspects (e.g., time to peak effects, time to recovery) of the common mechanism toxicity are characterized to determine the critical window of its expression.

Not all cumulative assessments need to be of the same depth and scope. Thus, early in the cumulative assessment process, it is important to determine the need for, or the capability to perform, a comprehensive risk assessment. This is done by considering the number and types of possible exposure scenarios in conjunction with the associated residue values available. Initial toxicological and exposure information is collected. A screening-level assessment may be conducted that applies more conservative approaches than would a comprehensive and refined cumulative risk assessment. For example, margins of exposure may be based on no-observed adverse-effect-levels (NOAELs) for the common toxic effect rather than modeling dose-response curves of each chemical member to derive more refined relative potencies and points of departures. For exposure to food, treatment of 100% of crops and tolerance level residues may be assumed for each CMG chemical registered for use on a crop. If a screening-level analysis including such overestimates of exposure indicates that there is no risk concern, then no further detailed assessment may be necessary. But if this conservative approach indicates a potential for unacceptable risk, then a refined assessment should be conducted. This may engender the need for additional data.

As the risk assessor proceeds with the cumulative assessment, it is important to determine candidate chemicals and uses, routes, and pathways from the CMG that may cause cumulative effects. Cumulative assessments should not attempt to quantify risk resulting from those common mechanism chemicals that will have a minimal toxic contribution to the cumulative hazard, or from minor exposure pathways, routes, or uses.

Exposures from minor pathways should be considered qualitatively. Thus, a subset of common mechanism chemicals to be included in the quantification of cumulative risk needs to be identified from the CMG. This subgroup is called the cumulative assessment group (CAG). The identification of the CAG is done throughout the process as a detailed understanding of each group member's hazard and exposure potential emerges from the analysis. Although a chemical(s) may be removed from the quantification of risk, the rationale for such decisions should be explained. Thus, all chemicals that were grouped by a common mechanism of toxicity should be accounted for (qualitatively or quantitatively) in the final assessment.

A dose-response analysis is performed on each CAG member to determine its toxic potency for the common toxic effect. The determination of toxic potency should, to the extent feasible with available data, be conducted on a uniform basis (i.e., same measure of potency, for the same effect, from the same test species/sex using studies of comparable methodology). The guidance recommends use of dose addition for determining the combined risk of the CAG. This approach is consistent with the Agency's approach to multichemical assessments that involve chemicals that are toxicologically similar and share a common toxic effect. Departures from the dose-addition approach are appropriate if there are data available to support an alternative method.

Once the toxic potency of each common mechanism chemical is determined, the relative potencies of the CAG members are established. To determine relative potency, a chemical from the CAG is selected to serve as the index chemical. The index chemical is used as the point of reference for standardizing the common toxicity of the other chemical members of the CAG. Once the index chemical is selected, relative potency factors (RPFs) are calculated (i.e., the ratio of the toxic potency of a given chemical relative to that of the index chemical). RPFs are used to convert exposures of all chemicals in the CAG into exposure equivalents of the index chemical. Given that the RPF method portrays risk as exposure equivalents to one chemical (the index compound), it is preferred that the index chemical: (1) have high-quality dose-response data; (2) have a toxicological/biological profile for the common toxicity that is representative of the common toxic effect(s); and (3) be well characterized for the common mechanism of toxicity. The last step in the dose-response assessment is to calculate a point of departure(s) for the index chemical so that the risk of the CAG can be extrapolated to anticipated human exposures.

Detailed exposure scenarios for all of the uses remaining for each pesticide in the CAG should be developed. This includes determination of potential human exposures by all relevant pathways, durations, and routes that may allow simultaneous exposures, or any sequential exposures among the CAG members that could contribute to the same joint risk of the common toxic effect (i.e., either by overlapping internal doses or by overlapping toxic effects). The framework for estimating combined exposures is based on exposure to individuals, representing differing attributes of the population (e.g., human activity patterns, place of residence, age) that link pathways/route of exposure through scenario building. Cumulative risk values for a given common toxic effect are calculated separately for each exposure route and duration and then combined. To the extent data permit, the temporal and spatial linkages should be maintained for the many factors defining a possible individual exposure. A decision must be made on the relative importance of scenarios and the need for their inclusion in a quantitative assessment, as well as on the populations of interest and locations for evaluation in the assessment. The potential for co-occurrence of possible exposure scenarios is evaluated. Spatial, temporal, and demographic considerations are major factors in determining whether a concurrent exposure is likely to occur. In other words, all exposure events need to occur over a specific interval of time; events need to agree in time, place, and demographic characteristics; and an individual's dose needs to be matched with relevant toxicological values in terms of route and duration.

Exposure input parameters are established. The magnitude, frequency, and duration for all pertinent exposure pathway/route combinations are determined. These parameters take into account appropriate sources of use/usage information, and residues in all appropriate media. Any modifying factors necessary for inclusion in the assessment are also identified. Where necessary, any appropriate surrogate datasets from other chemical-specific data, published literature, or generic datasets are considered. A trial run of a quantitative cumulative risk is conducted by assigning route- and duration-specific risk metrics. The outputs of this trial run are evaluated and a sensitivity analysis is conducted. Subpopulations or life stages of concern are assessed. A final quantitative cumulative risk assessment can then be conducted.

The last step of the assessment process is to characterize the risk. The results and conclusions of the cumulative risk analysis are clearly described, including the relative confidence in toxicity and exposure data sources and model inputs. The risk characterization also includes a description of the variability. Major areas of uncertainty should be described both qualitatively and quantitatively. The magnitude and direction of likely bias and the impact on the final assessment are discussed. Risk contributors are identified with regard to pesticide(s), pathway, source, time of year, and impacted subpopulations (with particular attention to children). The basis for group uncertainty and FQPA safety factors should be explained.

As a guidance document and not a rule, the policy in this guidance is not binding on either EPA or any outside parties. Although this guidance provides a starting point for OPP's risk assessments, OPP will depart from its policy where the facts or circumstances warrant. In such cases, OPP will explain why a different course was taken. Similarly, outside parties remain free to assert that a policy is not appropriate for a specific pesticide or group of pesticides, or that the circumstances surrounding a specific risk assessment demonstrate that a policy should be modified or abandoned. The cumulative risk assessment process will continue to evolve after this guidance is published. Thus, the Agency may update this guidance or provide supplementary materials as appropriate.

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Abbreviations and Acronyms

BMD	Benchmark Dose
BMD_{10}	A Benchmark Dose associated with a 10% response compared to background
BMR	Benchmark Response
CAG	Cumulative Assessment Group (of chemicals)
CMG	Common Mechanism Group (of chemicals)
CSFII	USDA in the *Continuing Survey of Food Intakes by Individuals*
CWS	Community Water Systems
ED_{10}	Effective Dose: central estimate on a dose associated with a 10% response adjusted for background
FQPA	Food Quality Protection Act
FFDCA	Federal Food, Drug, and Cosmetic Act
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
GIS	Geographical Information System
LOAEL	Lowest-Observed-Adverse-Effect Level
MOE	Margin of Exposure
NAS	National Academy of Sciences
NAWQA	National Water Quality Assessment Program
NASS	National Agricultural Statistics Service
NOAEL	No-Observed-Adverse-Effect Level
NRC	National Research Council
OPP	Office of Pesticide Programs
ORETF	Outdoor Residential Exposure Task Force
PBTK	Physiologically-based toxicokinetic
PDP	USDA's Pesticide Data Program
PHED	Pesticide Handlers' Exposure Database
POD	Point of Departure
RfD	Reference Dose
RPF	Relative Potency Factor
SAP	Scientific Advisory Panel
SOP	Standard Operating Procedures
UF	Uncertainty Factor
USGS	US Geological Survey

Key Terms Used in Document

Risk-Related Terms:

Aggregate Risk is the risk associated with all pathways and routes of exposure to a single chemical.

Critical Window of Expression for the Common Mechanism Effect is the time from exposure to expression of the common mechanism effect and continues until the effect is reversed and the exposed individual has effectively returned to a pre-exposure state.

Cumulative Risk[1] is the risk of a common toxic effect associated with concurrent exposure by all relevant pathways and routes of exposure to a group of chemicals that share a common mechanism of toxicity.

Cumulative Assessment Group (CAG) is a subset of chemicals selected from a common mechanism group for inclusion in a refined quantitative estimate of risk. The chemicals in the CAG, as well as their pathways/routes and pesticide uses, are judged to have a hazard and exposure potential that could result in the expression of a cumulative risk. Thus, negligible contributors are not included in quantifying the risk.

Dose Additivity is the Agency's assumption when evaluating the joint risk of chemicals that are toxicologically similar and act at the same target site. In other words, it is assumed that each chemical behaves as a concentration or dilution of every other chemical in the CAG (or chemical mixture). The response of the combination is the response expected from the equivalent dose of an index chemical. The equivalent dose is the sum of the component doses, scaled by each chemical's toxic potency relative to the index chemical.

[1]The definition of cumulative risk used in this document pertains to those chemicals that share a common mechanism of toxicity, as interpreted under FQPA. It should be noted that the EPA has, in other contexts, defined cumulative risk assessment in a broader manner–"The examination of the *accumulation* (over time, across sources, across routes, etc.) of stressors or exposures that can cause adverse effects, and then the *integration* of the effects these stressors or exposures cause into an estimate and characterization of the risk caused to the individual or population by the stressors *acting together*" (USEPA, 2001i).

A Group Uncertainty Factor for the CAG is applied after estimating the toxicity of the group, in order to cover areas of scientific uncertainty that pertain to the group as a whole (e.g., intra- and interspecies differences). Most database issues should be dealt with on an individual chemical basis. But the quality and completeness of the database on the common toxic effect for the group as a whole should be considered in developing a group uncertainty factor. Also, consideration of the l FQPA 10X safety factor for children should pertain to the common mechanism of toxicity and generally be based on the group rather than individual members of the group.

Index Chemical is the chemical used as the point of reference for standardizing the common toxicity of the chemical members of the CAG. The index chemical should have a clearly defined dose-response, be well defined for the common mechanism of toxicity, and have a toxicological/biological profile for the common toxicity that is representative of the CAG.

A Point of Departure (POD) is a dose that can be considered to be in the range of observed responses, without significant extrapolation. A POD can be a data point or an estimated point that is derived from observed dose-response data. A POD is used to mark the beginning of extrapolation to determine risk associated with lower environmentally relevant human exposures.

Relative Potency Factor (RPF) is a ratio of the toxic potency of a given chemical to that of an index chemical in the CAG. Relative potency factors are used to convert exposures of all chemicals in the CAG into their exposure equivalents of the index chemical.

Hazard-Related Terms:

Common Mechanism Group (CMG) is a group of chemicals determined to cause a common toxic effect by a common mechanism of toxicity. The CMG is defined using the previously released *Guidance for Identifying Pesticide Chemicals and Other Substances That Have a Common Mechanism of Toxicity* (1999a). Not all members of a CMG should necessarily be included in a more refined quantitative estimate of cumulative risk.

Common Mechanism of Toxicity pertains to two or more pesticide chemicals or other substances that cause a common toxic effect(s) by the same, or essentially the same, sequence of major biochemical events (i.e., interpreted as mode of action).

Exposure-Related Terms:

Concurrent Exposure is interpreted as potential human exposure by all relevant pathways, durations, and routes that allows one chemical to add to the exposure of another chemical such that the total risk is an estimate of the sum of the exposures to the individual chemicals. This includes simultaneous exposures as well as any sequential exposures that could contribute to the same joint risk, either by overlapping internal doses or by overlapping toxic effects.

Exposure Scenario is a combination of facts, assumptions, and inferences that defines a discrete situation or activity where potential exposures to two or more pesticides may occur. The cumulative exposure framework for estimating combined exposures is based on exposure to individuals, which represent differing attributes of the population (e.g., human activity patterns, place of residence, age) that link route of exposure through scenario building.

Pathway of Exposure is the physical course a pesticide takes from the source to the organism exposed (e.g., through food or drinking water consumption or residential pesticide uses).

Route of Exposure is the way a chemical enters an organism after contact (e.g., ingestion, inhalation, or dermal absorption).

Introduction

Background

Pesticides are regulated under several major Federal statutes: the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) and the Federal Food, Drug, and Cosmetic Act (FFDCA), as amended by the Food Quality Protection Act on August 3, 1996[2]. FIFRA requires that substances used as pesticides be registered with the U.S. Environmental Protection Agency (EPA) and that these pesticides not cause unreasonable adverse effects on humans or the environment. Under the FFDCA, EPA sets tolerances (or exemptions from the requirement of a tolerance) for pesticide residues on raw agricultural commodities (RACs) or processed foods. The tolerance for a pesticide residue represents the maximum legally allowable concentration of the residue that can be present in or on a raw agricultural commodity or processed food. In order to establish a pesticide tolerance or exemption from a tolerance, EPA must determine with reasonable certainty that consumption of RACs and processed foods containing residues of that pesticide will not cause harm to humans, especially infants and children.

Historically, EPA has generally evaluated the safety of pesticides on the basis of single-chemical and single-exposure pathway scenarios. In 1993, a report by the National Research Council (NRC) made several recommendations on how to improve the assessment of health risks posed by pesticides in the diets of infants and children (NRC, 1993). One recommendation included consideration of all sources of dietary and nondietary exposures to pesticides and assessment of risks from exposure to multiple pesticides that cause a common toxic effect (an example was provided for five organophosphorus pesticides). The Food Quality Protection Act (FQPA) of 1996 provides that when determining the safety of a pesticide chemical, EPA shall base its assessment of the risk posed by the pesticide chemical on *aggregate* (i.e., total food, drinking water, residential, and other nonoccupational) exposure to the pesticide. EPA is also required to consider available information concerning the *combined* toxic effects to human health that may result from dietary, residential, or other nonoccupational exposure to chemicals that have a common mechanism of toxicity.

[2]For details see *The Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), 7 U.S.C. §§ 136 et seq.,and Federal Food, Drug, and Cosmetic Act (FFDCA), 21 U.S.C. § 364a.*

History of Guidance

Over the past several years, a number of external reviews have helped shape OPP's cumulative risk assessment guidance. Additional experience in implementing the guidance itself with actual datasets on common mechanism pesticides has also led to refinements in cumulative risk assessments.

OPP has repeatedly sought scientific review by the FIFRA Scientific Advisory Panel (SAP). In September 1999, OPP first presented the hazard and dose-response components of its cumulative guidance document for review by the SAP (USEPA, 1999k).

In December 1999, OPP presented to the SAP for comment the exposure and risk characterization elements of the guidance (USEPA, 2000g). In addition to the SAP reviews on the guidance document itself, OPP has also requested SAP comment on the various exposure models and tools being developed for assessing aggregate and cumulative risk; Online (USEPA, 2001l).

Additionally, the concepts and methods that the risk assessor should consider in conducting cumulative risk assessments have been applied to actual datasets on common mechanism chemicals. In a pilot analysis of 24 organophosphorus (OP) pesticides, OPP demonstrated in detail the methods and parameters that should be considered in estimating cumulative risk associated with common mechanism pesticides by multiple pathways of exposure. The hazard and dose-response assessment and the exposure analyses of this pilot analysis were presented to the SAP for comment in September and December 2000, respectively (USEPA, 2000i ; USEPA, 2000e; USEPA, 2001j; and USEPA, 2001k). OPP revised its approach to the dose-response assessment of OPs based on comments provided by the September 2000 SAP review (USEPA, 2001d). Finally, OPP published in December 2001, its preliminary risk assessment on the organophosphorus pesticides, which is based on the general methodology described in this guidance (USEPA, 2001m).

In addition to the SAP reviews, the public has provided comments on OPP's proposed methods and approaches. The draft guidance document for conducting a cumulative risk assessment of pesticides that share a common mechanism of toxicity was issued for public comment on June 30, 2000 (USEPA, 2000a; 65 FR 40644). Later, a technical workshop was held in July 2000 to explain the approaches in the guidance document and to hear questions and comments from the public and various stakeholder groups. A technical briefing for stakeholder groups was also conducted in August 2001 on a dose-response approach for assessing the cumulative risk associated with OP pesticides, and OPP held a meeting at the SAP in September 2001 on the same subject (USEPA, 2001n).

The June 2000 Guidance Document has been revised to clearly describe the decision logic and elements of the cumulative risk assessment process, taking into

consideration comments offered by the public, SAP, industry organizations, and other Government agencies. This revised guidance document maintains the basic principles and approaches presented in the June 2000 guidance document.

Scope of Guidance

This document is only intended to provide guidance on performing cumulative risk assessments for pesticide chemicals that act by a common mechanism of toxicity. EPA is working on its approach for the consideration of "other substances" that have a common mechanism of toxicity. Until the Agency develops general guidance on this issue, EPA will handle this issue on a case-by-case basis. It is anticipated that most mechanisms of toxicity that have been elucidated will be consistent with nonlinearity or threshold biological phenomena. The dose-response methods presented in this guidance are more applicable to these situations. Finally, FFDCA does not regulate exposure to workers or effects on non-target wildlife, and thus, this document does not present guidance for performing cumulative risk assessments for those areas.

Purpose of Guidance

The purpose of this guidance is to set forth the basic assumptions, principles, and analytical framework that are recommended for use by OPP risk assessors in conducting cumulative risk assessments. It is also intended to inform decision makers and the public of the principles and procedures generally followed in the conduct of cumulative risk assessments on pesticide chemicals. The process for assembling and evaluating information that will constitute a cumulative risk assessment involving food, water, residential, and other nonoccupational exposures to multiple pesticides that share a common mechanism of toxicity is described in the following sections of this document. This guidance is intended to be flexible so as to accommodate a variety of common mechanisms and datasets, but not to provide an in-depth discussion of specific datasets. Furthermore, it does not impose binding rules on OPP or other parties. OPP remains open to consideration of alternative or new approaches to conducting cumulative risk assessments. It is important to emphasize that the cumulative risk assessment process is at an early stage of development and will continue to evolve after this guidance is published. Thus, there will be continued progress on advancing methods and tools. The Agency may update this guidance, or provide supplementary materials as appropriate, as the toxicological and exposure databases improve to accommodate the data needs for cumulative risk assessment, and as the Agency's knowledge increases about mechanisms of toxicity and how chemicals that share a common mechanism of toxicity interact with the biological target tissue at known or anticipated levels of human exposures.

Objectives of the Cumulative Risk Assessment Process

A cumulative risk assessment has several objectives. The risk assessor must proceed through a complex set of evaluations to achieve those objectives. The process begins with the identification of a group of chemicals that produce a common toxic effect(s) by a common mechanism of toxicity. Careful attention should be given to the time dimensions of the toxic effects and exposure. The mechanism of toxicity, pesticide exposure patterns, and treatment scenarios will determine the populations of concern. This multichemical, multipathway risk assessment should identify subgroups (particularly children) that may be disproportionately at risk to the common mechanism of toxicity, and the major pathways and routes of exposure and chemicals that are driving the associated risk.

Objectives of a Cumulative Risk Assessment

- Define the characteristics of the exposure to a group of chemicals that act by a common mechanism of toxicity
- Estimate multichemical, multipathway risks reflecting real-world exposure to pesticides, including the changing patterns of residue levels as they relate to differences in location, time, and co-occurrence
- Identify significant contributors to risk
- Characterize the confidence in the conclusions and the uncertainties encountered in the assessment
- Facilitate a greater understanding of the potential results of changes in pesticide uses and possible mitigation activities

It is important to keep in mind that a cumulative risk assessment differs from the single-chemical aggregate risk assessment both in focus and purpose. The relationship of pesticides as alternatives or complementary products is not considered in single-chemical aggregate analyses. Therefore, one cannot simply sum the aggregate risk estimates for the group of chemicals shown to have a common mechanism of toxicity to produce a cumulative risk assessment. In addition, aggregate assessments often contain conservative assumptions to ensure that they are adequately protective of human health. Care should be taken to avoid conservative assumptions that may be compounded in the cumulative assessment, inappropriately biasing the risk estimates produced. Attention should be focused on exposure estimation for use/pesticide combinations that make up the largest and most important sources of risk. The cumulative risk assessment should identify the likely exceedance of a cumulative exposure level. When a cumulative risk assessment reflects the real-world exposure situation (i.e., multichemical and multipathway), it permits the identification of significant contributors of risk so that mitigation strategies can be targeted more effectively.

The basic concept underlying cumulative risk assessment is that exposure occurs to a hypothetical individual whose demographic characteristics help define exposure scenarios. The data concerning this individual should be consistent with those characteristics. Risk should be estimated while maintaining the appropriate spatial (e.g., location and type of home; urbanization, watershed, or aquifer characteristics), temporal (e.g., duration, frequency, and seasonality of exposure; frequency of residential pest control), and demographic (e.g., age, gender, reproductive status, ethnicity, behaviors) linkages of exposure and toxicology data (ILSI, 1998). Cumulative risk assessment proceeds by establishing reasonable exposure scenarios for a hypothetical individual and groups of individuals over a specific interval of time. The exposure scenarios help to identify populations of concern, and to define critical windows of time and routes of exposure that should be linked to the common toxic effect. The potential for overlapping exposure to multiple chemicals by multiple pathways of exposure should be established.

Organization of the Document

The process of conducting a cumulative risk assessment is illustrated in Figure 1. The figure describes the series of steps needed to organize and explain the decisions, data collection, and evaluations envisioned. Although the steps are organized sequentially in the figure, they may actually overlap or occur in parallel, as each piece of information and each decision in the process is informed by the others, with some elements revisited as a result of subsequent analyses. In other words, the hazard, dose-response, and exposure analyses are, in reality, highly interactive and are integrated in the overall cumulative risk process. These elements are explained in Sections 1through 10 in the body of the document.

Examples of Supplementary EPA Guidance Documents

- Guidance for Identifying Pesticide Chemicals and Other Substances that have a Common Mechanism of Toxicity (1999a)
- General Principles For Performing Aggregate Exposure And Risk Assessments (USEPA, 2001h)
- Chemical Mixtures (USEPA, 1986d, 2000j)
- Monte Carlo Analysis (USEPA, 1997a)
- Exposure Factors Handbook (USEPA, 1999d)
- Risk Characterization Handbook(USEPA, 2000c)
- Peer Review Handbook (USEPA, 2000d)

It should be emphasized that the risk assessor should refer to several other Agency documents for supplementary guidance in certain areas integral to the cumulative risk assessment process. OPP developed *Guidance for Identifying Pesticide Chemicals and Other Substances that have a Common Mechanism of Toxicity* (USEPA, 1999a). *General Principles For Performing Aggregate Exposure And Risk Assessments* (USEPA, 2001h) describes certain aspects of the exposure assessment that must be accounted for in developing an integrated, single-chemical multipathway assessment. Detailed procedures for evaluating specific hazards (e.g., cancer, developmental toxicity, reproductive toxicity, neurotoxicity) can be found in the Agency's risk assessment guidelines (see USEPA, 1986a,b,c,d; USEPA, 1991a, 1992,

1996; 1998a; 1999c), and guidance on certain techniques of dose-response analysis can be found in the Agency's *Benchmark Dose Technical Guidance Document* (USEPA, 2000b). Risk characterization is a key element in cumulative risk assessment and is embodied in this document. Finally, the risk assessor should follow the Agency's policies and practices for the peer review of cumulative risk assessments of common mechanism pesticides.

Figure 1. The Cumulative Risk Assessment Process

Step 1. **IDENTIFY COMMON MECHANISM GROUP (CMG)** *-A cumulative risk assessment begins with the identification of a group of chemicals, a Common Mechanism Group (CMG), that induce a common toxic effect by a common mechanism of toxicity.*

Step 2. IDENTIFY POTENTIAL EXPOSURES *-For each CMG member, evaluate proposed and registered uses and use patterns to identify potential exposure pathways (i.e., food, drinking water, residential) and routes (oral, inhalation, dermal).*

Step 3. CHARACTERIZE AND SELECT COMMON MECHANISM ENDPOINT(S)*-For each CMG member, evaluate common effects that arise via the common mechanism of toxicity across all exposure routes and durations of interest, determine the time-frames of expression for the common toxicity, and evaluate the quality of the dose-response data for each CMG member. Recommend endpoints/species/sex that can serve as a uniform basis for determining relative potency.*

Step 4. DETERMINE THE NEED FOR A COMPREHENSIVE CUMULATIVE RISK ASSESSMENT*-Consider the number and types of possible exposure scenarios in conjunction with the associated residue values available. Evaluate the toxicological information on NOAELs and LOAELs collected for the common effect. This evaluation may suggest that a screening-level assessment for the CMG will indicate that there is no risk concern for this group of chemicals and no further detailed assessment will be necessary. This evaluation may also suggest that a cumulative assessment is simply not appropriate at this time.*

Step 5. DETERMINE CANDIDATE CUMULATIVE ASSESSMENT GROUP (CAG)*-Select pesticides, pesticide uses, routes, and pathways from the CMG that have an exposure and hazard potential to result in cumulative effects for inclusion in the quantitative estimates of cumulative risk.*

Step 6. CONDUCT DOSE-RESPONSE ANALYSES AND DETERMINE RELATIVE POTENCIES AND POINTS OF DEPARTURE*-Select and apply an appropriate dose-response method to evaluate the common mechanism effects and determine the relative toxic potencies of the CAG by each exposure route and duration of interest. Determine the point of departure(s) for extrapolating the risk of the CAG.*

Step 7. DEVELOP DETAILED EXPOSURE SCENARIOS FOR ALL ROUTES AND DURATIONS*-For all of the uses remaining for each pesticide in the CAG, determine their role in establishing the magnitude of possible exposures. Decide the relative importance of scenarios and the need for their inclusion in a quantitative assessment. Identify populations of interest and locations for evaluation in the assessment. Determine the co-occurrence of possible exposure scenarios.*

Step 8. ESTABLISH EXPOSURE INPUT PARAMETERS*-Determine magnitude, frequency, and duration for all pertinent exposure pathway/route combinations. Identify appropriate sources of use/usage information, residues in all appropriate media, and any modifying factors necessary for inclusion in the assessment. Where necessary, identify any appropriate surrogate datasets from other chemical-specific data, published literature, or generic datasets. Model any necessary exposure parameters for inclusion.*

Step 9. CONDUCT FINAL CUMULATIVE RISK ASSESSMENT*-Assign route/duration-specific risk metrics. Conduct trial run and evaluate output. Conduct sensitivity analysis. Assess subpopulations of concern, determine group uncertainty and FQPA safety factors.*

Step 10. CONDUCT CHARACTERIZATION OF CUMULATIVE RISK*-Describe the results and conclusions of the cumulative risk analysis, including the relative confidence in toxicity and exposure data sources and model inputs. Discuss major areas of uncertainty, the magnitude and direction of likely bias, and the impact on the final assessment. Evaluate the risk contributions from each pathway and route individually, as well as in combination. Identify risk contributors with regard to pesticide(s), pathway, source, time of year, and impacted subpopulation (with particular attention to children). Conduct sensitivity analyses to determine those factors most likely to impact the risk. Determine need for uncertainty and safety factors*.

SECTION 1. Identify Common Mechanism Group (CMG)

Step 1. *A cumulative risk assessment begins with the identification of a group of chemicals,* ***a Common Mechanism Group (CMG),*** *that induce a common toxic effect by a common mechanism of toxicity.*

Common mechanism of toxicity determinations should generally follow the weight-of-evidence approach described in the *Guidance for Identifying Pesticide Chemicals and Other Substances That Have a Common Mechanism of Toxicity* (USEPA, 1999a). In addition, the Agency has developed a framework for evaluating a chemical's mode of action (see USEPA, 1999c), which offers additional direction for establishing a mechanism of toxicity. Because separate guidance exists, the process for grouping chemicals by a common mechanism of toxicity will not be described within this document. However, a few important points follow.

Application of OPP's *Guidance for Identifying Pesticide Chemicals and Other Substances That Have a Common Mechanism of Toxicity*

- A Common Mechanism of Toxicity: The Organophosphate Pesticides (USEPA, 1999e)
- A Science Policy on a Common Mechanism of Toxicity: The Carbamate Pesticides and the Grouping of Carbamate Pesticides with Organophosphorus Pesticides (USEPA, 1999f)
- The Grouping of a Series of Chloroacetanilide Pesticides Based on a Common Mechanism of Toxicity (USEPA, 1997b, 2001b).
- Thiocarbamates: A Determination of the Existence of a Common Mechanism of Toxicity and a Screening Level Cumulative Dietary (Food) Risk Assessment (USEPA, 2001c, 2001o)
- The Determination of Whether the Dithiocarbamate Pesticides Share a Common Mechanism of Toxicity (USEPA, 2001e, 2001o)

The Food Quality Protection Act uses the term "mechanism of toxicity," which is defined in the January 29, 1999, Guidance Document and interpreted as mode of action–"*the major steps leading to an adverse health effect following interaction of a pesticide with biological targets. All steps leading to an effect do not need to be specifically understood. Rather, it is the identification of the crucial events following chemical interaction (with biological targets) that are required in order to describe a mechanism of toxicity."*[3] The identification of a group of chemicals having a common mechanism of toxicity (CMG) will precede analyses for cumulative risk assessments. Thus, the assessment for grouping a set of chemicals based on a common mechanism

[3]Since the passage of the FQPA, the term "mechanism of toxicity or action" has taken on a specific meaning in Agency-wide guidance documents. In the draft EPA guidelines for carcinogen risk assessment, the term "mode of action" is contrasted with "mechanism" which implies a more detailed molecular description of events than is meant by mode of action (USEPA, 1999c). The definition of "mechanism of toxicity" used in this Guidance and in OPP's earlier guidance (USEPA, 1999a) is equivalent to the definition of the term "mode of action."

of toxicity will normally be provided in a separate document issued by OPP prior to preparation of a cumulative risk assessment (see examples in text box). Key conclusions and toxicity data presented in these reports will be utilized and summarized when preparing a cumulative risk assessment report.

SECTION 2. Identify Potential Exposures

Step 2. *For each CMG member, evaluate proposed and registered uses and use patterns to identify potential exposure pathways (i.e., food, drinking water, residential) and routes (oral, inhalation, dermal).*

Aggregate exposure assessments should generally be conducted for each member of the CMG before a cumulative assessment is attempted. The aggregate assessments will identify important information concerning pathways and routes of exposure for each individual pesticide. The exposure and use data from the aggregate assessment should be evaluated to identify pesticides that have uses that are likely to result in significant exposures and in overlapping exposures with other pesticides. Similarly, those pesticides should be identified that are unlikely to result in a cumulative risk because the uses are limited or the expected exposures or effects will not overlap. For example, if a pesticide's uses are limited to contained methods of application such as bait boxes or gels designed for injection behind baseboards, a decision that essentially no exposure is anticipated would likely be made, and if so, the pesticide would not be included in the assessment.

Aggregate risk assessments on individual pesticides will provide useful exposure information to identify:

- Registered uses
- Tolerances
- %Reference Dose (RfD) of the single pesticide
- Significant sources and pathways of exposure (food, drinking water, residential)
- Use patterns
- Geographic distributions
- Times of application
- Average field trial values
- Monitoring data
- % Crops treated

The universe of registered uses of pesticides in the CMG will provide a first cut at determining which chemicals should be considered in the hazard analysis (Section 3) and the scope of exposure scenarios that require consideration in the cumulative assessment. Inherent in the types of uses registered is an understanding of the types of exposures to be anticipated. For example, the registration of a pesticide solely for application to food crops will result primarily in oral exposure (through the food ingested), but also potentially through drinking water as the result of runoff and leaching. Residential (dermal and inhalation) exposures should not be of concern in this case.

Tolerance information should also provide important details on the anticipated magnitude of the exposure. For example, if a pesticide's tolerances are *limit of detection* tolerances, the magnitude of residues anticipated in food may be found to be very small, and may provide justification for excluding the food exposure from the risk assessment. Similarly, it is unlikely that two pesticides will be encountered together if they are alternatives for each other for the same use and will not be used at the same time and place, thereby limiting the concern for co-occurrence. Some products may be used as combinations. This information suggests that the two pesticides should be considered together at least for a portion of the exposures considered (i.e., exposures will overlap). Finally, some products may be considered complementary, and the use of one will increase the likelihood of the use of the other.

SECTION 3. Characterize And Select Common Mechanism Endpoint(s)

Step 3. *For each CMG member, evaluate common effects that arise via the common mechanism of toxicity across all exposure routes and durations of interest, determine the time-frames of expression for the common toxicity, and evaluate the quality of the dose-response data for each CMG member. Recommend endpoints/species/sex that can serve as a uniform basis for determining relative potency.*

Once a series of chemicals has been identified that share a common mechanism of toxicity (i.e., the CMG), further hazard analyses are needed to characterize and select the common toxic effects[4] that should be considered in the cumulative risk assessment. An important aspect of this hazard assessment is to identify the common effects associated with the common mechanism, the test species/sex that provides the most extensive data on the common effects, and the exposure routes and durations by which the common toxic effects are manifested. An initial quantitative evaluation of the data will help guide the final selection of common toxic endpoints and choice of dose-response methodology for determining the relative toxic potency[5] among chemical members for quantifying risk (discussed in Section 6).

Key Objectives of the Hazard Assessment in Cumulative Risk

- Identify the common toxic effects pertaining to the common mechanism for determining the relative toxic potencies of each chemical
- Identify routes and durations of exposure by which the common mechanism effects will occur
- Identify the species/strains and sex in which the common mechanism of toxicity occurs
- Identify the studies that provide the most robust and extensive datasets for determining cumulative hazard
- Identify potential susceptible subgroups or life stages

[4]Common toxic effect is defined in the *Guidance for Identifying Pesticide Chemicals and Other Substances That Have a Common Mechanism of Toxicity* (USEPA, 1999a) as the same toxic effect in or at the same anatomical or physiological site or locus (e.g., same organ or tissue).

[5]Relative toxic potency refers to a comparison of the exposure level or dose required for an individual chemical to the exposure levels or doses required of other chemicals to cause a common toxic effect of an equivalent magnitude by a common mechanism of toxicity.

3.1 Selection and Characterization of Effects Associated with the Common Mechanism of Toxicity

To guide the selection of common mechanism endpoints that will provide a scientifically sound basis for determining relative potency of chemicals in a cumulative risk assessment, the risk assessor should assess the available data to determine the following:

- ❏ pertinent and sensitive endpoints associated with the common mechanism
- ❏ tissues in which common mechanism effects occur
- ❏ species/strain or sex in which the common mechanism occurs noting in particular whether there are species/strain or sex differences)
- ❏ other, more sensitive toxic effects not related to the common toxic effect caused by individual CMG members.

The above areas of inquiry are important for a number of reasons. First, there may be a number of different responses pertaining to the common mechanism of toxicity on which the cumulative assessment might be based. Some mechanisms will be associated with a cascade of events that lead to the adverse toxic effect. For example, certain antithyroid chemicals (e.g., amitrole, mancozeb, ethylene thiourea) cause thyroid follicular cell carcinogenesis by disruption of thyroid-pituitary homeostasis. This results in chronic reduction in circulating thyroid hormones (T3, T4) and increases in thyroid stimulating hormone (TSH), which in turn leads to cell proliferation, changes in thyroid weight, and eventually neoplasia (Hurley et al., 1998). Some mechanisms may not be tissue specific, and the chemicals of interest may operate in different tissues. For example, organophosphorus pesticides exert neurotoxicity via binding to and phosphorylation of the enzyme acetylcholinesterase (AChE), which is found in both the central and peripheral nervous systems (Mileson et al., 1998). Therefore, all relevant responses need to be evaluated to identify effects pertaining to the common mechanism of toxicity. This will provide the most robust basis for determining the relative potency among the chemicals of interest, as well as determining which endpoint(s) is most protective of the common mechanism of toxicity.

It is important to characterize species and strain differences for the common mechanism effects to determine species/strain or sex sensitivities. Furthermore, the common mechanism effect(s) from different species/strains and sexes should be evaluated so the members of the CMG can determine what response data will provide a uniform and common basis for determining the chemicals' relative potencies. As discussed later in Section 6, when estimating cumulative risk, response data from the same species, strain, and sex for all the members of the CMG is preferred. If there are pronounced species/strain or sex differences among the test animals or subjects, and it is unknown which test species responds most like humans to the test substances, data from the most sensitive animal should be used to determine cumulative risk. When response data in the most sensitive species/strain or sex are not available for all the chemicals, this should be accounted for in the cumulative assessment or in the characterization of uncertainties (see Section 10).

Another important aspect of the hazard assessment is the characterization of other toxicities caused by each CMG member and not related to the common mechanism. This evaluation determines whether the common toxic effect is more or less sensitive than other toxic effects caused by CMG members. A chemical may be encountered that is found to produce several types of toxicities, each by a different mechanism. For example, the pesticides acetochlor, alachlor, and butachlor induce nasal turbinate tumors by one mechanism (via formation of a tissue reactive metabolite, a benzoquinone imine intermediate) and thyroid follicular cell tumors by another mechanism (via enhancement of hepatic microsomal enzymes and perturbation of thyroid hormone levels) (see USEPA, 1998b, 2001b). Refined quantitative estimates should generally focus on common effects that represent the principal toxicities for the CMG. Thus, in a situation where a chemical may be grouped by several different common mechanisms of toxicity, in quantifying cumulative risk that pesticide should be considered for its most sensitive and pertinent mechanism of toxicity.

Another situation may occur in which a CMG member produces another toxic effect for which the mechanism of toxicity is not understood. The common mechanism effect is expressed only at high doses of the chemical, whereas the other toxicity is induced at much lower doses. In this situation, the pesticide could be grouped in a CMG that is not based on its principal toxicity. If that pesticide is regulated at a much lower exposure level on the basis of a much more protective toxic effect, then exposure to this chemical and its common mechanism will be limited by the more adverse effect or the effect with the lower regulatory endpoint. As discussed in Section 5, it may be appropriate to exclude this chemical in quantifying cumulative risk. The basis for excluding a CMG chemical from the quantification of risk should be included in the cumulative risk assessment.

3.2 Characterization of Route Specificity and Time Course of Effects

As discussed later (Section 9), the temporal characteristics and route specificity of the common mechanism effect are key criteria for defining the exposure scenarios of interest. Thus, an important aspect of hazard assessment is to characterize the route specificity of and the time course of effects for the common mechanism effects by evaluating the following:

- ❏ routes of exposure (oral, dermal, inhalation) for which the common effect is found

- ❏ time to onset and peak effects, duration of effects, and time to recovery (if the effect is reversible) of the common effect for each exposure route and duration anticipated

- ❏ toxicokinetic data that are available to help determine how exposure to the CMG relates to dose in the target tissue(s) over a given time frame for the exposure routes of interest.

If a chemical is found to produce route-specific effects for the common mechanism (e.g., it is not absorbed dermally), then those routes not pertinent to the common mechanism should be eliminated from the exposure scenarios considered in the cumulative risk assessment. Understanding the time frames (e.g., time to onset and peak effects, recovery time) for the common toxic effect will help determine the likelihood of the overlapping of effects given use patterns and likely patterns of exposure. For example, if the common mechanism effect is reversible and recovery is rapid, accumulation of common toxicity is not likely to occur if exposures and duration of effects are separated in time (and thus near-simultaneous exposures are necessary for cumulative effect to be seen). On the other hand, if the mechanism of toxicity results in persistent toxicity or persistence of tissue residues, then simultaneous exposures are not required for the chemicals to act by a common mechanism. Understanding the time frames associated with the common toxic effect will help guide the exposure analysis in selection of modeling scenarios.

Toxicokinetic information (e.g., data on absorption, distribution, metabolism, and excretion), as well as biological half-life for the chemicals of interest, should be considered in defining the route specificity and temporal kinetics of the common mechanism for the chemicals of interest.

3.3 Characterization of Potential Chemical Interactions

Cumulative toxicity represents the net change in toxicity that results from the combined exposure to multiple chemical substances relative to the toxicity caused by each substance alone. Although the nature of cumulative toxicity is often identical or similar to an effect caused by one or more of the substances individually, cumulative toxicity among chemicals can be manifested in many ways. Exposure to multiple chemical substances may result in an additive effect, antagonism, synergism, or no change in toxic effect(s) caused by any one of the substances alone. Many factors determine whether the cumulative toxicity resulting from exposures to pesticides and other chemicals that occur individually as discrete residues in multiple sources such as the diet (e.g., fruit, vegetables, meat, milk, water), air, or on residential surfaces will be greater than, equal to, or less than the toxicity caused by any of the chemicals alone. These factors include exposure patterns that result in simultaneous or overlapping exposures, the toxicokinetics/dynamics of each substance causing the common toxic effect, the duration of the common toxic effect, and the toxicokinetic/dynamic interactions between the substances. Information should be considered that allows one to discern the precise nature of the interactions that may occur following exposure to a group of chemicals that share a common mechanism of toxicity.

3.4 Initial Quantitative Characterization of the Common Effect(s)

A preliminary quantitative screen of available data for the common toxic effect(s) is conducted on all the studies in different animal species/strains/sexes for each chemical and for each exposure route/duration of interest. This initial screen will help guide and determine the level and scope of the dose-response analysis described later in Section 6.

3.5 Characterization of Potential Susceptible Subpopulations or Life Stages to the Common Mechanism of Toxicity

When characterizing hazard potential, attention should be given to subpopulations or life stages[6] that may be more susceptible to the common toxic effect and mechanism. For example, infants and children may not have fully developed metabolic pathways for detoxifying or bioactivating chemicals in a common mechanism grouping. In such a case, the dose level that would produce an effect in infants and children could proportionally be much lower (or higher) than the dose level that would produce the effect in adults. The importance of describing the potential increased sensitivity of infants and children is described in Executive Order 13045, and Agency guidance is provided in EPA's *Rule Writer's Guide to*

[6]Life stage is used to reflect a stage of development through which an organism passes through rather than a condition that may be permanently expressed such as gender or genetic make-up.

Executive Order 13045: Guidance for Considering Risks to Children During the Establishment of Public Health-Based and Risk-Based Standards (USEPA, 1998d).

3.6 Characterization of Human Information

If available, human information–such as data from epidemiological studies, case reports, worker health studies, exposure monitoring studies with humans, and toxicokinetic data from clinical studies–can contribute to understanding the common mechanism of toxicity and characterize the hazards of the CMG. Used in conjunction with experimental animal data, human data may contribute to hazard characterization and assessment in several ways. They may:

- ❏ add to the mechanistic understanding of the common effect and contribute to the weight of the evidence that the common mechanism of toxicity may be operative in humans
- ❏ contribute to identification of the appropriate common endpoint(s) for use in hazard and dose-response assessments
- ❏ provide insight into interindividual variability
- ❏ identify specific subpopulations at risk
- ❏ support an interspecies uncertainty factor more appropriate than the default factor of 10 (see Section 10).

Both the design and the execution of studies with human subjects must be rigorously reviewed and found to meet appropriate standards of scientific merit and ethical conduct before the resulting information should be relied on in an risk assessment. The standards for scientific and ethical acceptability of human studies are currently under review.

3.7 Characterization of Data Issues: Adequacy and Quality

Another important aspect of the hazard assessment is the characterization of the adequacy and quality of the available data. The risk assessor needs to consider the following:

- ❏ the reproducibility and consistency of the results for the common- mechanism effects among studies in the same laboratory and among studies of different laboratories

- ❏ the availability of response data for the common toxic effect based on several different studies that utilized comparable methodologies and the same species, strain, and sex of animals

- ❏ the availability of route-specific, time course, and toxicokinetic data

- ❏ the experimental design and methods used to conduct the study.

3.8 Weight-of-the-Evidence Evaluation of the Common Effect(s)

A weight-of-the-evidence approach should be used in addressing and providing an integrative assessment that considers the above topic areas and questions. This analysis is incorporated in the overall characterization of risk (discussed in Section 10). It requires a discussion of the characteristics of the data on each chemical in the common mechanism of toxicity grouping, and how the strengths and weaknesses of the data on each chemical influence confidence in the potential cumulative hazard identified for the grouping as a whole. In presenting the weight-of-evidence evaluation, the risk assessor should include a summary of: (1) the mechanism of toxicity identified for the CMG; (2) the key data on the common endpoint of toxicity expressed as a result of a common mechanism; and (3) a recommendation of the toxicological endpoint(s) to be considered in the cumulative assessment. It should also be noted whether other toxic effects are expressed by members of the CMG at lower doses than the common mechanism effect, and whether a mechanism of toxicity can be identified for those other toxic effects. An evaluation of each member's toxicological profile should allow the risk assessor to make recommendations regarding which chemicals should be included in the cumulative risk assessment for a particular common mechanism. The rationale and recommendations for excluding a particular chemical, route, or duration of exposure should be explained.

SECTION 4. Determine the Need for a Comprehensive Cumulative Risk Assessment

Step 4. *Consider the number and types of possible exposure scenarios in conjunction with the associated residue values available. Evaluate the toxicological information on NOAELs and LOAELs collected for the common effect. This evaluation may suggest that a screening-level assessment for the CMG will indicate that there is no risk concern for this group of chemicals and no further detailed assessment will be necessary. This evaluation may also suggest that a cumulative assessment is simply not appropriate at this time.*

4.1 Screening Assessment

A simple or less data-intensive method for evaluating cumulative risk may suffice when the CMG has:

- Small number of chemicals
- Limited pesticide uses (e.g., no residential uses)
- Low aggregate risks
- Monitoring data show non-detectable levels of residues

Not every cumulative risk assessment needs to have the same scope or depth. There may be certain CMGs that will require only screening-level assessments to decide whether to invest resources in collecting and analyzing data for a more extensive cumulative risk assessment. Screening-level assessments are more likely to apply to CMGs that comprise only a few chemicals and have low exposure potential given use patterns of the pesticides. A screening-level assessment for exposures to food, for example, might assume treatment of 100% of crops with each CMG chemical registered for use on a crop, and assume tolerance-level residues for the exposure component rather than a more refined estimate of actual residue levels from monitoring. Although modeling dose-response curves to derive refined relative potencies and points of departure for the CMG is preferred, margins of exposure[7] may be developed using NOAELs when dose response data are not amenable to modeling.

[7]A Margin of Exposure (MOE) is a numerical value that characterizes the amount of safety to a toxic chemical–a ratio of a toxicological endpoint (usually a NOAEL) to exposure. The MOE is a measure of how closely the exposure comes to the NOAEL.

An example screening-level assessment was conducted on the thiocarbamate pesticides (see USEPA, 2001c, 2001o). Thiocarbamates are a subgroup of carbamates that induce neuropathology of central or peripheral nerves. Although these pesticides could not be grouped by neuropathology as a common mechanism of toxicity, neuropathology was the most sensitive effect found for these pesticides. Therefore, this endpoint was used in this screening assessment as a conservative approach. Conservative estimates of chronic food exposure were conducted under a DEEM™ screening analysis with tolerance levels and assuming treatment of 100% of crops.

4.2 When to Conduct a Comprehensive Cumulative Risk Assessment

A CMG generally should not be the subject of a screening-level cumulative risk assessment if individual pesticide aggregate risk estimates have been found to be unacceptable. For example, if the individual aggregate risks are unacceptable, there is a higher likelihood that a CMG may pose a cumulative risk, particularly if the aggregate assessments were based on effects associated with the common mechanism of toxicity. In addition, a screening assessment is unlikely to provide meaningful results or save resources if the CMG consists of a large number of chemicals with widespread usage. The likelihood of compounding conservatisms causing an unacceptable outcome will increase with increasing numbers of uses. If a screening-level assessment does not appear to be reasonable for a CMG, a determination must be made as to whether the data for the chemicals in the CMG will support a quantitative cumulative risk assessment. This evaluation includes consideration of whether the exposure and toxicological data are sufficiently detailed to support such an assessment. It also considers the logic of the assessment and whether the questions asked by the assessment with regard to overlapping exposures are reasonable, and addresses exposure conditions likely to be encountered. A number of conditions and considerations to be addressed prior to initiating a more refined cumulative risk assessment are listed below.

A more refined cumulative risk assessment should be considered when the CMG is:

- Is composed of a large number of chemicals
- Has widespread pesticide uses
- Has high aggregate risks
- Has monitoring data showing detectable levels of residues

- **A cumulative exposure assessment generally should not be conducted until an aggregate exposure assessment has been conducted for each member of the CMG.**

  As stated previously, the aggregate assessments will provide the assessor with information needed to define the exposure parameters of the cumulative exposure assessment. They will also permit evaluation of the strengths and weaknesses of the data that will be used to develop the cumulative risk assessment. Examination of aggregate exposure assessments will provide important information for directing the decision making process as to whether a particular pesticide-source and/or pathway combination should be included in the quantitative assessment. Particular attention should be given to identifying and including those sources of exposure that are likely to contribute significantly to the final exposure estimate. At the same time, identifying components that are minor contributors to the final risk estimate is critical to bounding the scope of the cumulative exposure assessment and, ultimately, the cumulative risk assessment.

- **For chemicals where multiple and/or overlapping exposures are likely to occur, a further evaluation should be conducted to determine qualitatively their likely contribution to the impending cumulative exposure assessment.**

  Pesticide use patterns greatly affect potential exposure scenarios. By evaluating a pesticide's geographic and temporal pattern of use, a qualitative profile for each chemical from the CMG can be developed to establish the potential routes, durations, frequencies, and relative magnitude of exposure. Also, the evaluation of chemical use profiles allows for the identification of exposure scenarios that may overlap, co-occur, or vary among chemicals.

- **Data availability and quality may also play a role in the determination of whether to proceed with a full multipathway cumulative risk assessment.**

  The quantity of data available may vary among routes and pathways, making interpretation of analytical results difficult. For example, ample data may exist to provide an estimate of exposure from several pesticides though the food pathway; however, pesticide-specific data on residential exposure may be scarce or nonexistent, requiring the use of default values to generate quantitative estimates. In such a case, the uncertainties for the default values may be far in excess of the uncertainties for the exposure in food, and combining the two would be problematic. Similarly, where datasets differ in quality, i.e., how well they represent real-world concentrations, combining exposure assessments may produce misleading results. Generally,

assessment of pesticide exposures from food will be conducted using highly refined distributional estimates of residues from monitoring. As a result, the estimates will closely reflect anticipated exposures likely to be encountered by the public, with limited uncertainty in the results. Estimates of exposure from residential sources or pesticide residues in water are anticipated to be less certain because they will be the result of indirect estimation procedures using calculated residue values. Interpretation of combined results of direct and indirect estimation techniques will be complicated by the need to determine if a particular source of estimated exposure is biased and over- or under-reflecting real-world exposures. The mixing of two major sources of uncertainty in a highly complex exposure assessment would make it more difficult, if not impossible, to evaluate the source of any apparent exceedance of acceptable exposure levels. Where issues of data quality or quantity indicate that combining pesticide exposures across multiple routes would result in significant uncertainties, exposures that are pathway-specific should be combined and the implications considered qualitatively in the risk characterization.

SECTION 5. Determine Candidate Cumulative Assessment Group

Step 5. *Select pesticides, pesticide uses, routes, and pathways from the common mechanism group (CMG) that have an exposure and hazard potential to result in cumulative effects for inclusion in the quantitative estimates of cumulative risk.*

A **Cumulative Assessment Group (CAG)** may be a subset of the CMG because not all chemicals grouped by a common mechanism toxicity may be included in the *quantitative* cumulative risk assessment. In general, initial cumulative assessments should not attempt to quantify risk resulting from chemicals with a low hazard potential or from minor exposure scenarios, but should instead focus on those chemicals and exposure scenarios that are likely to be risk contributors and that may require mitigation actions. This focus on likely risk contributors is important because, as indicated in the Agency's *Supplementary Guidance for Conducting Health Risk Assessment of Chemical Mixtures* (USEPA, 2000j), the uncertainties and biases for even a small number of chemical components of a mixture can be substantial. When cumulative risk is assessed, a large number of chemicals may increase the complexity and uncertainty with no substantial change in total exposure. Additionally, including a large number of chemicals in the refined quantification of risk also may confound the interpretation and utility of the assessment results for risk management decisions.

The following could be removed from the quantitative cumulative risk assessment:

- A particular use of the pesticide
- A route of exposure
- A pathway of exposure (e.g., residential, drinking water)
- An entire chemical

In reviewing the initial cumulative assessment, careful attention should be paid to any decisions to exclude exposure scenarios in order to evaluate whether the exclusions had a meaningful effect on the assessment. The exposure and hazard data will serve as a basis for determining which members of the CMG, routes, pathways, and pesticide uses should be retained for quantifying cumulative risk. Although an entire chemical, a route or pathway of exposure, or a particular use may not be included in the final quantitative risk assessment, all chemicals, routes or pathways, and uses should at least be qualitatively assessed. It is critical that all CMG chemicals and their exposure scenarios are accounted for in the cumulative risk assessment. Thus, the rationale for not including an entire CMG pesticide or a particular pesticide use or route/pathway combination should be clearly described in the cumulative risk assessment. These decisions should be based on consideration of the totality of the hazard, dose-response, and exposure data. Although the exclusion of negligible contributors may be prudent, caution should be exercised such that d chemicals do not constitute a major portion of the total risk. Examples of reasons for not including an entire chemical or an exposure

route/pathway or pesticide use in quantifying risk follow:

An Entire Chemical: The risk assessor may remove any chemical whose contribution from all uses is expected to be negligible.

- ❑ The chemical's common toxic effect is the critical effect, but it shows a very low toxic potency for the common toxic effect compared to the other CMG members for all routes/durations of interest, and thus a low hazard potential for the common mechanism.

- ❑ The toxicity upon which the CMG was based is not the principal mechanism by which the pesticide exerts its potential adverse effect. The pesticide is regulated at a much lower exposure level based upon a much more potent toxic effect. For example, some thiocarbamate pesticides are weak cholinesterase inhibitors, but have much more serious and irreversible effects at dose levels significantly below those that induce cholinesterase inhibition. The regulatory endpoints for these pesticides reflect the principal adverse effects, which are irreversible. Although these chemicals exhibit characteristics of the CMG at very high doses, in the long term, exposure to these chemicals will be limited by the effects with the lower regulatory endpoint.

- ❑ On further detailed analysis, an individual chemical member of a CMG is found to exhibit toxicokinetic and pharmacodynamic behavior that is substantially different from the other members of the CMG.

A Particular Pathway/Route or Pesticide Use: Careful removal of scenarios in which exposure is very low or nonexistent can serve to focus the cumulative risk assessment on exposures that are more likely to be risk contributors. The sequential removal of scenarios as a part of a sensitivity analysis will be helpful in identifying the important sources of exposure for the cumulative risk assessment, accounting for uncertainties in the data inputs, evaluating the impact of any assumptions used, and explaining the outcomes of the assessment to risk managers and the public.

- ❑ Routes that have significantly less (or minimal) toxicity for the common mechanism effect(s), or routes for which the common mechanism is not expected to occur, should be excluded from the cumulative risk assessment. For example, a pesticide may be shown to have negligible dermal absorption.

- ❑ A particular pathway for a specific chemical in the CMG should be removed if it is likely to contribute only a very small percentage of the total exposure in the most refined analysis performed. The pesticide-pathway combination should be noted in the exposure characterization as present but not included in the quantitative exposure assessment. For example, a granular formulation of a herbicide that is used for turf treatment would most likely not contribute significantly to inhalation exposure.

- ❑ A specific pesticide-pathway combination that makes a negligible contribution to the exposure assessment should be removed because of limited use or low consumption of a treated commodity. For example, a pesticide that is used only once per season on one low-consumption food crop or during a period of dormancy would be expected to make a negligible contribution to overall exposure to the pesticide.

- ❑ Exposure scenarios should be removed for situations where there is a rapid onset of and recovery from the common toxic effect, and overlapping exposures with other pesticides are unlikely to result. Thus, attention should be given to concurrent exposure for acute or short-term toxic effects or chronic effects mediated through reversible precursor events, compared to irreversible chronic effects for which long-term exposure is necessary.

SECTION 6. Conduct Dose-Response Analyses and Determine Relative Potencies and Points of Departure

Step 6. *Select and apply an appropriate dose-response method to evaluate the common mechanism effects and determine the relative toxic potencies of the CAG by each exposure route and duration of interest. Determine the point of departure(s) for extrapolating the risk of the CAG.*

The key objectives of the dose-response analysis of the cumulative assessment group (CAG) members are to:

- ❑ select a common endpoint to estimate the toxic potency of each chemical in the CAG on a consistent and uniform basis

- ❑ select a method for estimating the relative potency of each chemical to account for the different toxic potencies of the CAG, normalizing the exposure data, and determining what fraction of the total risk comes from each chemical for each route/duration of exposure

- ❑ determine a point of departure for each exposure/duration for extrapolating the risk of the CAG. This point should be based on high-quality dose-response data and should be near or approaching the background response but yet can be reliably said to be due to dosing with the chemical

- ❑ evaluate the members of the CAG to determine whether they exhibit appropriately similar dose-response curves consistent with the assumption of proportionality and dose-additivity.

The dose-response modeling of multiple common mechanism chemicals for determining relative potency and point of departure for the CAG is in an early stage of development and experience is limited. It is anticipated that data and methods will continue to improve and evolve as more experience is gained in this area. Thus, the guidance below is a general framework intended to accommodate advancements in methodology and a variety of data situations. For additional guidance, the risk assessor should refer to EPA's *Benchmark Dose Technical Guidance Document* (USEPA, 2000b), the Agency's *Supplementary Guidance for Conducting Health Risk Assessments of Chemical Mixtures* (USEPA, 2000j), and the Draft Revisions to the EPA's *Guidelines for Carcinogen Risk Assessment* (USEPA, 1999c). The July 2001 dose-response assessment on organophosphorus pesticides (USEPA, 2001d) and the FIFRA SAP comments on that analysis (USEPA, 2001n) as well as the December 2001 preliminary organophosphorus pesticide cumulative risk assessment (USEPA, 2001m).

6.1 Dose Addition: A Method of Combining Cumulative Potency for Common

Mechanism Chemicals

Several methods are available for combining risks of chemical mixtures. These approaches are described in detail in the Agency's *Supplementary Guidance for Conducting Health Risk Assessment of Chemical Mixtures* (USEPA, 2000j). Because the focus of this guidance is on the cumulative risk associated with multiple chemicals that act by a common mechanism of toxicity and elicit the same common toxicity in the same target tissue, only methods that use the concept of dose addition[8] will be described. Dose addition is regarded as a reasonable and appropriate approach for estimating the cumulative risk associated with exposure to common mechanism chemicals. The assumptions and scientific support for use of dose addition in the risk assessment of chemical mixtures is discussed in detail in USEPA (2000j) and thus will only be dealt with briefly in this guidance.

The mathematical definition of dose addition requires a constant proportionality among the effectiveness of the chemicals (USEPA, 1986d, 2000j; Hertzberg et al., 1999). In other words, it is assumed that the ratios of toxic potencies among the chemicals remain constant along their dose-response curves. As discussed in the following paragraph, simple dose addition assumes no chemical interactions. In reality, common mechanism chemicals may not behave identically (the exact same toxicokinetics and pharmacodynamics). Furthermore, dose addition may be limited to some range of exposure conditions (dose level and frequency, as well as route). Therefore, dose addition is an Agency default assumption, and when applied it is only an approximation of the joint chemical risk. The risk assessor should use an alternative approach that is more appropriate when data support an alternative approach.

When applying dose-addition methods, it is assumed that at lower levels of exposure typically encountered environmentally no chemical interactions are expected (i.e., simple additivity) (USEPA, 1986d, 2000j). When adequate chemical interaction data (at low chemical doses near anticipated human exposures) are available for the CAG and indicate significant departures from the "no interaction" assumption [i.e., interactions showing greater (synergism) or lesser (antagonism)], alternative approaches to dose addition should be considered. Although there is limited practical experience for incorporating interaction data in chemical mixture assessments, the Agency's supplementary guidance for assessing chemical mixtures offers approaches (USEPA, 2000j).

As indicated above, there are several types of dose addition approaches, and the risk assessor can refer to the Agency's *Supplementary Guidance for Conducting*

[8]In contrast to dose addition, response addition applies when chemicals act on different systems or produce effects that do not influence each other (i.e., each chemical effect is independent) (USEPA, 2000j).

Health Risk Assessment of Chemical Mixtures (USEPA, 2000j) for a detailed discussion of these approaches. This document will only discuss the Relative Potency Factor (RPF) method which applies dose addition. At this time, OPP will use the RPF approach for estimating cumulative risk because it can utilize dose-response information to provide an estimate of the common toxicity, and thus allows for the quantification of exposure as it relates to the joint risk of the CAG. However, if an alternative approach to the RPF method is more appropriate then that should be considered. Briefly, the RPF approach uses an index chemical as the point of reference for standardizing the common toxicity of the chemical members of the CAG. Relative potency factors (i.e., the ratio of the toxic potency of a given chemical to that of the index chemical) are then used to convert exposures of all chemicals in the CAG into exposure equivalents of the index chemical. The steps involved in the RPF approach are depicted in the accompanying text box and will be described in detail below.

6.2 Determination of the Relative Potency for the CAG

Steps in the Relative Potency Factor Approach

- Determine **Toxic Potency** of each chemical member in the CAG by route and duration of interest
- Select an **Index Chemical** as a reference point to put each chemical member on a common scale
- Calculate **Relative Potency Factors** based on the index chemical's toxic potency
- Determine the **Point of Departure** for the index chemical by routes and durations of interest

Although the chemical members of the CAG produce the same common effect(s), they will likely have different toxic potencies in doing so. Thus, to estimate the joint risk of the CAG, the different chemical potencies must be put on a common scale so the exposures to the chemicals can be normalized. The following steps should be taken in applying the RPF approach: (1) determine the toxic potency of each chemical; (2) select an index chemical to use as the point of reference for standardizing the common toxicity of each chemical member; (3) calculate RPFs for each chemical member that will be used to normalize their exposure; and (4) Finally, a point of departure is determined for the index chemical. These steps are explained below.

6.2.1 Determination of Toxic Potency

Principles for Determining the Toxic Potency for the Chemicals of Interest

To the extent possible, toxic potency should be based on a uniform point of comparison using:

- Same common toxic endpoint for **all** exposure routes/durations of interest
- Same measure of potency for **each** exposure route/duration of interest
- Same species/strain and sex for **all** exposure routes/durations of interest
- Studies of comparable methodology

The toxic potency for each chemical member should be calculated using a consistent and uniform dataset for the chemical group. Thus, to the extent possible the toxic potencies of each member of the CAG should be based on the same common effect derived from the similar studies using comparable methodologies evaluating the same species/strain and sex for the exposure route/durations of interest. As explained below, there are several measures of potency, as described in Section 6.2.1.1, that can be used to estimate the relative potency of the CAG. The same measure should be used for each exposure route of interest to provide a consistent and uniform basis to derive relative potencies of the CAG. If mixing of species/sexes, endpoints, or measures of potency is necessary, then additional uncertainties are introduced to the assessment and must be clearly noted, and some characterization of their impact on the total cumulative assessment should be given.

6.2.1.1 Measures of Potency

Approaches to Determine Relative Toxic Potencies Among the Members of the CAG

Ideal: Biologically- and Toxicokinetically-based Modeling
Appropriate: Empirical Curve Fitting Model
Least Desired: Use of *NOAELs*
Inappropriate: Use of *RfDs* from the single-chemical aggregate assessments

There are several measures to describe the toxic potency of each chemical in the CAG. If the dataset for the CAG contains information amenable to dose-response modeling, the ideal approach for determining toxic potency is to use a biologically- and toxicokinetically-based model. Although the development of these models is encouraged, they are not yet standard methods and are data intensive. Thus, the more likely approach taken will be to use a curve fitting model that is appropriate to the response data. The dose-response relationship is described for each member of the CAG with the same mathematical model function. A benchmark dose (BMD) then can be derived from modeling the dose-response of each chemical to determine each

chemical's toxic potency. A BMD associated with the same designated level or percent of response relative to the control or baseline level of response (this is referred to as the benchmark response) should be used all CAG members. For purposes of determining relative potency, the BMD should be based on a central tendency estimate rather than the 95% lower confidence limit on dose. The use of the central tendency on dose is considered appropriate when determining relative toxic potencies for multiple chemicals which are being normalized to a common scale because the 95% confidence limits may result in compounding the conservatism in a multiplicative manner. The BMD should represent a response level that is within the observable range of the dose-response curves for which the toxicity studies have reasonable power to detect. Furthermore, if a BMD is used to determine the relative potency of the CAG, then the benchmark response should be the same that is used to determine the point of departure for the index chemical unless there is justification for use of another benchmark response (discussed later in Section 6.2.3.). An alternative approach to using a BMD is use of a dose scaling factor (units expressed as inverse of the dose units, e.g., $mg/kg/day^{-1}$) for calculating the absolute potency of each chemical.

If the data available for the CAG are not amenable to curve fitting, then NOAELs may be used as a default approach to approximate the toxic potencies of the CAG. This is a less desirable approach with several disadvantages. NOAELs do not necessarily reflect the relationship between dose and response for a given chemical, nor do they reflect a uniform response across different chemicals. The "true" NOAEL may be close to the background response level, may be well below the background response level, or may approach or be at an effect level not observed owing to the dosing levels or the insensitivity of the study. An evaluation of the NOAEL versus the LOAEL may provide some insight into how close an empirically measured NOAEL approaches the background level of response. If NOAELs are not available, use of a LOAEL can be considered. In this case, the LOAEL for that chemical should be adjusted by a factor (usually 3- or 10-fold as a default adjustment) to estimate the NOAEL.

Finally, determinations of relative potency generally should not be based on an individual chemical member's reference doses (RfD)[9]. It is inappropriate to use the RfDs previously determined for single-chemical assessment for a number of reasons. First, they were derived for a different purpose. An RfD is based on an evaluation of all toxicities produced by the chemical and on identification of the most sensitive effect occurring in the most sensitive species. In cumulative risk assessment, the most sensitive endpoint is not necessarily the common toxic effect. Although the RfD effect may pertain to the common mechanism, it may not be the endpoint or species/sex selected to determine the relative potency of the CAG. Finally, RfDs contain uncertainty factors that may differ from those pertaining to the common toxic effect.

6.2.1.2 Endpoint and Study Selection

A comprehensive review of the data pertaining to the common toxicity in different strains and sexes and at various time points should be conducted to determine which studies can contribute valid information for the dose-response analysis. Reasons for excluding specific studies should be documented. Following the complete review of the toxicity database, the common toxic endpoints and species/strain and sexes that have the most extensive databases should be selected to provide a uniform basis to determine the relative potencies of the CAG for each route and duration of interest. Studies with more dose groups will generally be more useful to dose-response modeling and the determination of relative potencies and points of departure for the CAG.

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[9]A chronic reference dose is defined as an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily oral exposure to the human population (including sensitive subgroups) that is likely to be without appreciable risk of deleterious effects during a lifetime. OPP also determines RfDs for less than lifetime risk assessments (e.g., acute dietary risk). An RfD can be derived from a NOAEL, LOAEL, or benchmark dose, with uncertainty factors generally applied to reflect limitations of the data used. RfDs are generally used in EPA's noncancer health assessments.

A description of the RfD process for single-chemical assessments can be found at EPA's website for its Integrated Risk Information System (USEPA, 1999i) or in Barnes and Dourson (1988).

6.2.1.3 Data Collection and Entry

The studies to be used in the dose-response analysis should be fully documented. A summary format should be prepared that includes the following information: type of study, route, duration, doses evaluated, number of animals per dose group, species/strain/sex, and the measured effect for each dose group including the mean and standard deviation. Study design elements that may influence a chemical's toxic potency should be noted by the risk assessor. Examples include the schedule of intermittent dosing, and the vehicle (especially for oral exposures), as well as whether the vehicle effects are known to influence the toxic effect of concern.

6.2.1.4 Combining Response Data

Estimates of each chemical's toxic potency for the common effect should be derived, if possible, for several relatively consistent studies, as opposed to a single study. This may be done by modeling each separate study and then combining the resulting potency estimates using appropriate statistical methods. The potency estimates from different time measures within and across studies may also be combined if appropriate (for example, steady state may be reached for a given endpoint). Using more than one study and/or more timepoint data has benefits in that it will allow for more robust estimates of the central value for the potency of each chemical. If there are no differential effects between the two sexes, those datasets may be combined. Combining data from multiple studies (or multiple timepoints within a study) will allow for a better estimate of the uncertainty associated with estimations of relative potency. When results from several studies are combined, statistically appropriate methods must be used and justified, and the rationale should be clearly presented, including a discussion of the variability among the single studies.

6.2.1.5 Use of Surrogate Toxicity Data

As stated earlier, it is preferred that determinations of relative potency be based on the same species/strain and sex. Where there are inadequate or missing data for a chemical(s) for the common toxic effect(s) in the species/strain or sex that is selected to estimate the relative potency of the CAG, "surrogate" data for a particular endpoint/species/sex for a route or duration of exposure may be used if it is appropriate to do so both statistically and biologically (i.e., there are no, or minimal, species/strain or sex differences). It should be noted that there is limited experience in using surrogate data to replace missing datasets to estimate relative potency. An example of the use of surrogate data can be found in EPA's report on dioxins and furans (USEPA, 1989 and USEPA, 2000h). The FIFRA SAP recommended the following: "*The use of surrogate data is reasonable when*

the data utilized for the extrapolation are of high quality, and there is an adequate understanding of the relationships among the data that are utilized for the estimation of the surrogate data. It is imperative that the Agency be transparent in why and how the surrogate data are chosen. There should be a discussion as to the "degree of confidence" or "level of uncertainty" the Agency has in the surrogate data." (USEPA, 2001j). The risk assessor should use these recommendations to guide its analysis.

6.2.1.6 Modeling the Data

The selection of a mathematical model structure to fit the data being analyzed should be guided by the biology of the common mechanism of toxicity, the toxicokinetics of the chemicals, and the observed shapes of their dose-response curves and the experimental designs used to generate the data. If available, pharmacodynamic and pharmcokinetic data should be considered in order to account for tissue concentrations and to aid in defining dose-response relationships across different species, routes, and time-frames of exposure.

This guidance does not specify a particular set of models. Rather, the goal of mathematical dose-response modeling is to select and fit a model that best describes the dose-response of the given datasets for the common toxicity, and is descriptive with the biology of the common mechanism. Various dose-response models have been used to estimate noncancer and cancer dose-response functions (see USEPA, 1999c, 2000b). The risk assessor should refer to the EPA's technical guidance for deriving benchmark doses (USEPA, 2000c) for a more detailed discussion of considerations concerning the model selection and fitting. The choice of a modeling procedure should be done on a case-by-case basis. The assumptions underlying the model and application of the model to the common toxicity dataset should be clearly explained. Although it is not possible to recommend the use of specific models, a few points that should be considered in modeling the data follow:

- ❏ Modeling of individual animal data is desirable; however, if this is not practical, then use of summary data such as means and standard deviations can be alternatives

- ❏ Care should be taken with modeling high-dose data (particularly extreme doses) because the model shape in the low-dose region can be influenced by high-dose data

- ❏ Log transformation of data should be justified because such a transformation may distort the dose-response curve

- ❏ Data variability should be described by appropriate statistical techniques and reflected in the potency estimate (e.g., by weighting the data in the fitting procedure)

- ❏ Confidence intervals or limits should be included in the analysis because they can be valuable for evaluating the influence of variability on the potency estimates

- ❏ An estimate for the uncertainty of the model used in the analysis should be included

- ❏ The statistical fitting method used must be clearly described.

A statistical criterion (e.g., P values) should be used to evaluate how well the model describes the data. The rationale for the statistical criteria should be justified. The risk assessor should refer to the Benchmark Dose Guidance on how to evaluate the goodness of fit (USEPA, 2000b). A failure of a model to describe a dataset may be due to a number of possibilities, such as quality of the data, limitation of the model, or toxicokinetic and dynamic differences for a chemical that may raise doubts as to whether that particular chemical is appropriately considered in the CAG. The risk assessor should describe how these situations are dealt with in the assessment. If a chemical is to be excluded from the CAG for quantifying risk, the biological rationale for this exclusion should be presented (see Section 5).

6.2.1.7 Interspecies Adjustment of Dose

Ideally, when adequate data are available, the doses used in animal studies should be adjusted to equivalent human doses by using physiologically-based toxicokinetic (PBTK) models. This approach for dose extrapolation between species is not possible for most chemicals given that the use of PBTK models requires extensive comparative metabolism and toxicokinetic data that rarely exist. In the absence of these data, estimates of human equivalent doses are based on science policy defaults. The risk assessor should follow current Agency policy for interspecies adjustments of dose for cancer and noncancer effects and for ingested doses versus inhaled doses (see USEPA, 1999c; 1994).

6.2.1.8 Route-to-Route Extrapolation

Completeness and reliability of endpoint-specific data may be a particular concern for the dermal and inhalation routes. Extrapolations based on toxicokinetic models may be reliable enough for use in risk assessments, but they are rarely available. Simple extrapolations based on toxicokinetic defaults are sometimes unreliable because they assume that both routes are toxicokinetically and toxicologically similar. Uncertainty in a cumulative risk assessment is compounded with each chemical that lacks route-specific data, and too much uncertainty can render an assessment less meaningful. Thus, a default-based route-to-route extrapolation should not be included in a cumulative risk assessment unless there is a reasonable rationale for doing so (see USEPA, 2000j). That justification must be clearly stated. Additional guidance on route-to-route extrapolations can be found in EPA's *Inhalation Risk Characterizations and the Aggregate Risk Index* (USEPA, 1998c).

6.3 Criteria for Selection of an Index Chemical

As indicated above, the RPF method evaluates the equivalent index chemical exposure on its dose-response curve in order to estimate the risk of the CAG. Thus, it is essential that the index chemical be well characterized (qualitatively and quantitatively) because any imprecision in its data may be compounded with every chemical against which it is compared. The most important consideration in selecting an index compound is that high-quality dose-response data are available for the common toxic effect/species/sex and for the exposure route/pathways of interest. Furthermore, the compound should be well characterized for the common mechanism of toxicity, and the common mechanism of toxicity should be its principal toxicity. The index chemical should have a toxicological profile for the common toxic effect(s) that is representative of the other chemical members. It is preferable to have one index compound to scale the potencies across all routes/durations of interest.

6.4 Determination of a Point of Departure for the CAG

The last key step in the dose-response analysis is to determine an extrapolation point or point of departure for the CAG. A **point of departure (POD)** is a point estimate on the index chemical's dose-response curve that is used to depart from the observed range of empirical response (or incidence) data for extrapolating risk to the exposure anticipated in the human population. The POD should be either an observed dose or an estimated dose that approximates a "minimally toxic" response or a point in the dose-response curve at which a change in response can be reliably said to be due to dosing with the chemical. The choice of a POD will depend on the quality of the dose-response data and the degree of confidence in the relationship between the observed adverse effects or lack thereof. The traditional POD used by

the Agency is a NOAEL. The preferred POD, however, is one derived from modeling the dose-response curve of the index chemical to derive a benchmark dose (BMD)[10] that estimates a pre-specified level of response. The benchmark response (BMR) quantifies that level of response.

As stated earlier, biologically-based or physiologically-based toxicokinetic models, which incorporate specific data on kinetic processes, are the most desirable approaches for quantifying toxic effects. Although the Agency encourages the development of such models, it is unlikely that the data will be available in the near term for the required input parameters. Thus, the use of a standard curve-fitting model will more likely be the practical approach at this time. The dose-response model used for the determination of relative potency should be the same one that determines the POD for the index chemical. A 10% effect level (BMD_{10}) has been proposed by the Agency as the standard default point of departure for quantal endpoints (e.g., tumor responses). For some toxicities, a point of departure other than the BMD_{10} may be appropriate. For example, if statistically significant responses for the individual chemicals are lower than the 10% level of change in the response, then a lower point of departure (e.g., a $BMD_{5\text{ or }1}$) may be more appropriate for the CAG. For continuous endpoints (e.g., changes in hormonal or enzyme levels), the *Benchmark Dose Technical Guidance Document* (USEPA, 2000b) recommends that a dose be selected that would be expected to yield a change in the mean equal to one control standard deviation. The choice of a BMD response level and the justification for that choice should be provided on a case-by-case basis. Both the central estimate (BMD) and the 95% lower confidence limit on a dose (BMDL) should be presented to provide the risk manager with the magnitude of uncertainty associated with the POD. For interim guidance on modeling and deriving a benchmark response for extrapolation, the risk assessor should refer to the Agency's benchmark dose guidance (USEPA, 2000b).

[10]The term "benchmark dose" refers to the modeling of both quantal and continuous endpoints, whereas the term "effective dose" is typically used to refer only to quantal endpoints.

6.5 Calculation of Relative Potency Factors

Once the toxic potency of each member of the CAG is determined and an index chemical has been selected, relative potency factors (RPFs) may be calculated based on the index chemical's toxic potency. The RPF method[11] expresses the toxic potency (e.g., BMD or NOAEL) of each CAG chemical in relation to the potency of one member in the group selected as the index chemical (e.g., if Chemical Y is one-tenth as toxic as the index chemical, the RPF for compound Y is 0.1):

Equation 6.1: $$RPF_n = \text{Toxic Potency}_{[\text{Index Chemical}]} \div \text{Toxic Potency}_{[\text{Chemical n}]}$$

Using this method, each chemical's exposure pathway is adjusted by its RPF to express it as a toxicity equivalent (TEQ) exposure, and then the exposure equivalents are summed. The index chemical's point of departure is then used to determine the margin of exposure for each exposure pathway/route/duration of interest, as explained in Section 9.6.3.

6.6 Presenting the Results of the Dose-Response Assessment

Sufficient information should be provided for others to clearly understand the dose-response analysis; for example, a graphic display could be provided of the dose-response curves for each CAG member, as well as summary tables of the studies used, calculated statistics, estimated toxic potencies, and points of departure for each route/duration of interest. The summary table should also include pertinent information on the time course of the effects (e.g., steady state, recovery). The analysis should discuss or identify the following:

- ❏ rationale for the choice of endpoints, selection of studies, and model
- ❏ dose-response patterns across endpoints, species/strains, and sexes for different routes and durations of exposure
- ❏ applicability of results to varying exposure scenarios–issues of route of exposure, dose rate, frequency, and duration

[11]The toxicity equivalency factor (TEF) approach (described in USEPA, 2000j) is conceptually a more rigorous type of RPF approach. In contrast to the more general RPF method, a key assumption of the TEF approach is that, for each chemical in the CAG, only one potency adjustment factor is needed because it applies to all effects by all routes and all durations (USEPA, 2000j).

- ❑ uncertainties, assumptions, adjustments, and defaults related to the approach for estimating the toxic potencies for each CAG member

- ❑ chemical members that display dose-response curves that are not consistent with other members of the CAG (in which case there should be accompanying biological and statistical discussion concerning whether they are appropriately included in the CAG).

Finally, the cumulative dose-response assessment should include a discussion concerning the applicability of the assumption of dose additivity and proportionality of the dose-responses among the CAG. It should be cautioned that studies that are likely to be available on the CAG may not have been designed to address the issue of dose additivity at low exposures. The FIFRA SAP (USEPA, 2001j) indicated that when evaluating the appropriateness of dose addition, substantial reliance would have to be placed on what is known about the commonality of the mechanism of toxicity for the CAG. The application of dose additivity requires the assumption of no toxicologic interactions. Thus, as described in Section 3.3, a literature search should be conducted on chemical interactions studies as well as whole-mixture studies for the members of the CAG to determine support for or departure from dose addition. Furthermore, the mathematical definition of dose addition requires a constant proportionality among the effective doses of the chemicals (USEPA, 1986d, 2000j; Hertzberg et al., 1999). A statistical examination of whether the dose-response curves for each chemical member of the CAG are consistent with the assumption of dose additivity should be considered in the analysis. If a mathematical dose-response model were applied to the CAG to estimate toxic potency, then one could also evaluate whether that same model function adequately describes the datasets for common toxicity of the CAG. If evidence exists that is judged to disagree with dose addition, particularly at low doses, then the chemical(s) in question should be re-evaluated for inclusion in the quantification of cumulative risk.

SECTION 7. Develop Detailed Exposure Scenarios for All Routes and Durations

Step 7. *For all of the uses remaining for each pesticide in the CAG, determine their role in establishing the magnitude of possible exposures. Decide the relative importance of scenarios and the need for their inclusion in a quantitative assessment. Identify populations of interest and locations for evaluation in the assessment. Determine co-occurrences of possible exposure scenarios.*

After the members of the CAG have been identified, the next step in developing a cumulative risk assessment is to elaborate the exposure scenarios resulting from the uses for each member compound. This process is described in detail in the *General Principles For Performing Aggregate Exposure And Risk Assessments (*USEPA, 2001h), and will allow a determination of whether the exposure scenarios identified present any likelihood of overlapping exposures. Exposures are considered to overlap if chemicals are likely to be encountered from more than one source or pathway within the time frame in which the common mechanism effect is still operative from previous CAG exposures. The pathways of exposure for a chemical in the CAG may be such that overlapping exposure to another chemical will never occur.

For acute or short-term toxic effects, the evaluation of the likelihood of overlapping exposure events may be more difficult if there is rapid onset of and recovery from the toxic effect. In such cases, a much more detailed estimation of the time course of exposures will be necessary.

For chronic and cancer effects mediated through reversible precursor events, overlapping exposure should also be considered to determine whether durations of exposure are sufficient to trigger adverse effects, and to determine whether a subsequent exposure will occur before recovery is complete. Where **effects are reversible**, if sufficient time has passed such the recovery can be reasonably expected to have occurred, subsequent exposures would be considered to have no cumulative effect. The exposed individual has effectively returned to a state as though no prior exposure had occurred.

In the case of chronic and cancer effects for which long-term exposure is necessary to cause the effect of concern and for which **the effect is irreversible**, concurrent exposures are not required for the chemicals to act by a common mechanism. The risk assessor should assume that each additional exposure will result in an accumulation of toxic effect with no potential for recovery.

Single-chemical aggregate assessments should be used to inform the risk assessor in designing the cumulative risk assessment. However, a refined, quantitative, multipesticide cumulative risk assessment should not be performed by summing single-pesticide aggregate assessments. The cumulative risk assessment should reflect linkages and co-occurrences of use between complementary and competing pesticides. These factors generally cannot be established from single-chemical aggregate assessments because they were not relevant for an aggregate (single-chemical) assessment and therefore were not considered. Some of the underlying assumptions regarding the use of the toxicity data for a single chemical, such as the endpoint selected, may differ markedly from those for a CAG. The selection of typical versus high-end use data may differ depending upon whether the assessment focuses on multiple pesticides or a single pesticide. The cumulative risk assessment cannot be reconstituted from preexisting single-pesticide aggregate assessments, but should be conducted beginning anew from the base data.

Using the data and results from the single-chemical aggregate assessments for the members of the CAG, the cumulative risk assessment should be planned with the following questions in mind:

- ❏ Who is exposed?
- ❏ To which chemicals and in what amounts?
- ❏ What is the timing of the exposures and do they overlap?
- ❏ Do the exposures occur in the same location such that they will be experienced together?
- ❏ What are the pathways, routes, and duration by which the exposures will occur?

For example, a mosquito treatment in the Southeast should be matched with other potential exposures during the spring and summer in the Southeast. The cumulative exposure assessment should be carefully structured to avoid nonsensical combinations, such as an individual being subjected to exposure resulting from spraying for black flies in Minnesota in the summer and treating for termites in Georgia in the fall.

Three key pathways of exposure to pesticides are the dietary pathways of food and drinking water, and the nondietary pathway from exposure in residential and other nonoccupational settings. Chemical use patterns greatly affect potential exposure scenarios. By evaluating a pesticide's use pattern, a profile for each chemical from the CMG can be developed to establish the potential routes, durations, frequencies, and magnitude of exposure. Also, the evaluation of chemical use profiles allows for the identification of exposure scenarios that may overlap, co-occur, or vary between chemicals.

The time-frame over which an exposure occurs is a key criterion for defining scenarios of interest. For example, depending upon the nature of the common toxic effect and the use patterns for a pesticide, the assessment may focus on the day an item of food is consumed, or extend the time of evaluation over several days following a home pesticide use. The time-frame will determine how exposures from different pathways and routes will be evaluated. This step depends heavily upon examination of the toxicity data, but requires the concurrent determination of what scenarios it is appropriate to represent. The nature of the adverse effect from the toxicity data will determine the time course over which exposure should be assessed. The consideration of the time-frames from the toxicity study should include an evaluation of time to onset of effect, impact of dose on time to onset, and time required for reversal of the effect (if the effect is reversible) following cessation of exposure. Where exposure scenarios are found to be of insufficient duration to trigger the common toxic effect, careful consideration may be given to eliminating some of the scenarios from the assessment. Duration alone, however, cannot be considered as a criterion for removal in a risk assessment because the final exposure that is analyzed in the cumulative risk assessment will be an accumulation of exposures from many pathways. Several exposures of short duration may overlap to produce a cumulative exposure that exceeds an acceptable level. Additional information about time intervals that may be useful in the development of exposure assessments can be found in the EPA’s *Exposure Factor Handbook* (USEPA, 1999d).

7.1 Dietary Food Pathway

OPP has extensive experience in conducting pesticide exposure assessments that account for differences in consumption patterns by region of the country and season. To a large extent, consumption is independent of geographic region and season. This is likely owing, in part, to the widespread distribution of both domestic and foreign commodities across the United States and, for many commodities, the predominance of storage facilities available for domestic commodities and the availability of foreign sources of fresh agricultural commodities throughout the year. Similarly, OPP has looked at the patterns of residues from data collected from USDA's Pesticide Data Program (PDP) and believes that there is little evidence for enough seasonal or spatial variation in pesticide residues to substantially alter OPP exposure assessments.

As a result, exposure to pesticide residues in foods will be considered without regard for time of year or geographic location unless specific information indicates another approach should be taken. Region-specific exposures from residential uses and drinking water will be superimposed on the food exposure estimates.

7.2 Dietary Drinking Water Pathway

Exposures in drinking water to individuals should be incorporated into cumulative exposure assessments on a local or regional basis. Factoring drinking water exposure into the framework already contemplated for food-related exposures means developing a "person-by-person" approach to estimating drinking water exposure to pesticides over time. Because exposure to pesticides in drinking water is a local or a regional concern, and additionally, because the food portion of the dietary exposure assessment is being done on an individual basis, each hypothetical person included in a cumulative risk assessment should be assigned to a location and a drinking water source consistent with that location.

Once an individual has been associated with a representative drinking water source, the available data should be examined for the occurrence and co-occurrence of pesticides in the drinking water source over time. Geographical Information System (GIS) tools, cropping and pesticide use information, fate and transport data, modeling results, monitoring data, and information on the effects of blending and treatment should be used to determine the pesticides most likely to occur or co-occur in that water source, and potential pesticide concentrations over time. Initially, OPP expects to assume that a person would be exposed only to those pesticides that are used in the recharge area above an aquifer for groundwater, or in the watershed of the drinking water source for surface water. As a guide to determining likely regions upon which to focus risk assessment scrutiny, the risk assessor should consider using information such as the National Agricultural Statistics Service (NASS) database or data from Doane’s Marketing Service to evaluate the use of pesticides in the CAG in areas where more than one of the CAG

pesticides are used. Alternatively, an analysis of cropping patterns and pest pressure may be explored to identify likely areas for concentration of effort.

7.3 Residential and Nonoccupational Pathway

Applications of pesticides made in and around homes, schools, offices, and other public areas may result in potential exposure via the oral, dermal, and inhalation routes. Consideration of co-occurrence and linkage of uses where appropriate is particularly important for residential uses. Linked uses are those in which two products are or may be used in combination, such as dipping a pet and treating the carpet of a flea-infested home, or used in such a way that using one product substantially increases the probability of using a second product. The recognition and maintenance of these potential linkages will be critical in developing realistic estimates of exposures to a hypothetical individual with defined demographic characteristics. At this time, the understanding of patterns of use is limited, although the Agency is aware of efforts to conduct surveys describing the pesticide use practices of the U.S. public. Exposure assessments for residential and other nonoccupational sources will focus on those use scenarios outlined in the *Residential Standard Operating Procedures* (USEPA, 1999g).

The factors for consideration in developing reasonable exposure scenarios for residential, nonoccupational, and institutional exposures are described in detail in a previous EPA document (USEPA, 1999b and USEPA, 2001h). As described in that document, the patterns of use for pesticides in residential, nonoccupational, and institutional settings are highly dependent upon location, season, dwelling type, and a myriad of other factors that impact the behavior of a potential pesticide user. Where appropriate, an assessor should link residential pesticide use preferences with particular classes or categories of individual, based on data, when performing cumulative exposure assessments. Where data are limited in quantity or are of poor quality, the residential SOPs should serve as the basis for initial estimates of exposure.

Age/gender/pathway considerations play a role in cumulative assessments related to the behavior of individuals. Young children may be exposed to more pesticide residues for a variety of reasons. For example, young children engage in more hand-to-mouth activity (nondietary ingestion) than do adults. Some national surveys of home and garden pesticide usage suggest that more males than females treat lawns, whereas females are more likely to treat the interior of the house. Consideration of data of this type will aid in developing reasonable and realistic cumulative exposure and risk assessment scenarios.

To the extent possible, the assessment of residential, nonoccupational, and institutional use patterns should characterize seasonal and geographic variations, and associated pest pressures. Residential uses cannot necessarily be assumed to be consistent with or coincide with the large national or broad regional breakouts

currently used in the food exposure assessment arena. For instance, a food exposure assessment might cover the entire Pacific Northwest region of the United States. However, the coastal regions of Washington and Oregon are more humid and have milder temperatures than would be found in Idaho. Thus, residential uses of pesticides would likely differ considerably between these two areas because of differences in pest pressure, even though they are within the same "region." Cumulative risk assessments should reflect use patterns and practices on a scale sufficient to capture the variability in pesticide use, but not so large as to inappropriately dilute real and significant differences. An example is the very localized use of fenthion for mosquito control in parts of southern Florida. This pesticide should have only limited consideration in an assessment of other organophosphorus pesticides, including those used for mosquito control. In addition, a national overlay of market share by region may help to direct the risk assessor in determining the CAG to combine on a geographic basis.

SECTION 8. Establish Exposure Input Parameters

Step 8. *Determine magnitude, frequency, and duration for all pertinent exposure pathway/route combinations. Identify appropriate sources of use/usage information, residues in all appropriate media, and any modifying factors necessary for inclusion in the assessment. Where necessary, identify any appropriate surrogate datasets from other chemical specific data, published literature, or generic datasets. Model any necessary exposure parameters for inclusion.*

The data for the three major sources of pesticide exposure (food, drinking water, residential or other nonoccupational) that will be used to develop single-chemical aggregate assessments will constitute the majority of the data required to conduct the cumulative risk assessment. Strengths and weaknesses inherent in the data for each individual chemical assessment will be carried over to the cumulative assessment. In addition, the data available for the three sources of exposure may vary widely in quantity as well as in their ability to describe the range of the exposures likely to be encountered by each pathway. The data that OPP anticipates using for each pathway are discussed below.

8.1 Dietary Food Pathway

The body of information for the food pathway is generally much greater than that available for the other pathways. Some of the types of data and their sources that can be used in assessing exposure to pesticides in food are depicted in the text box. Cumulative exposure assessments for this pathway are anticipated to be accurate and refined because of the availability of monitoring data that will provide a clear picture of residues in foods far down the chain of commerce. In addition, data defining the consumption patterns for the U.S. population have been collected in a number of surveys. Current OPP food risk assessments rely upon the food consumption data collected by USDA in the *Continuing Survey of Food Intakes by Individuals* (CSFII). Cumulative exposure assessments for residues of pesticides in foods can be performed for each hypothetical individual used to estimate the distribution of anticipated exposures. Using detailed individual consumption records such as those provided by the CSFII, combined with analytical results from monitoring programs such as USDA's PDP

Sources of Dietary Food Data

- Continuing Survey of Food Intakes by Individuals (CSFII) (1994-1996, 1998)
- Field Trial Data (studies submitted to EPA that are required for registration or re-registration).
- Monitoring Data from USDA's Pesticide Data Program (PDP)
- FDA's Surveillance Monitoring Data
- Market Basket Monitoring Data

program, a refined exposure estimate can be developed that incorporates the likelihood of consuming multiple residues in a single food and the likelihood of consuming more than one food that may contain a residue of concern. Food exposures will be assumed to be national in scope unless there is evidence to the contrary.

The development of cumulative exposure scenarios may be driven by the information contained in the food consumption and residue databases. Cumulative assessments should be performed on an individual-by-individual basis in order to maintain any necessary linkages and associations between consumption data and demographic data. Food consumption data files provide demographic information on the region (and urbanization) of residence, the season of response, and socioeconomic status of the consumption survey respondents, among others. These data may be used in constructing subpopulation characteristics that can be matched to appropriate residential and drinking water exposure scenarios. Similarly, differences in pesticide use and usage rates that are available from a variety of sources may also be related to region, and may permit development of more refined and focused individual-based cumulative risk assessments. Regional factors will also be important in selecting the appropriate localized drinking water data and residential use scenarios to include in the cumulative risk assessment. More detailed discussion of the importance of demographic information in structuring a risk assessment is presented in EPA's guidance for performing aggregate risk assessments (USEPA, 1999b and USEPA, 2001h).

Monitoring data are unlikely to be available for all commodities under consideration. OPP commonly translates residue data between similar commodities that have common cultural practices in order to take full advantage of the available monitoring data. This translation process includes an evaluation of treatment rates and frequencies to be certain that the assumption of relevance of data between commodities is appropriate.

When residue monitoring information for most food uses of CAG pesticides is available, the risk assessor should limit the residue data used in cumulative exposure assessment to monitoring data that reflect actual measurements of pesticide residues and their co-occurrence. Empirical estimation of co-occurrences in a cumulative assessment is critical because the co-occurrence of residues of two or more chemicals in a single food item is not necessarily independent; a co-occurrence may be the result of intentional application practices. For example, some products are sold as mixtures of pesticides, so the presence of one may be correlated with the presence of another. In addition, the rotation of multiple pesticides within a single growing season may result in the co-occurrence of pesticides. Therefore, the use of monitoring data in which co-occurrence was measured may provide the only basis for conducting a cumulative food exposure assessment that describes this situation with any degree of certainty.

At this time, OPP does not have adequate methodology to combine monitoring data with residue field trial data into cumulative assessments. Although such combined data are routinely used in aggregate risk assessments for individual pesticides, several factors suggest that use of such data in cumulative risk assessments would yield results with unacceptably high uncertainty. First, use of residue field trial data presents a conservative picture (i.e., an estimate that errs on the side of overstating exposure and risk) of residue levels because use of such data is premised on the assumption that all uses of the pesticide occurred at maximum label rates. This conservatism would be compounded by the aggregation of such conservative values. Second, field trial data do not (and cannot) account for co-occurrence of pesticide residues in single items, and such consideration is a relevant aspect of any cumulative assessment. PDP data provide a direct measure of concurrent exposure to pesticides, and as such implicitly account for actual usage practices. The alternative is to rely upon indirect estimation of likely overlapping use, extrapolating from data on use areas, use rates, season of application, and many other factors. The combination of conservative residue values with an indirect approach to estimating co-occurrences would introduce uncertainty, making the cumulative risk assessment less reliable for regulatory purposes. Thus, when OPP does not have monitoring information for most food uses of the CAG chemicals, OPP may combine the field trial values to produce a bounding estimate of exposure by the food pathway that will provide qualitative information about the upper-bound exposure and relative contribution of different uses. This approach is similar to the screening-level assessment described above in Section 4. Inherent in a bounding estimate of this type is the premise that an acceptable risk under these circumstances indicates no possibility that an unacceptable risk may pass unidentified. However, it is difficult or impossible without further refinement to determine whether the indication of an unacceptable risk is real or an artifact of the estimation process. In general, the risk assessor should not combine data from monitoring with data from field trials because of the qualitative difference in the two datasets.

OPP often has information regarding the impact of food preparation (washing, peeling, cooking) to adjust the pesticide residues in raw commodities to reflect processing and handling. These data should be applied, where appropriate, to monitoring data on a pesticide-specific basis. In addition, data on the percent of the crop treated are available to permit estimation of the likelihood that a given pesticide has been applied to a commodity. The percent of crop treated should also be applied on a pesticide-specific basis taking into account the quality of the data.

8.2 Dietary Drinking Water Pathway

The dietary food pathway in many cases will be based on higher quality monitoring data than for the drinking water (or residential) pathway. Thus, the co-occurrence of pesticide residues in water in most cases will be estimated rather than based on monitoring data. Although it is desirable to use direct measurements of

pesticide concentrations in tap water in cumulative exposure assessments, this approach may not always be feasible. Pesticide concentrations vary considerably across space and time; thus, obtaining an adequate number of tap water samples could be prohibitively expensive. Accordingly, the risk assessor should be using a combination of monitoring and modeling to develop reasonable approximations of pesticide concentrations in tap water. These can include:

- ❏ direct measurements of pesticide concentrations at the point of distribution from Community Water Systems (i.e., finished water)

- ❏ direct measurements of pesticide concentrations prior to treatment (i.e., raw water measurements) with adjustments for the effects of blending and treatment

- ❏ model-based estimates of pesticide concentrations in raw water with adjustments for the effects of blending and treatment.

Corrections for treatment and blending should be made to the extent that they are reflected in available data. It is OPP's intent to utilize in a scientifically defensible manner all available and relevant monitoring data and modeling results to develop its best approximation of pesticide concentrations in tap water over time for use in cumulative risk assessments.

Evidence of the co-occurrence of pesticides within a drinking water source for a CAG is a critical piece of information needed prior to making a decision to include more than one pesticide in a cumulative drinking water exposure assessment. Direct measurements of combinations of pesticides in finished drinking water are rarely available. However, U.S. Geological Survey (USGS) and National Water Quality Assessment Program (NAWQA) databases do contain information on the co-occurrence of a wide variety of pesticides in ambient surface water, and some registrant-sponsored studies provide co-occurrence data for specific compounds in drinking water. Further, information on the use of different pesticides within the same geographic region, combined with information on the timing of use and the fate and transport properties of these pesticides, can also be used to identify pesticides that are likely to co-occur. Once the likelihood of co-occurrences has been established, the risk assessor should use, where appropriate, a combination of direct measurements of pesticide concentrations at the intakes from community water systems; direct measurements of pesticide concentrations prior to treatment, with adjustments for the effects of blending and treatment; and model-based estimates of pesticide concentrations in raw water, with adjustments for the effects of blending and treatment, as reasonable approximations of concurring pesticide concentrations in tap water.

For pesticides with sufficient monitoring data in finished drinking water, the risk assessor should use these data in cumulative risk assessment to approximate tap

water concentrations over time. In cases where sufficient raw water monitoring data are available, the risk assessor should use these data in combination with data on the effects of blending and treatment to adjust raw drinking water concentrations to approximate tap water concentrations over time.

For pesticides with insufficient or no monitoring data, concentrations over time could be estimated using modeling in combination with pesticide-specific fate and transport data. A tiered approach to estimating drinking water concentrations is being developed to incorporate model estimates of pesticide concentrations in drinking water into aggregate and cumulative risk assessments. The risk assessor should generally use the highest tier assessment in quantitative cumulative risk assessments. This approach will incorporate multiyear climate data to simulate likely rainfall events in selected locations and will retain the temporal nature of the data, which is critical for time-based exposure estimates. The sites used in the analysis will reflect areas of high pesticide use and vulnerability to ensure that the outputs reflect health-protective estimates of potential pesticide concentrations in water consistent with use patterns, important cropping systems, and soil characteristics of the regions represented. The risk assessor should compare the results of modeling with monitoring data for similar compounds to confirm whether those pesticide concentrations in raw and/or finished drinking water predicted by modeling appear to be consistent with measured values. OPP is developing more sophisticated predictive models to approximate pesticide concentrations over time in drinking water for cases where monitoring data are scarce or lacking.

Modeling tools are especially useful and valuable when monitoring data are scarce or unavailable. This is often the case for pesticide degradates and always the case for pesticides pending registration. Further, and importantly, it is extremely difficult to accurately characterize (based on monitoring data alone) peak exposures for those pesticides that have acute toxicological endpoints. Thus, given the large number of samples that would be needed, developing adequate monitoring programs to estimate peak or high-end concentrations could be very difficult.

8.3 Residential and Other Nonoccupational Pathway

Current exposure assessments for residential and other nonoccupational sources for single-pesticide assessments are most commonly conducted using the Residential Standard Operating Procedures (USEPA, 1999g). This is because of the limited amount of chemical-specific generic exposure data that are available to support exposure assessments. In the cumulative risk assessment, the SOPs generally would not provide the level of detail required to develop a reasonably descriptive residential exposure assessment. Rather, the residential SOPs would serve as the starting point for developing a set of residential exposure assessments that provide a more detailed portrait of the anticipated use of each pesticide in the residential and nonoccupational environment. The SOPs will define the scenarios of interest and the types of additional data required. These data may include the range of typical application rates, pests of interest within a region, likelihood that a pesticide will be applied, time of application for a given use, likelihood and frequency of reapplication, concentrations of pesticides on surfaces or in air following application, and dissipation rate for the pesticide after application.

Sources of Information for the Estimation of Residential Exposure

- Residential Standard Operating Procedures (USEPA, 1999g)
- General Principles For Performing Aggregate Exposure And Risk Assessments (USEPA, 2001h)
- Product Labels
- Exposure Factors Handbook (1999d)
- Monte Carlo Guidance Document (1997a)
- National Home and Garden Use Survey

OPP is exploring the use of surrogate (bridging) data to assess residential exposure for pesticides with similar use patterns. This will allow EPA to extrapolate from one pesticide, for which high-quality residential exposure data are available, to other pesticides, similar to what is done for assessing occupational exposure using the Pesticide Handlers' Exposure Database (PHED) and the Outdoor Residential Exposure Task Force (ORETF) dataset. Furthermore, OPP is aware that additional data that will increase the ability to estimate residential and institutional exposures are being developed by the Residential Exposure Joint Venture, the ORETF, and the National Pest Control Association. OPP has developed a pilot cumulative assessment on a set of organophosphorus pesticides that demonstrate the concepts in data application described here. OPP presented this assessment to the SAP for review/comment in December 2000 (USEPA, 2000e). The assessment provides tangible examples of how surrogate/bridging data may be used in such an assessment.

The factors for consideration in developing reasonable exposure scenarios for residential, nonoccupational, and institutional exposures are described in detail in a previous EPA guidance document (USEPA, 1999b and USEPA,2001h). The patterns of use for pesticides in residential, nonoccupational, and institutional settings are highly dependent upon location, season, dwelling type, and other factors that impact the behavior of a potential pesticide user. An assessor should use the available data in such a way that preserves significant intrinsic links between residential pesticide use preferences and types of individual when performing cumulative exposure assessments. Where data are limited in quantity or are of poor quality, the residential SOPs should serve as the basis for initial estimates of exposure. The residential SOPs are by nature designed to produce screening-level assessments that are intentionally conservative. Combining exposures for the members of the CAG based on this screening-level assessment should be approached with caution because of the potential for compounding conservative assumptions. Furthermore, as in the case of drinking water, the estimation of co-occurrence and residue levels will not be as refined as it is with the food pathway because of the significantly more limited data.

SECTION 9. Conduct Final Cumulative Risk Assessment

Step 9. *Assign route/duration-specific risk metrics. Conduct trial run and evaluate output. Conduct sensitivity analysis. Assess subpopulations of concern, determine group uncertainty and FQPA safety factors.*

The design of the cumulative risk assessment should include consideration for the relevance of the time-frame appropriate to the CAG, how input parameters may systematically vary with geographic location and time of year or season, and the population of concern in the risk assessment. The data assembled to conduct the assessment should be combined in such a manner as to provide a coherent, realistic picture of the range of potential risks likely to be encountered by exposed populations and their associated probabilities. Inappropriate combinations of data may result in nonsensical outputs that are inaccurate and misleading. The use of data in the cumulative risk assessment process is described below.

9.1 Time-frame

A cumulative risk assessment should be conducted using a time-frame considering the time to onset of the common mechanism effect and also the time for reversibility of the effect (if it is reversible). A major determinant in the selection of the time-frame is the condition of expression for the common toxicity by duration and route. However, use patterns and likely patterns of exposure will also provide input. The risk assessor should assume that pesticides that have food uses may cause chronic exposures. Such an assumption is generally appropriate given the nature of food distribution and storage in the United States, unless the only uses are highly seasonal in nature and the commodities in question are only consumed fresh. For products with residential or institutional uses, the time-frames for consideration can also be bounded by the period of time over which a likely exposure is anticipated to occur. In practice, the assessment should be conducted one time-frame at a time, using a rolling time period over the calendar year. In other words, if the critical time-frame for consideration is one week, a cumulative assessment should be performed sequentially for individuals on days 1 to 7 of the likely exposure window, then days 2 to 8, days 3 to 9, and so forth (i.e., a rolling time-frame). This approach is described in greater detail in a previous document (USEPA, 1999b and USEPA, 2001h).

9.2 Geographic Scale and Site Selection

The outcome of a cumulative risk assessment will be a group of geographically oriented assessments rather than a single national-level assessment as is commonly conducted for single-chemical food risk assessments. The construction of a multichemical, multipathway assessment can be envisioned as assembling a series of clear plastic overlays in different combinations depending upon the geographic variability and scale of each component. Each overlay would contain a map unit of a different scale depending upon whether a highly localized area (e.g., a single watershed) or a much larger area (e.g., as would be used when defining residential lawn care uses) was represented. The food risk assessment is a national assessment that assumes a random distribution of treated commodities across the entire United States, with the potential for added geographic or demographic specificity (i.e., a breakout by gender or age) to permit accommodation of differences in consumption patterns. This assessment can be envisioned as the base over which smaller scale risk assessments for residential/institutional and water may be superimposed. Residential/institutional risk assessments should be tailored to geographic location because of differences in climate and pest pressure that occur across the United States. The differences in climate will reflect temperature zones and seasonality variations encountered throughout the country, producing geographic areas of interest ranging in size from portions of a few States to large multi-State regions. Examination of the range of residential use practices and patterns across different geographic regions would provide a means of identifying specific regional breakouts, which appropriately account for differing patterns of residential use. For example, Maine, Vermont, New Hampshire, and Massachusetts might exhibit similar use patterns for residential lawn care products, with a relatively short window of application in the late spring to early summer. This use area could be overlaid upon a grosser scale of food risks to provide a more detailed, smaller scale use area. Finally, the source of drinking water could further be superimposed to focus the risk assessment. Consideration of water source and its incorporation into a risk assessment is anticipated to produce a much finer scale, more localized type of assessment, potentially varying from large urban metropolises drawing water from a variety of geographically and hydrographically distant sources to smaller areas using highly localized supplies such as single watersheds or wells. Conceptually, one way of implementing this type of assessment would be to use GIS approaches in conjunction with adequate definition of the distribution of residues in drinking water. Sufficient understanding of the regional component of residential and institutional pesticide use as well as the nature of the resulting residues would be a prerequisite for implementation of such an approach. The output from this information would consist of a series of risk assessments reflecting the uses and potential exposures specific to that geographic area and similar areas for which it may serve as a surrogate.

A pesticide with a broader use pattern may require drinking water exposure assessments that include multiple counties, States, or even a large geographic

region. One approach to such an assessment would combine residue data from various drinking water sources if the data are judged to be sufficiently similar through appropriate statistical tests. However, pesticide use usually impacts different drinking water sources to different degrees. This should be taken into account. For example, a particularly vulnerable community water system would be suitable for use in estimating the potential drinking water exposure for individuals who drink from that system, but should not be the basis for an exposure assessment for individuals living nearby and drinking from another, less vulnerable source. In situations where residue data from several sources may be combined into one distribution of residue data, it is desirable to know the population associated with any specific source included in the exposure assessment.

Knowing the size of the population served by a specific drinking water source allows for population-weighted exposure assessments. A population-weighted exposure assessment accounts for the probability that a specific portion of the population may be more highly exposed than the majority. Depending on the quality of the data chosen for the assessment, i.e., how representative they are of actual drinking water concentrations, a drinking water assessment for the members of the CAG to permit the focus of further risk assessment efforts on areas of greatest concern. If, however, a high-end, deterministic screening-level assessment is all that is available, it should not be combined with a highly refined food risk assessment because of the previously stated concern of obscuring results with increasing uncertainty. Rather, the screening-level assessment should be considered in the context of its implications relative to a separate, highly refined food assessment.

As stated previously, demographic information available from the food consumption and residue databases can be used to characterize potentially exposed subpopulations. Each assessment should focus on a single subpopulation for which the demographic characteristics have been carefully defined. The age, gender, and geographic location of the group included in the investigation of the food exposure pathway can be linked with exposure scenarios in the drinking water and residential pathways. The individual food consumption records in the database, which also contains the demographic and other descriptors, will be used as a basis of simulating the consumption patterns of the population or subpopulation of interest. The likelihood and frequency assumptions associated with residential scenarios could be used to superimpose a pattern of exposures that would reasonably be expected to occur throughout the year and is consistent for that individual.

The population subgroups that are most commonly of concern to OPP can be defined by a number of factors, including demographics, geographic location, and season. Demographic considerations would include age, gender, ethnicity, and any other considerations that may be important in evaluating subpopulations with potential special susceptibilities. The geographic location of the exposed population will be needed to help match geographically-based exposure data (e.g., probability of applying a termiticide treatment in the South) to appropriate subpopulations. Location may be particularly important in evaluating the impact of water data or regional use patterns on anticipated exposures. Geographic location will also be an important consideration in evaluating seasonal aspects of residential exposures. Highly localized exposures may suggest very different strategies for risk mitigation than do exposures that are widely disseminated. The size of the affected subpopulation should be estimated where possible. The estimates of percentiles of exposure and associated risk should be factored against the target population size to determine the magnitude of the risk. The following example may serve to illustrate these concepts:

> Herbicide B is used widely on lawns, home gardens, and flower beds as a pre-emergent agent. There are numerous food uses, but the residue data indicate that Herbicide B is not detected in food. The herbicide is widely used by commercial lawn services. It has been detected in many urban surface water sources as well as in many major surface water bodies in the United States. Although the herbicide has widespread use in all areas of the United States, the residential use patterns differ according to the different climates. In this scenario, the subpopulation of concern cannot be ascertained from the food exposure assessment because there is no appreciable exposure from this pathway. The use pattern of Herbicide B indicates that recreational activities on lawns are likely to be a major source of exposure. Individuals most likely to engage in these activities (possibly children) would be the subpopulation of concern. In addition, individuals consuming water from surface water sources would require greater scrutiny, including evaluation of the efficacy of water treatment to remove Herbicide B. Individuals who raise home gardens would be another potential group of concern. Finally, the use period of Herbicide B would vary with use region based upon climate. The period of the year upon which the assessment would focus would vary depending upon location.

Note that this example scenario does not lead to a highly detailed, multipathway quantitative cumulative risk assessment. It does, however, identify subpopulations of potential concern. Additional exposure data would be needed to confidently estimate multipathway cumulative risk.

9.3 Subpopulations of Concern

Cumulative risk assessments should characterize multiple subpopulations depending upon the nature of the common toxicity and the geographic distribution of use and attendant exposure. The nature of the common toxic effect will determine which portions of the population are susceptible to experiencing the common toxic effect in question. For example, males would not be considered a reasonable target population for adverse effects related to pregnancy. For a common toxic effect that is limited in its applicability, the cumulative assessment should be tailored to focus on those groups that are sensitive. Similarly, if the use of a chemical is limited to a specific geographic locale, the subpopulation of concern should be selected considering potential for exposure in drinking water, appropriate residential and institutional use patterns that are reflective of the region under consideration, and any peculiarities of food consumption patterns or residue distributions that might impact the assessment result.

9.4 Constructing the Assessment

All of the dose-response characteristics (RPFs and PODs), exposure data, and exposure scenarios should be combined in a manner to produce a logical outcome consistent with exposures likely to be encountered by the public. There are several different exposure models in different stages of development that can integrate various pathways while simultaneously incorporating the time dimensions of the data. Currently, the Calendex™ and LifeLine™ models are available to conduct cumulative risk assessments. Calendex™ provides a focused, detailed profile of potential exposures to individuals across a calendar year. LifeLine™ focuses on identifying key points in a lifetime during which important exposure events are likely to occur. At this time, LifeLine™ permits incorporation of only a limited number of residential exposure scenarios and does not support estimates of exposure from drinking water. Other models such as Cumulative and Aggregate Risk Exposure Model (CARES) and RExY (Residential

Models That Can Account for the Temporal Aspects of Exposure

- **Calendex**™ (Novigen ,2001)-a calendar-based, probabilistic approach that can integrate different pathways of exposure and reflect exposure to discrete individuals on a daily basis over a 365-day calendar year
- **LifeLine**™ (Hampshire Research Institute, 2000)-a calendar-based, probabilistic approach that models longitudinal aspects of exposure to discrete individuals across the a substantial portion of a lifetime
- **Cumulative and Aggregate Risk Exposure Model** (CARES) (ACPA, 1999)-a calendar-based, probabilistic approach that can integrate different pathways of exposure and reflect exposure to discrete individuals on a daily basis over a 365-day calendar year
- **Residential Exposure**-Year (RExY) (InfoSciences) - a calendar-based, probabilistic residential tool identifying possible sources of exposure and estimating their magnitudes

Exposure-Year) are under development. CARES is being developed to accept a variety of inputs and will make the conduct of fully quantitative, cumulative risk assessments easier. RExY is being developed to provide a user-friendly means of exploring the full range of possible exposures anticipated from the residential uses of a CAG and identifying the likely risk contributors.

The risk assessor should accept and review risk assessments performed with those models that have been subjected to the public peer-review process. The model selected to perform the cumulative risk assessment should be able to provide information concerning a variety of issues of interest and concern to the risk assessor, such as the range of possible exposures from each source of pesticide exposure and from all sources combined, the risks associated with those exposures, the contribution of each pesticide and each application method to the estimated exposures, and the difference in exposure among subpopulations of concern. The construction of the assessment can be approached on a pathway-specific basis, involving separate development of the datasets for food, water, and residential exposure.

9.5 Expression of Cumulative Risk-Combining Multiple-Pathway Risk

The cumulative risk assessment should develop all of the underlying data used for a chemical-specific evaluation and more. The same basic procedures used in a single-chemical aggregate assessment can be carried over into the cumulative framework. These processes are presented briefly below.

9.5.1 Dietary Food and Dietary Water Pathway

To derive a cumulative residue, chemical-specific residue (on a food sample or estimated to occur in water) is converted to a residue expressed in equivalents of the index compound. Any processing factors for foods or treatment impacts for water should be factored in just prior to this stage because they will be chemical- and medium-specific.

Equation 9.1: $$\text{Residue}_{IE} = \text{Residue}_{compound} \times PF \times RPF$$

where: Residue_{IE} is the compound-specific residue concentration expressed as equivalents of the index compound,

$\text{Residue}_{compound}$ is the compound-specific residue concentration,

PF is a compound-specific process factor (for food) or treatment factor (for water), and

RPF is the relative potency factor used to normalize the compound-specific residues to the toxicity of the index compound. This factor converts the compound-specific concentration to an index-compound-equivalent basis.

Once all of the residues for a given food or water sample are converted to index compound equivalents, they are summed to give a total cumulative residue value for each sample.

Equation 9.2: $$\text{Residue Cumulative} = \sum_{CAG} \text{Residue}$$

The residue data, normalized to index equivalents and accumulated for each sample, are ready for introduction into a probabilistic risk assessment.

9.5.2 Residential and Other Nonoccupational Pathways

Residential and other nonoccupational exposures rely upon estimates of exposure that are calculated, drawing upon the equations in the Residential SOPs (USEPA, 1999g). These estimates are converted to index equivalent exposures as in the dietary portion of the assessment. However, for residential and other nonoccupational assessment, the assessor is faced with the added complexity of developing datasets for oral, dermal, and inhalation exposures, with the ultimate goal of accumulating exposures from all members of the CAG by each route in a manner reflecting the potential for exposure to more than one chemical within a time-frame.

The assessor develops an inventory of the uses registered for each compound. The basic equations from the residential SOPs (i.e., exposure scenarios) should be evaluated to identify equation parameters for which distributions can be substituted for default values. Distributions should be used to the extent possible to introduce the full range of possible exposure combinations. Generally, the scenarios under consideration will be addressed by the general equation:

Equation 9.3 $\text{Exposure} = \text{Contact} \times \text{Residue}$

where, the contact function defines the duration of contact, the portion of the body exposed, how much of the available residue can be transferred to the body for dermal exposure, and the duration of contact and respiratory characteristics of the exposed individual for inhalation exposure. The input parameters for each scenario/chemical combination are combined to reflect the characteristics of the chemical and its particular application rates, frequencies, and seasonal attributes. The dissipation rates, transfer factors, and other attributes that reflect the physical-chemical properties of the chemical should also be factored into the calculation of residues prior to normalization to index equivalents.

An example of the types of data that can be used to flesh out the many complexities of a detailed cumulative residential assessment is presented in the document *Cumulative Risk: A Case Study of the Estimation of Risk from 24 Organophosphate Pesticides* (USEPA, 2000e). This case study was presented to the SAP in December 2000. The section on residential exposure clearly demonstrates the types of data that are useful in more fully characterizing the potential for pesticide exposure from residential uses. It also illustrates the use of generic data, including those generated by task forces or provided in Agency publications such as the *Exposure Factors Handbook*, and the use of chemical-specific data from one compound to serve as a surrogate for another, similar compound. The case study also illustrates the use of survey data to develop profiles of activities by users and the frequency with which activities are performed. Finally, the case study illustrates the role of professional judgment and the importance of regional knowledge and expertise in developing detailed scenarios.

9.6 Accumulating the Risk

The risk assessor should express the total pesticide residues for the CAG in terms of the Index Chemical (see Section 6). This approach requires conversion of the residues of each member of the CAG to concentration equivalents of the index chemical. This can be done using RPFs developed to normalize the toxic response of each pesticide to the toxicity of the index chemical. The point of departure (e.g., an BMD_{10}) for the index chemical is then used to calculate route-specific MOEs for the CAG. Generally, the expression of risk from the CAG can be expressed as:

Equation 9.4 $$MOE = POD_{Index} \div \sum_{Route} Exposure$$

EPA uses margins of exposure (MOE) for aggregating the risk posed by exposure to a single pesticide via multiple pathways (USEPA, 1999b and USEPA, 2001h) and has extended this approach to estimating the cumulative risks of multiple chemicals (see USEPA, 2000e). Route-specific MOEs can be used and combined to generate a total MOE while preserving the route-specific nature of the risk estimates.

Equation 9.5: $$MOE_{total} = \frac{1}{\frac{1}{MOE_{oral}*} + \frac{1}{MOE_{dermal}} + \frac{1}{MOE_{inhalation}}}$$

**Oral is the total oral exposure from food and drinking water plus oral, nondietary contacts such as hand-to-mouth exposure from residential pesticide uses.*

This method is illustrated in *Cumulative Risk: A Case Study of the Estimation of Risk From 24 Organophosphate Pesticides* (USEPA, 2000e). In this method, exposure can be calculated on a route-specific basis within a source (e.g., residential risk for inhalation, dermal, and oral routes of exposure) and then combined across sources of exposure (food, drinking water, residential and other nonoccupational pathways). Using a calendar-based exposure model, the contributions from each pathway can be calculated simultaneously for every exposed individual for every day reflected during the time-frame of the exposure estimates.

In developing a cumulative assessment, the risk assessor must have a clear understanding of the probability that one or more exposures to a member of the

CAG will occur on any given day of the year. This information will permit the risk assessor to develop a series of internally consistent individual exposure values across the calendar year that provide an understanding of the potential exposures to members of the CAG on any given day, and the sources of these exposures. The estimated cumulative exposures can be expressed as a family of exposure distributions that reflect the changing use patterns of CAG chemicals across the year, and for subpopulations of interest. The assessment will permit identification of the source of the exposure (pesticide, use pattern, rate, location, time of year) and evaluation of the magnitude of exposure and the appropriate subject(s) of any mitigation activities.

SECTION 10. Conduct Characterization of Cumulative Risk

Step 10 . *Describe the results and conclusions of the cumulative risk analysis, including the relative confidence in toxicity and exposure data sources and model inputs. Discuss major areas of uncertainty, the magnitude and direction of likely bias, and the impact on the final assessment. Evaluate the risk contributions from each pathway and route individually, as well as in combination. Identify risk contributors with regard to pesticide(s), pathway, source, time of year, and impacted subpopulation (with particular attention to children). Conduct sensitivity analyses to determine those factors most likely to impact the risk. Determine need for uncertainty and safety factors.*

Risk characterization is the interpretation phase of the assessment process. It is an integrative process that brings together the assessments of hazard, dose response, and exposure to characterize risk estimates for the exposure scenarios of interest, and presents the major results and conclusions of the risk assessment as well as the associated uncertainties. A risk characterization provides a discussion for a diverse audience that minimizes the use of technical terms. It is an appraisal of the science that supports the risk manager in making public health decisions. Additional guidance on risk characterization can be found in the Agency's Handbook (USEPA, 2000c).

10.1 Risk Characterization Summary

A risk characterization summary should accompany a cumulative risk assessment, and should present the conclusions of the analysis and include a discussion of the significant contributors and sources of risk. It should provide descriptions of risk for the exposed population as a whole (i.e., average levels of exposure) as well as those individuals in the high end of the distribution. Important subgroups of the population (e.g., children) who may be at disproportionate risk (e.g., through unique susceptibility to the common mechanism of toxicity, or human activity exposure patterns) should be highlighted. Methods of estimation should be described (e.g., deterministic versus probabilistic methods, or screening-level exposure methods versus highly refined monitoring data reflective of residues close to the point of consumption or contact). As discussed

Risk Characterization Summary

- Statement of purpose, scope, level of detail of the assessment
- Pesticides and exposure scenario(s) covered
- Kinds and quality of data available
- Methods of estimation
- Strengths, limitations, and uncertainties inherent in data and analysis
- Key assumptions and their potential impact on the outcome of the assessment
- Significant issues relating to each exposure pathway and impact on the overall assessment
- Special groups (including children) at disproportionate risk

below, significant uncertainties in the cumulative risk assessment should be highlighted.

As indicated throughout the document, conducting a cumulative risk assessment requires the coalescing of a variety of data sets of highly variable characteristics. Each source of exposure data, and the data defining potential hazard for each pesticide is anticipated to have unique strengths and limitations, resulting in potential difficulties in interpretation of the results. As the scenarios for each pathway are constructed, the risk assessor is encouraged to maintain a record of the attributes of each parameter used as an input into the assessment. These include, but are not limited to: estimate of direction and magnitude of bias in the data; data format, e.g., point estimate, range as uniform distribution, or descriptive distribution; confidence in the data. The risk assessor can use this compilation of data attributes to evaluate the potential for bias in the results of the assessment. For example, if the majority of data bias is in the conservative direction, the assessment may be determined to err on the side of overestimation bias. Where directional bias is mixed, the factors may offset and result in a more balanced result. Inclusion of sensitivity analyses to determine the impact of particular parameters on the resulting assessment may be helpful to determine whether or not directional bias in parameters is of concern.

10.2 Describing Uncertainty

The goal of any cumulative analysis should be to produce estimates of exposure through the pathways of concern that are health protective but use the available data to the greatest extent possible. Uncertainty in the cumulative assessment is also an important consideration and should be discussed in at least a qualitative sense whenever possible in the assessment. It is only when the uncertainties about the cumulative risk estimates can be adequately evaluated and conveyed to risk managers, interested parties, and the general public that productive dialogue on potential refinements, responses, and mitigation actions can take place.

Because data are unlikely to permit robust evaluation of all the critical parameters needed for a highly refined cumulative risk assessment (e.g., kinetic data on the common mechanism of toxicity, descriptive dose-response data for chemicals by all routes of interest, monitoring data for all exposure pathways of interest), the cumulative assessment should describe the significant sources of uncertainty, variability, and limitations inherent in the analysis. Uncertainty should be described qualitatively, but also captured quantitatively to the extent possible. No definitive standard Agency policy or detailed procedure on how to perform uncertainty analysis is available. However, several references in the published literature provide useful information on this topic (Hattis and Anderson, 1999; Hattis and Minkowitz, 1996; Hattis and Burmaster, 1994; Baird et al., 1996). In evaluating uncertainty, unique issues for both the toxicological and exposure inputs into calculating risks for each pathway of exposure should be highlighted. The precision of each pathway analysis (e.g., food, drinking water, residential and other

nonoccupational sources) should help determine the uncertainty in combining the different pathways in the cumulative assessment. The following two sections address uncertainty issues with respect to cumulative risk assessment.

10.3 Application of Uncertainty Factors and the FQPA 10X Safety Factor

FQPA directs that EPA ensure that there is a reasonable certainty that no harm will result to infants and children from aggregate exposure to the pesticide chemical residue when setting tolerances. In the case of "threshold effects," FQPA requires "an additional tenfold margin of safety for the pesticide chemical residue, and other sources of exposure shall be applied for infants and children to take into account the potential pre- and post-natal toxicity and completeness of the data with respect to exposure and toxicity to infants and children....[and that] the Administrator may use a different margin of safety for the pesticide chemical residue only if, on the basis of reliable data, such margin will be safe for infants and children." This is referred to as the FQPA Safety Factor provision. A risk assessment addressing cumulative effects of a pesticide chemical residue will have major bearing on OPP's determination of whether the reasonable certainty of no harm finding can be made. Accordingly, several of the core aspects of the cumulative assessment, such as the identification of the nature of the common toxic effect and the scope of the toxicity and exposure databases relative to the cumulative assessment, will need to be considered by OPP in applying traditional uncertainty factors as well as determining the need for a special FQPA safety factor. Consideration of the FQPA Safety Factor should be based on the group rather than on individual members of the group.

OPP has developed guidance entitled *Determination of the Appropriate FQPA Safety Factor(s) for Use in the Tolerance-Setting Process* that describes the policies employed in making determinations regard the FQPA safety factor for single chemical risk assessments(USEPA, 1999h, 2001f). Although many of the principles in that document apply to a cumulative risk assessment, OPP is preparing a separate paper, *Consideration of the FQPA Safety Factor and Other Uncertainty Factors in Cumulative Risk Assessment of Chemicals Sharing a Common Mechanism of Toxicity*, that presents the general approach attendant to making determinations regarding the traditional uncertainty factors and the FQPA safety factor for cumulative risk assessments (USEPA, 2001g). The risk assessor should refer to that document.

10.4 Uncertainty With Respect to Exposure Assessment

Exposures through the food, water, and residential pathways merit consideration for their contributions to uncertainty in the cumulative assessment and should be discussed. Some examples of potential sources are offered below. As deemed appropriate by the risk assessor, they should be described in conjunction with the assessors' best estimate of how they may influence the outcome of the risk assessment. Uncertainty about the cumulative exposure assessment also pertains to the decision regarding the FQPA safety factor. The risk assessor should refer to the separate document entitled *Consideration of the FQPA Safety Factor and Other Uncertainty Factors in Cumulative Risk Assessment of Chemicals Sharing a Common Mechanism of Toxicity* (USEPA, 2001g).

10.4.1 Uncertainties Associated with the Cumulative Food Pathway May Arise from the Following Sources

Although temporal and geographic considerations are being incorporated into the cumulative exposure assessment with respect to water and residential exposures, these are not generally considered relevant with respect to the food pathway for the reasons stated earlier. Exposure to pesticides from foods is generally considered on a national basis. OPP does not believe, however, that uncertainty due to this treatment of food exposures is significant, and recommends that they be considered only in a qualitative sense in the cumulative assessment unless data indicates otherwise. Limitations and uncertainties with respect to the source of residue data should be considered. Other issues involve: (1) how nondetects are treated; (2) how percent crop treated is or is not incorporated; (3) to what extent PDP or Total Diet Study data are or are not used; and (4) the degree to which residue data are translated to other similar commodities (and to what extent those commodities are expected to share similar residue profiles). These and other appropriate issues should be discussed in the cumulative risk assessment.

10.4.2 Uncertainties Associated with the Cumulative Water Pathway

The uncertainties associated with the cumulative water pathway are likely to be quite different from those outlined for pesticide exposures from foods. The following examples illustrate some sources of uncertainty that should be discussed in evaluating the results of the risk assessment. Uncertainties in the drinking water portion will most likely be due to the nature of the data source. In most instances for the foreseeable future, drinking water data will be derived from monitoring-assisted modeling or from PRZM-EXAMS/IR model. The use of model-derived data is expected to be a conservative (health-protective) estimate of drinking water concentrations that represent high end use sites but do not grossly overestimate real-world water concentrations. Some of the potential sources of uncertainties associated with use of such data include

physicochemical properties and other parameters (e.g., degradation) of the CAG pesticides; rates, frequencies, and patterns of use including the percent of a crop within a region that is treated[12]; the actual co-occurrence of the pesticides in water bodies; and potential for degradate formation, persistence, and toxicity. Qualitative discussion of these and other factors should be included in the cumulative assessment. To the extent possible, comparison to available monitoring data should be used to check the model outputs.

10.4.3 Uncertainties Associated With The Cumulative Residential Pathway

The uncertainties associated with the cumulative residential pathway will often be similar in etiology to those associated with estimation of cumulative exposure from water. As with drinking water, estimation of exposure from residential uses of pesticides will generally be indirect. For example, sources of uncertainty follow below:

- ❏ For some pesticides, chemical-specific data or data from the literature (including EPA's *Exposure Factors Handbook*) will be available and should be used to the extent possible. For others, specific data will not be available and appropriate professional judgment and expertise will need to be applied by the risk analyst in using surrogate data. Where data distribution fitting or other distribution analysis is performed, or where limited data cause the assessor to rely upon a uniform distribution, the impact of these analyses on the outcome of the assessment should be described. The reasons for the selection of a particular distribution should be provided along with a discussion as to the uncertainties associated with this decision. Specific factors or inputs in which distributional assumptions may be necessary include among others, transfer coefficients, cross-formulation exposure assumptions, turf transferable residues, various aspects and components of hand-to-mouth behavior of toddlers, and lawn sizes.

[12]For a regional analysis, such factors as soil characteristics, precipitation, and evapotranspiration will likely, of necessity, be averaged across a watershed and uncertainty would be associated with any such spatial homogenization.

- ❏ For some behavior patterns, data from the literature (including EPA's *Exposure Factors Handbook*) will be available and should be used to the extent possible. Distributions of behavioral patterns (e.g., hand-to-mouth activity of toddlers) and durations of exposure (e.g., time spent on lawn) can be obtained from the *Exposure Factors Handbook* or the open literature. Significant uncertainties may still remain, owing in part to the limited number of studies available. The impact of any modeling of human behavior on the results of the assessment should be discussed.

- ❏ Few data exist on the probability of concurrent uses of pesticides, whether complementary (e.g., flea treatment of lawn and simultaneous flea treatment of a residence) or competitive (e.g., if one member of a CAG is used one time in the March to May time frame to treat lawns for grubs, how likely is it that a second member of the CAG will be used on that same lawn at a later application window). For the foreseeable future, this aspect of residential pesticide exposure is likely to be modeled on the basis of use information. The impact of this process on the cumulative risk assessment should be discussed.

- ❏ In certain instances where data on the CAG chemicals of interest are not available or are of limited utility, surrogate chemicals or formulations can be used in the cumulative assessment. Uncertainties associated with this translation should be discussed.

In any risk assessment, there will be numerous identified and unidentified uncertainties. Assessment of cumulative exposures to pesticides is no exception. The risk assessor should be aware of and communicate these uncertainties to the risk manager. Sensitivity analyses will provide direction as to where best to focus resources and efforts to improve the quality and quantity of data to inform the risk assessment process.

10.5 Presentation of Results

The outcome of a cumulative risk assessment usually will *not* be a single estimate of risk. Rather, it will contain a series of estimates that represent time and geographically dependent distributions and estimates of risk from exposure to more than one common mechanism pesticide from the same source, and the combined risk to multiple pathways and routes of exposure. The values will be unitless, cumulative MOEs or a comparison to the index chemical's point of departure. Cumulative risk values should be expressed only as whole numbers and not as fractional values so as not to imply greater precision than actually exists. Results should be presented for different age groups (e.g., the 18+ adult, various children's ages, women of child-bearing age), and an evaluation of the impact of the behavior of different age groups on exposure should be provided. The risk assessor should present MOEs as a range of percentiles of exposure for the risk manager, with an explanation of the significance of each percentile.

Decisions regarding the acceptability of a particular outcome will require evaluation of the entire data set used in the assessment, including the decisions regarding the group uncertainty factor and the relationship of the toxicological response in the test species to the anticipated human response. In other words, a halving of the cumulative MOE does not necessarily indicate a doubling of risk potential. The MOE outcome should be compared to or incorporate the group uncertainty factors (e.g., intra- and interspecies uncertainty factors), and if necessary, the FQPA safety factor. A cumulative MOE or cumulative %POD should be carefully interpreted in the context of the supporting information, magnitude and direction of biases, assumptions used, and attendant uncertainties.

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