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

NOTICE

THIS DOCUMENT IS A PRELIMINARY DRAFT
It has not yet been completed nor formally reviewed or released by the Agency.

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Office of Pesticide Programs
U.S. Environmental Protection Agency
Washington D.C. 20460

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**DISCLAIMER**

The current document constitutes a **work-in-progress**. It is not yet completed and has not received full Agency review. EPA is requesting early review from the FIFRA Scientific Advisory Panel (SAP) and the public at the September 1999 SAP meeting on the hazard and toxicological issues related to cumulative risk assessment. EPA would like the SAP to focus on Chapters 3 and 5 of this document. The issues that EPA would like input from the SAP are related to both the hazard and dose-response analyses needed when accumulating risk from exposure to two or more chemicals that share a common mechanism of toxicity. These issues cover, for example: end point selection; application of chemical specific adjustment factors and a group uncertainty factor; interspecies dose adjustments; utilization of dose-response data and selection of a point of departure; methods for estimating the cumulative effect of a common mechanism.

The EPA will address the SAP recommendations from the September meeting, and anticipates to provide a completed guidance document on cumulative risk assessment containing the exposure component (Chapters 4 and 6) for review at the December 1999 SAP meeting.

This draft document does not constitute U.S. Environmental Protection Agency policy. Mention of trade names or commercial products does not necessarily constitute an endorsement or recommendation for use, and should not be interpreted as intent to regulate.

# TABLE OF CONTENTS

## LIST OF TABLES



## LIST OF FIGURES

## LIST OF ABBREVIATIONS

| | |
|---|---|
| **BMD** | Benchmark Dose |
| **CAG** | Cumulative Assessment Group (of chemicals) |
| **CMG** | Common Mechanism Group (of chemicals) |
| **$ED_{10}$** | Effective Dose - central estimate on a dose associated with a 10% response adjusted for background. |
| **FQPA** | Food Quality Protection Act |
| **FFDCA** | Federal Food and Drug Cosmetic Act |
| **FIFRA** | Federal Insecticide, Fungicide, and Rodenticide Act |
| **$LED_{10}$** | Lower Limit on a Effective Dose - 95% lower confidence limit on a dose associated with 10% response adjusted for background |
| **LOAEL** | Lowest-Observed-Adverse-Effect Level |
| **MOE** | Margin of Exposure |
| **$MOE_{CAG}$** | Margin of Exposure for the Cumulative Assessment Group for all pathways and routes of exposure |
| **$MOE_{pathway}$** | Margin of Exposure for a pathway of exposure |
| **NAS** | National Academy of Sciences |
| **NOAEL** | No-Observed-Adverse-Effect Level |
| **NRC** | National Research Council |
| **OPP** | Office of Pesticide Programs |
| **PK** | Pharmacokinetics |
| **PD** | Pharmacodynamics |
| **PoD** | Point of Departure |
| **RAC** | Raw Agricultural Commodities |
| **RfC** | Reference Concentration |
| **RfD** | Reference Dose |
| **RGDR** | Regional Gas Dose Ratio |
| **RDDR** | Regional Deposited Dose Ratio |
| **RPF** | Relative Potency Factor |
| **SAP** | Scientific Advisory Panel |
| **TEF** | Toxicity Equivalency Factor |
| **UF** | Uncertainty Factor |

## AUTHORS AND CONTRIBUTORS

**Technical Workgroup (Office of Pesticide Programs, Health Effects Division):**

Karl Baetcke, Ph.D.
Vicki L. Dellarco, Ph.D.
Stephen C. DeVito, Ph.D.
Elizabeth Doyle, Ph.D.
Karen Hamernik, Ph.D.
Alberto Protzel, Ph.D.
John Whalan, DABT.

**Intra-Agency Technical Advisory Group:**

Angela Auletta (Office of Pollution Prevention and Toxic Substances)
Carole Braverman (Region 5)
V. James Cogliano (Office of Research and Development, National Center for Environmental Assessment)
Rick Hertzberg (Office of Research and Development, National Center for Environmental Assessment
Peter Grevatt (Office of Solid Waste and Emergency Response)
Edward Ohanian (Office of Water, Office of Science and Technology)
Jane Ellen Simmons (Office of Research and Development, National Health and Environmental Effects Laboratory)

**Science Policy Council Steering Committee:**

Penelope Fenner-Crisp, Ph.D., DABT (Office of Pesticide Programs)
Jennifer Orme-Zavaleta, Ph.D., (Office of Research and Development, National Health and Environmental Effects Laboratory)
Jeanette Wiltse, Ph.D., J.D., (Office of Water, Office of Science and Technology)
Vanessa Vu, Ph.D., (Office of Research and Development, National Center for Environmental Assessment)

# 1 INTRODUCTION

## 1.1 BACKGROUND

Pesticides are regulated under major federal statutes: the Federal Insecticide, Fungicide, and the Rodenticide Act (FIFRA) and the Federal Food, Drug and Cosmetic Act (FFDCA), as amended by the Food Quality Protection Act on August 3, 1996.[1] FIFRA requires that substances used as pesticides be registered with the EPA and that these pesticides do not cause unreasonable adverse effects to humans or the environment. FFDCA mandates that EPA set tolerances for pesticides that are used in or on raw agricultural commodities (RACs) or processed foods. The tolerance for a pesticide residue represents the maximum legally allowable concentration of the pesticide residue that can be present in or on a raw agricultural commodity or is present in a processed food. In order to establish a pesticide tolerance or exemption from a tolerance, the EPA must determine with reasonable certainty that consumption of raw agricultural commodities and processed foods containing residues of that pesticide will not cause harm to humans, especially infants and children.

Historically, EPA has evaluated the safety of pesticides based on 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 non-dietary exposures to pesticides and assessing 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 non-occupational) exposure to the pesticide and available information concerning the *combined* toxic effects to human health that may result from dietary, residential, or other non-occupational exposure to other substances[2]

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[1]For details see *The Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) and Federal Food, Drug, and Cosmetic Act (FFDCA) As Amended by the Food Quality Protection Act (FQPA) of August 3, 1996;* U.S. Environmental Protection Agency, Office of Pesticide Programs, document # 730L97001, March, 1997.

[2]"Other substances" includes pesticide chemicals, pharmaceutical substances (e.g., drug products), industrial chemicals, and other substances to which the general

that have a common mechanism of toxicity. *FFDCA does not regulate workers exposure and, thus, this document does not present guidance for performing occupational, cumulative risk assessments.* It should also be stressed that FQPA does not require cumulative risk assessments for chemicals that do not act by a common mechanism of toxicity. Thus, this document focuses solely on guidance for those substances that act by a common mechanism of toxicity. The Agency must also include in its risk assessments available information concerning the *combined* (i.e., cumulative) effects on infants and children to the pesticide and other substances that have a *common mechanism of toxicity*. These factors are considered because of the possibility that low-level exposures to multiple chemicals that act by a common mechanism of toxicity could lead to the same adverse health effect as would a higher level of exposure to any of the chemicals individually. A person exposed to a single pesticide at a level that is considered safe may in fact experience harm if that person is also exposed to other substances that cause the same toxic effect by a mechanism as that of the subject pesticide, even if the exposure levels to the other substances are also considered safe.

OPP is employing a step wise approach to the development of science policies and guidance documents to provide EPA staff and decision makers with the necessary guidance and perspectives to conduct cumulative risk assessments to support tolerance assessments of pesticides.

Before one can determine a cumulative risk under FFDCA, one must define what constitutes a mechanism of toxicity, and determine how to group a set of substances acting via the common mechanism of toxicity. Toward this end, OPP published final guidance on grouping substances that have a common mechanism on February 1999 (US EPA 1999a). Furthermore, before one can cumulate risk for multiple substances sharing a common mechanism of toxicity across different sources and routes of exposure, one needs to aggregate exposure for a single compound. OPP published an interim approach for aggregate exposure and risk assessment in 1997, and presented a revised draft with extended guidance to the FIFRA Scientific Advisory Panel (SAP) for review in February 1999 (US EPA, 1999b). The International Life Sciences Institute, Risk Sciences Institute under a cooperative agreement with the OPP, convened a scientific panel to develop approaches for a framework for a cumulative risk assessment (Mileson et al., 1999). The information contained in the ILSI report were also considered and incorporated, as appropriate, in this guidance document.

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population is exposed. (See US EPA, 1999a).

## 1.2 STATE-OF-THE-SCIENCE

Conducting a cumulative risk assessment presents a complex and multi-dimensional challenge for the risk assessor. The cumulative risk guidance presented here is intended to facilitate implementation of FFDCA as amended by FQPA, and to serve as initial guidance for the Office of Pesticide Programs. This cumulative risk assessment guidance document incorporates existing basic principles and science policies of the Agency for conducting health risk assessments. This guidance is viewed as a **Work-in-Progress** given that the Agency's understanding of the cumulative effects on human health stemming from exposure to multiple chemicals with a common mechanism of toxicity is at an early stage. Furthermore, preferred data for conducting a cumulative risk assessment are not currently available (See discussion of research needs at the end of this document.) The existing toxicological databases for pesticides were generated primarily to evaluate the hazard potential of individual chemicals. Robust empirical data are generally lacking on dose-response relationships, on effects by all routes of exposure, and on pharmacokinetic and pharmacodynamic interactions for chemicals that have been grouped by a common mechanism of toxicity. Similarly, when conducting risk assessments on pesticides, attention has historically focused on single sources of exposure for individual chemicals (e.g., food, water, or residential) and not on the potential for individuals to be exposed to multiple chemicals via multiple sources that share a common mechanism of toxicity. Exposure analyses ideally should address regional patterns (i.e., is usage such that exposure to multiple pesticides can be expected only in a defined geographic area?) and temporal issues (e.g., are individual pesticides that have a common mechanism of toxicity applied during the same season so that multiple pesticide exposures can be anticipated?). Such exposure information should be considered in parallel with data on time of onset and time to peak effects, as well as the nature of effects (e.g., persistence and reversibility) that occur following acute, subchronic, or chronic exposure to the chemicals that produce a common toxic effect by a common mechanism of toxicity. The persistence of a chemical in biological tissues is also an important consideration when making judgements on the potential of two or more chemicals to accumulate and for interactions to occur that could lead to increases in tissue burdens and increases in a toxic response following exposure, whether exposures to individual chemicals are simultaneous or not.

It is important to emphasize that the cumulative risk assessment process will require continued method and tool building, as well as science policy development. As the exposure and health 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, the Agency will update this guidance, as

appropriate.

## 1.3 GOAL, PURPOSE, AND SCOPE

The goal of this guidance document is to provide risk assessors with basic principles and an analytical framework for assembling and evaluating information that will comprise a cumulative risk assessment involving food, water, or residential and other non-dietary exposure of the human population to multiple chemicals that produce a common toxic effect by a common mechanism of toxicity. This guidance is not intended to provide in-depth discussions of evaluations that normally precede a cumulative risk assessment such as hazard identification and assessments of individual chemicals. This guidance is contained in many existing documents including *Guidance for Performing Aggregate Exposure and Risk Assessments* (USEPA, 1999b) and the *Guidance for Identifying Pesticide Chemicals and Other Substances that have a Common Mechanism of Toxicity*, (USEPA, 1999a), as well as Agency-wide guidelines for the risk assessment of specific health points (USEPA, 1986a,b,c, 1991a, 1996a,b, 1998a) and exposure assessment (USEPA, 1991b). These topics are described in those sources and will be dealt with briefly in this document. The guidance contained in this document focuses on elements and characteristics of hazard and exposure information that should be used to derive an estimate of potential cumulative risks from exposure to multiple chemicals (or substances) that share a common mechanism of toxicity.

A cumulative risk assessment has several objectives. First, it must identify a group of chemicals producing common toxic effect(s) by a common mechanism of toxicity. It should be noted that chemicals from one or more structural classes may be established as a group of chemicals that act via a common mechanism. Grouping of chemicals sharing a common mechanism of toxicity does not automatically lead to a cumulative risk assessment involving all members of that group. One must determine, based on the exposure durations, patterns, and frequencies, as well as the pharmacokinetic and pharmacodynamic behavior of the chemicals, whether there is an opportunity for an individual to be exposed to two or more members such that the combined exposure will lead to an enhancement[3] of the common toxic effect[4]. Therefore,

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[3]Enhancement is defined as an increase in the incidence and/or the severity of the response at a given dose resulting from exposure to two or more chemicals that produce a common toxic effect by a common mechanism of toxicity.

[4]The default assumption, in the absence of data to the contrary, is that dose additivity will occur if exposure to two or more chemicals that operate by a common mechanism of toxicity is such that exposure to one chemical will occur in a time frame which is concurrent with exposure to a second chemical. Concurrent exposure assumes that exposure occurs to one chemical during the same time period when there is an

cumulative risk analyses seek to determine whether an individual will be exposed to chemicals which form a group that acts by a common mechanism. It further seeks to determine whether exposure to this group of chemicals will result in an overlapping of toxic events that precede the clinical outcome. The analyses must measure or estimate for that group of chemicals distributions of exposures (or dose) that an individual will receive from exposures by all relevant routes from all non-occupational sources under given circumstances. Such an estimate of individual dose may vary as a function of place and time. The cumulative analysis seeks to define as a distribution the range of individual doses that may be received in a well-defined population of individuals exposed to a group of chemicals acting by a common mechanism. This range will reflect the influence of varying individual characteristics (*e.g.*, age, sex, ethnicity, place of residence).

## 1.4 ORGANIZATION

The Agency's risk assessment guidelines traditionally are organized around the 1983 and 1994 NRC paradigm of: hazard identification, dose-response assessment, exposure assessment, and risk characterization (NRC 1983, 1994). This structure is embodied in this guidance. The purpose of these characterizations is to summarize and explain the extent of the data, weight-of-the-evidence, major points of interpretation, rationale for decisions/judgments, and the weaknesses, strengths, and uncertainties in the analysis. These characterizations are critical to the cumulative risk assessment given the complexity of the process and the uncertainties that are encountered. Thus this guidance adopts the 1994 NRC approach to adding a characterization step to the hazard, dose-response, and exposure assessment. This guidance also embodies the 1996 EPA Administrator's Directive (USEPA 1996c) and the Executive Order 13045: *"Protection of Children from Environmental Health Risks and Safety Risks"* (62 FR 19885, April 23, 1997), to identify and assess environmental health risks that may disproportionately affect children.

Hazard, dose-response, exposure assessments and characterizations are integrative processes for reviewing and evaluating all relevant biological, toxicological and exposure data on a chemical for the purpose of constructing a comprehensive description of potential human health risks and the conditions for expression of the risk (via route, pattern, duration, magnitude of exposure). The hazard, dose-response, and exposure technical characterizations are interactive and are integrated in the overall cumulative risk process.

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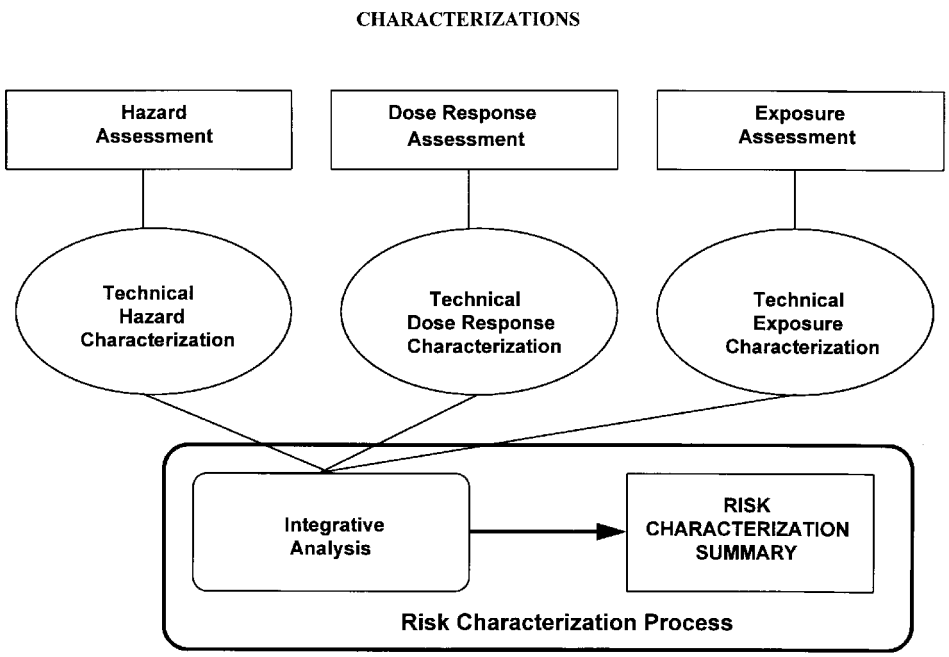
exposure to a second chemical (or more). Exposure and effects to a chemical during a period when tissue residues or toxicity remain after exposure to another chemical may also be determined to represent concurrent exposure.

Additional guidance for presenting a risk characterization appears in an Agency policy document issued by the Science Policy Council (USEPA, 1995a). Supporting documents provide the principles and guidance to be followed for risk characterizations by Agency offices involved in risk assessment activities (USEPA, 1999c, Draft). The principles emphasize the need for transparency and consistency in summarizing the key issues and conclusions of each component of the risk assessment along with its strengths and weaknesses. Principles presented in the guidance document encompass identification and descriptions of key toxicological data, the nature of the response, quality of the data reviewed, use of human evidence, relevance of laboratory animal data, what biological mechanism is operational that leads to adverse effects, and confidence in conclusions with discussion of alternative conclusions that are also supported by the data. The Agency-wide guidance and principles on risk characterization are applicable to cumulative risk assessment and should be observed when preparing such documents. While keeping in mind that in addition to characterizing the hazard and exposure potential of individual chemicals, it will also be necessary to assess and characterize the potential combined effects of exposures to multiple chemicals. Thus, under FQPA a cumulative risk assessment must focus, as a unit, on multiple chemicals that are grouped on a common mechanism of toxicity and a common toxic effect, and on the potential of humans to be exposed to that group such that the toxicity expressed reflects the outcome of the combined exposure to the common mechanism of toxicity group of chemicals.

**Figure 1-1. Risk Characterization (taken from USEPA, 1999d Draft)**



Following evaluation and identification of chemicals that express a common toxicity(ies) through a common mechanism, a cumulative risk assessment and characterization incorporates on a daily basis for an individual:

- ❑ potential toxicity of each individual chemical by route and duration.

- ❑ toxicity from aggregate exposure for the common endpoint for the chemicals in a common mechanism group that is expected when the exposure by each route is combined (i.e., the toxicity anticipated by combining the exposure (dosage) to the chemicals comprising the common mechanism group by the oral route, by the dermal route, and by the inhalation route),[5]

- ❑ Cumulative risk that may be anticipated following exposure to multiple chemicals by all routes (i.e., the combined risk estimated by combining the risks identified in the aggregate risk assessment for each route) and computing the total, cumulative risk estimated for exposure to all chemicals by combining exposures from all routes.

Grouping of chemicals that have a common mechanism of toxicity is based on a determination that the individual chemicals in a group cause toxicity by a common mechanism, and that each chemical assigned to the group affects the same target site. Exposure patterns must also be such that the opportunity exists for the expression of effects that may be expected from the combined exposure to multiple chemicals sharing a common mechanism of toxicity.

It is important to recognize that hazard identification and characterization discussions presented on individual chemicals for establishment of an RfD may not be suitable for evaluating cumulative risks since the endpoint (and NOAEL) selected to establish an RfD for an individual chemical may not be the endpoint of toxicity that has been shown to be the common endpoint for the common mechanism group of pesticides. Information such as dose-response data on effects other than the critical effect from a critical study used to establish an RfD may not be presented in an RfD report.

[5]In an aggregate risk assessment on a single chemical, aggregation of exposure and estimations of “aggregate” risks are based on combining exposures by the oral, dermal, and inhalation routes followed by estimating the total exposure (mg/kg/day) and then determining the margin of exposure using an appropriate quantitative method (*Guidance for Performing Aggregate Exposure and Risk Assessments,* USEPA, 1999b).

**Figure 1-2. Cumulative Risk Assessment: General Process**

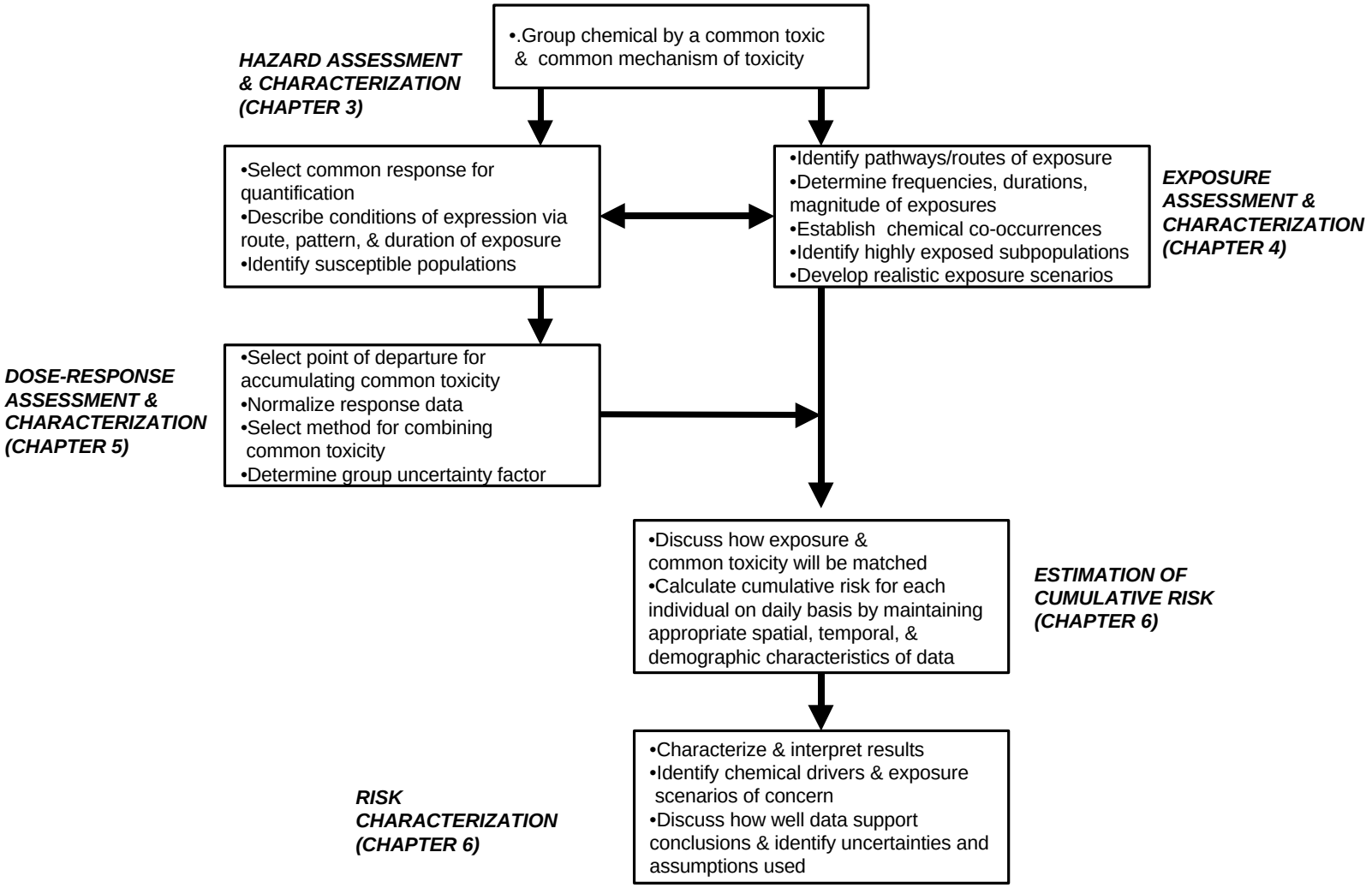


Figure 1-2 depicts the overall process that will be followed in performing a cumulative risk assessment and what chapters of the guidance document will discuss more fully the issues that are to be addressed. Note that the process incorporates the concepts of:

- ❑ **Hazard** - What is the potential for the occurrence of a toxic effect in humans that is the result of exposure to multiple chemicals with a common mechanism of toxicity?; under what circumstances will the common toxic effect cumulate (via route, duration, pattern of exposure)?; are there population subgroups that have increased susceptibility or sensitivity to the common toxic effect?

- ❑ **Dose response** - At what doses and frequencies of exposure might accumulation of common toxic effects occur? How do multiple chemicals interact with respect to dose-response interactions?

- ❑ **Exposure** - What are the spatial and temporal levels and conditions for human exposure that allows for the potential for the group of chemicals to result in a cumulative effect (i.e., to act via a common mechanism)?; and are there regional and subpopulation concerns?

- ❑ **Risk Characterization** - What is the character and magnitude of the cumulative risk? How well do data support conclusions about the nature and extent of the potential cumulative risk of humans? What are the uncertainties? What are the major chemical contributors to the cumulative risk and the scenarios of concern? Are there subpopulations at increased risk?

A cumulative risk assessment considers hazard and exposure data in an integrative step wise process. First, the potential oral, dermal, and inhalation hazard and the potential for exposure by each route of each pesticide belonging to a group of pesticides initially identified as sharing a common mechanism of toxicity is assessed[6]. Next, the hazard assessment information is assimilated into an aggregate risk assessment where the combined hazard associated with exposure to two or more chemicals by each route is determined. Prior to, or

[6]*Common mechanism of toxicity is defined as "two or more pesticide chemicals or other substances that cause a common toxic effect to human health by the same, or essentially the same, sequence of major biochemical events. Hence, the underlying basis of the toxicity is the same, or essentially the same, for each chemical." (USEPA, 1999a).*

during this analysis, individual chemicals initially identified as belonging to a group of chemicals with a common mechanism of toxicity may be eliminated from further consideration in the assessment if exposure information indicates there is no opportunity for overlapping exposures with other members of the group. A decision to eliminate a chemical from a group of chemicals also involves integrating exposure information and toxicology data such as persistence of effects and presence of tissue residues following acute, short term, intermediate, or chronic exposure. At this point in the assessment, a final selection of the chemicals that should be included in the cumulative risk assessment may be made. The defined group of chemicals that share a common mechanism of toxicity and a common toxic effect, and for which exposure data show a potential for toxicity to be expressed as a reflection of exposure to multiple pesticides; i.e., the cumulative assessment group of chemicals, or *CAG* is assessed, as a group, in the final step of the process which is the assessment of the cumulative risk that may result from the combined exposure to the *CAG* by all routes and pathways.

# 2 PRINCIPLES AND DEFINITIONS [TO BE COMPLETED]

Certain key principles and definitions are important for an understanding of the cumulative risk assessment process. This chapter outlines the principles and concepts that will be applied in a cumulative risk assessment in general terms. A more detailed technical discussion appears in the subsequent chapters of this document. Additionally, definitions and terms used in this guidance are provided in the glossary. Below are some basic principles that were used in developing the guidance. Because of a lack of knowledge in certain areas, some principles contain judgmental decisions (i.e., science policy decisions). Thus, assumptions and first approximations must be made to deal with inherent limitations found in available data bases for both hazard and exposure information. (Note: a list of key assumptions will be added when the exposure component of this document is completed.)

## 2.1 DEFINITIONS

- **Cumulative Assessment Group (*CAG*)** is the final group of chemicals that have been identified as being the chemicals that should be included in a cumulative risk assessment. The cumulative assessment group, or *CAG*, is comprised of chemicals that share a common mechanism of toxicity and are chemicals for which data show exposures can occur concurrently with exposures to other chemicals in the same group. A chemical included in the common mechanism group may be excluded from the cumulative group for other reasons such as quality of the toxicity data for a specific route of exposure, lack of toxicity data on the common effect by a specific route of exposure, or low confidence in the conclusions reached in the hazard assessment.

- **Common Mechanism Group (*CMG*)** is the candidate group of chemicals selected for consideration in a cumulative risk assessment that have been identified as being toxic by a common mechanism. Selection of the *CMG* is made in accordance with guidance provided in *Guidance for Identifying Pesticide Chemicals and Other Substances That Have A Common Mechanism of Toxicity* (USEPA 1999a) and without considering relevant exposure information. Candidate chemicals may or may not be included in a final cumulative risk assessment depending on exposure considerations or hazard assessment considerations or hazard factors (e.g., poor quality of toxicity data).

- **Concurrent Exposure** is intended in this document to mean those conditions of potential human exposure by all relevant routes and pathways that allow exposures (mg/kg/day) to cumulate (i.e., exposure to one chemical adds to the exposure of a second chemical) such that the toxicity of the common mechanism of toxicity group is an estimate of the sum of the exposures of all members of the group that are toxic by a common mechanism. The accumulation of the toxic effect may or may not depend on simultaneous or overlapping exposures depending on the nature of the mechanism of toxicity. For example, 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.

- **Cumulative Toxicity** or **Cumulative Toxic Effect** is the net change in magnitude of a common toxic effect resulting from exposure to two or more substances that cause the common toxic effect by a common mechanism, relative to the magnitude of the common toxic effect caused by exposure to any of the substances individually.

- **Cumulative Risk** is the risk associated with a group of chemicals that are toxic by a common mechanism by all pathways and routes of exposure. Unless data to the contrary are available, it is estimated by summing (dose addition) the exposures by multiple routes to the *CAG* of chemicals followed by calculating an RPF value or by summing individual MOEs.

- **Point of Departure** (PoD) is a dose or concentration corresponding to a fixed marker of toxicity, so that all contributing chemicals can be scaled by a consistent measure of toxicity. The PoD is derived from empirical data--for incidence or for key event(s)–for each chemical and for each route and duration of exposure in order to accumulate the common toxic endpoint. The objective for the PoD is to select either a measured data point or an estimated point (within or near the range of observable responses) that on a chemical dose-response reflects a uniform measure of effect that is close or approaches the background (or baseline) level of response as seen in control groups.

## 2.2 PRINCIPLES

- The **Common Toxic Effect** is central to the cumulative risk assessment process. The common toxic effect for a group of chemicals is selected during the identification of chemicals that produce a specific toxic effect

by a common mechanism of toxicity. The effect identified as "common" may or may not be the effect that was used as a basis for establishing an individual chemical's Reference Dose (RfD) value or Reference Concentration (RfC). The common toxic effect may be produced at, above, or below doses that produce other toxicological effects that are not associated with the common mechanism of toxicity and which may have been used to set an RfD or RfC value.

- ❑ A **"Group Uncertainty Factor**" for the common mechanism group is applied more appropriately after estimating the toxicity of the group to cover areas of scientific uncertainty that pertain to the group as a whole (e.g., intra- and inter-species differences). The rationale for the group uncertainty factor is based on the chemical members being bridged by a toxic effect that arises by a common mechanism of toxicity. Issues concerning the quality and completeness of the database on the common toxic effect for the group as a whole are also considered in developing a group uncertainty factor. Factors that concern adjustments of the common toxic response based on data and scientific underpinnings (e.g., extrapolation of a LOAEL to a NOAEL) are applied as appropriate on individual chemical members before accumulating the toxicity of the group in order to express a uniform effect level to the extent possible.

- ❑ A **Weight-of-the-Evidence** and characterization approach is taken in this guidance to promote the use of available data to the fullest extent possible. This guidance provides a structural framework for considering features of the available data that strengthen or reduce confidence regarding conclusions reached on the toxicological aspects of individual chemicals of a *CAG* and of the *CAG* considered as a whole. The guidance also encourages the generation of the best data and future research to provide an even better scientific foundation for the cumulative risk assessment process.

- ❑ The framework for estimating combined exposure is based on **Exposure to Individuals,** which represents differing attributes of the population (e.g., human activity patterns, place of residence, age) that link routes of exposure through **Scenario Building**.

- **Spatial, Temporal, and Demographic** considerations are major factors in determining whether a concurrent exposure to two or more chemicals in a group 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. Cumulative risk values need to be calculated separately for each exposure route and duration for a given common toxic effect and then combined.

- The outcome of a cumulative risk assessment is not a single estimate but rather **Varying Risk Estimates or Values** for differing proportions of populations exposed to chances of adverse health effects resulting from different time scales of exposures. Once a cumulative risk assessment is completed for one individual, population and subpopulation distributions of exposures and risk are constructed by probabilistic techniques or a combination of probabilistic and deterministic methods.

- **Additivity,** applied as dose addition to account for interactions following exposure to multiple chemicals, is the default assumption for estimating the toxicity that may be expected as a result of exposure to two or more chemicals that are toxic by a common mechanism. It is the approach used to sum the exposures (mg/kg/day) by each route (oral, dermal, and inhalation) for each chemical in a *CAG*.

# 3 HAZARD ASSESSMENT AND CHARACTERIZATION

The initial step in performing a cumulative risk assessment is to identify those chemicals that share a common mechanism of toxicity. This step is followed by selecting a specific toxicity endpoint for a certain exposure duration (e.g., acute, chronic), shared by each member of the *CMG* that will be used for a cumulative risk assessment. Hazard identification, assessment, and characterization should be consistent with Agency policies and guidance documents. This chapter is intended to provide guidance for selecting, assessing and characterizing hazard data that should be included in a cumulative risk assessment.

This chapter will briefly highlight how to determine whether chemicals act by a common mechanism of toxicity. A comprehensive description of this process is provided in *Guidance for Identifying Chemicals and Other Substances That Have a Common Mechanism of Toxicity* (USEPA 1999a). The chapter also focuses on additional hazard, biological, and exposure considerations for selecting a final group of chemicals deemed suitable for a cumulative risk assessment. It is important to recognize that it may be determined that it is not appropriate to include all members of a *CMG* in a cumulative risk assessment.

## 3.1 IDENTIFICATION AND CHARACTERIZATION OF CHEMICALS THAT SHARE A COMMON MECHANISM OF TOXICITY

A process for identifying chemicals that have a common mechanism of toxicity has been developed by the Agency and is described in *"Guidance for Identifying Pesticide Chemicals and Other Substances that have a Common Mechanism of Toxicity"* (USEPA, 1999a). Mechanism of toxicity, as defined in the guidance document is *"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".* The phrase "mechanism of toxicity" is equivalent to the phrase "mode of action" (*Guidelines for Carcinogen Risk Assessment*, USEPA, 1999d, Draft). Mechanism of toxicity is the phrase used by OPP so as to be consistent with the language of the FQPA.

Figure 3-1 presents the weight-of-the-evidence approach used in the process of identifying chemicals that are toxic by a common mechanism. The weight-of-the-evidence evaluation lists factors that should be considered in order to make determinations regarding mechanisms of toxicity of pesticides and other substances. As shown in step 3b of Figure 3-1, an essential feature of the

process is to develop a scientifically defensible putative mechanism of toxicity when a mechanism of toxicity has not been previously established. Recently, and subsequent to the development of the guidance document for identifying chemicals that have a common mechanism of toxicity, the Agency has developed a framework for mode of action analysis that is designed to test (establish cause and effect) the hypothesis that a particular mode of action is operative for a given chemical (*Guidelines for Carcinogen Risk Assessment*, US EPA, 1999d, Draft). The framework is complementary to the *Guidance for Identifying Pesticide Chemicals and Other Substances That Have a Common Mechanism of Toxicity,* USEPA 1999a) and offers additional direction for establishing a mechanism of toxicity and for characterizing assessments of mechanisms of toxicity. The mode of action framework should be used in conjunction with the guidance on identifying chemicals that have a common mechanism of toxicity. Steps in the process for evaluating whether a mechanism of toxicity is supported by the available data are:

- ❏ Present a *Summary Description of the Postulated Mechanism(s) of Toxicity*
- ❏ Identify and describe the *Key Events* that lead to the toxic response
- ❏ Discuss *Strength, Consistency, Specificity of Associations of Responses with Key Events*
- ❏ Discuss *Temporal Associations,* i.e., do key biochemical events precede, accompany, or occur after the toxic response and are effects reversible or persistent
- ❏ Discuss the *Biological Plausibility and Coherence of the Database* on the proposed mechanism including a discussion of data gaps, quality of the data, concurrence of critical biochemical events and toxicity, dose-response relationships (i.e., do critical biochemical events occur at, below, or above doses that result in toxicity?)
- ❏ Discuss *Other Mechanisms of Toxicity* that are possible or that are possible but can be discounted based on available data
- ❏ Briefly summarize the *Conclusion* regarding whether or not the hypothesized mechanism of toxicity has been demonstrated.

Identification of a group of chemicals having a common mechanism of toxicity (*CMG*) will precede analyses for cumulative risk assessments. The

rationale for grouping a set of chemicals based on a common mechanism of toxicity will be provided in reports issued by the Health Effects Division prior to preparation of a cumulative risk assessment. Key conclusions, and toxicity data, presented in the reports will be utilized when preparing a cumulative risk assessment. Since a separate report will be available on the *CMG* chemicals, the rationale and process followed for identifying chemicals that have a common mechanism of toxicity will not be presented in a cumulative risk assessment document. It will only be necessary to include information from the common mechanism report on conclusions reached and on specific toxicity data that are needed to proceed with other elements of a cumulative risk assessment.

Figure 3-1. Weight-of-Evidence Process for Identifying Pesticides and Other Substances that Cause a Common Toxic Effect by a Common Mechanism (taken from U.S. EPA 1999a)

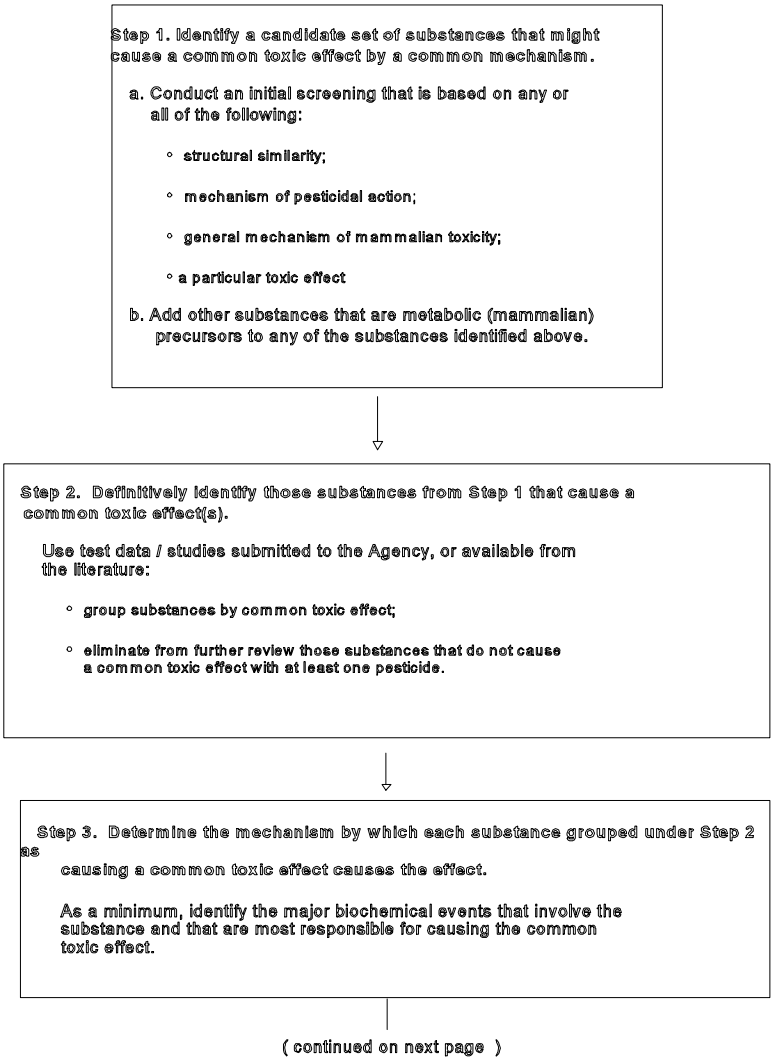
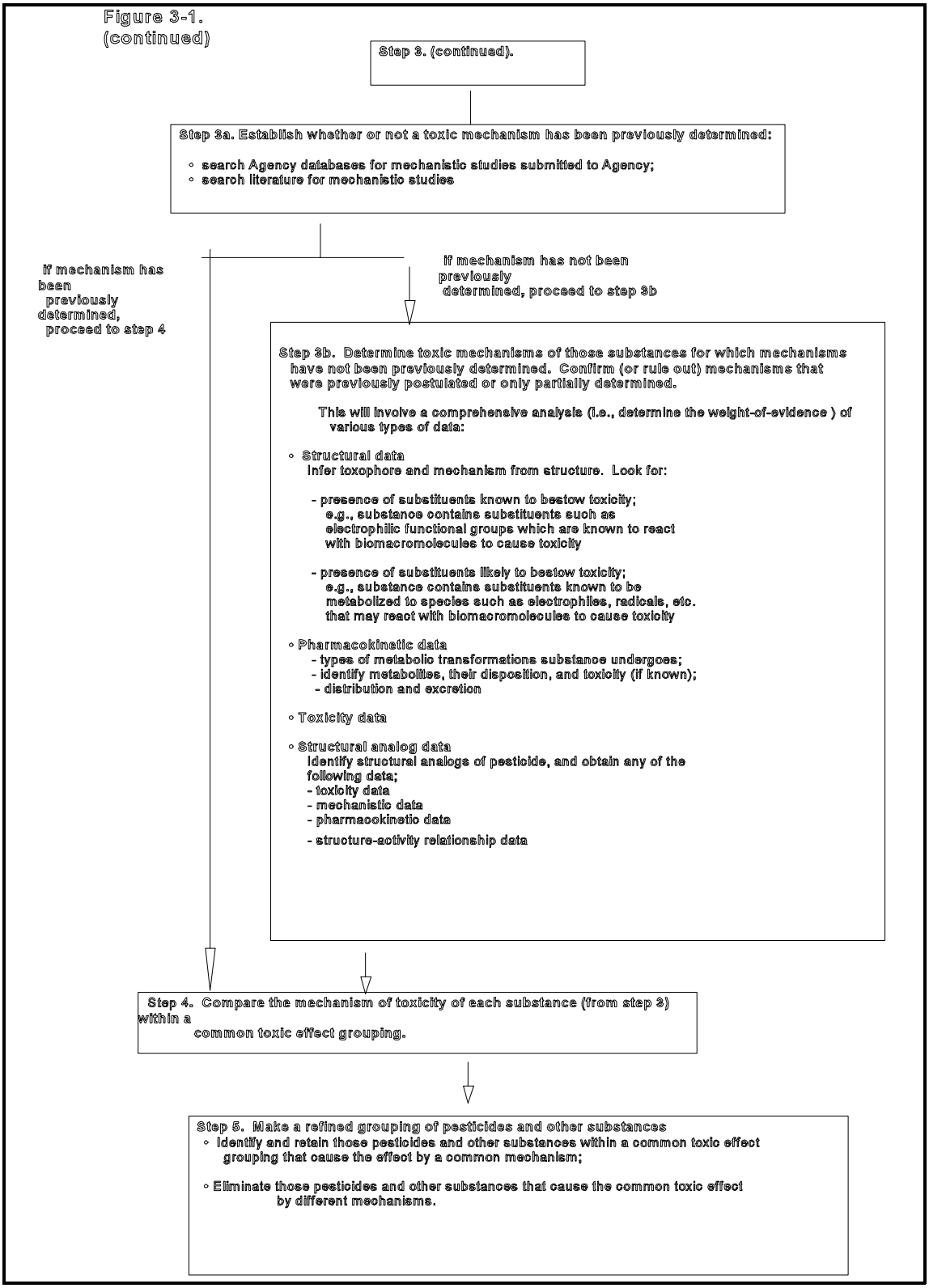


Figure 3-1.
(continued)



## 3.2 FURTHER ANALYSIS OF CHEMICALS THAT HAVE A COMMON MECHANISM OF TOXICITY

Once a series of chemicals has been identified that share a common mechanism of toxicity (Section 3.1.), additional analyses are required to determine which members of the series should be considered in a cumulative risk assessment. The additional analyses also help identify exposure scenarios of concern (Chapter 4) and provide support for the approach to quantification of *cumulative risks* (Chapter 5 & 6). Factors that need to be addressed in the analyses are listed below. They include both the potential for the accumlation of multiple chemicals in a specific body tissue or overlapping of critical precursor events that lead to the common toxic effect, which can lead to an enhancement of the toxicity caused by each chemical.

- ❏ What are the conditions of hazard expression? What are the risks of concern? Can onset, duration, and reversibility (or irreversibility) of the common effect be determined from the available data for each exposure duration anticipated and are these characteristics similar across the chemical group?

- ❏ Are route specific data available or will route-to-route extrapolations be needed to quantify risk?

- ❏ Are results reported in studies used for endpoint selection reproducible?

- ❏ Is selection of a common toxic endpoint based on utilization of data from studies of equal duration? If not, does the design of the study (e.g., serial sacrifices in chronic testing) allow comparison of data for equal time intervals?

- ❏ Are there features of the common toxicity among the individual chemicals that could impact evaluation of the hazard potential of the entire grouping when exposures are identified and incorporated in the risk assessment (e.g., persistence or reversibility of effects)?

- ❏ Is selection of a common toxic effect or precursor event based on bioassay data from similar study designs and from the same species or strain of animals? If data are from different species or strains of animals, can differences in responses be identified and accounted for?

- ❏ Is the common toxic response selected for grouping chemicals well defined and quantifiable for each chemical?

- ❑ Is the mechanism of toxicity identified consistent with a linear or nonlinear dose-response extrapolation approach?

- ❑ Are pharmacokinetic data available that define dose levels that result in saturation of metabolic pathways? If so, can it be assumed that dose addition due to exposure to two or more chemicals at ambient exposure levels will be below saturation levels?

- ❑ Is the toxic effect relevant to human toxicity?

### 3.3 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. While 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[7], antagonism, synergism, or no change in toxic effect(s) caused by any one of the substances alone. Whether the cumulative toxicity resulting from exposures to pesticides and other chemicals that occur individually as discreet residues in multiple sources such as the diet (e.g., fruit, vegetables, meat, milk), air, or water will be greater than, equal to, or less than the toxicity caused by any of the chemicals alone is dependent on many factors. Factors include exposure patterns which result in simultaneous or overlapping exposures, the pharmacokinetics/dynamics of each substance causing the common toxic effect, the duration of the common toxic effect, and the pharmacokinetic/dynamic interactions that take place between the substances. Information is not currently available that allows one to discern the precise nature of the possible interactions that may occur following exposure to a group of chemicals that are combined based on a common mechanism of toxicity. For the purpose of implementing the requirements of FFDCA as amended by FQPA, the EPA will regard cumulative toxicity of multiple chemicals sharing a common mechanism of toxicity, in the absence of evidence to the contrary, as the effect predicted by summing the exposure (dose addition) to the individual chemicals that are

[7]*An additive effect is defined for purposes of a cumulative risk assessment as the effect of the combination of a group of chemicals estimated by summing the exposure levels, by dose addition, of the individual chemicals. The manner in which dose addition is incorporated in cumulative risk estimates is discussed further in Chapter 5 and application of dose addition is illustrated in the case study (Appendix A).*

combined.

## 3.4 POTENTIAL SENSITIVE OR SUSCEPTIBLE POPULATIONS

When characterizing hazard potential, attention should be given to subpopulations that may, because of health status, age, or genetic predisposition, 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 comprising a common mechanism grouping. In such a case, it is possible that 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 Executive Order 13045: Guidance for Considering Risks to Children During the Establishment of Public Health-Based and Risk-Based Standards[8]. Similar concerns exist for individuals who, because of illness, are on medications that might predispose the individual to chemical interactions that can lead to untoward effects if exposed to additional chemicals.

## 3.5 WEIGHT-OF-THE-EVIDENCE EVALUATION

The Agency uses a weight-of-the-evidence approach for evaluating and characterizing toxicity endpoints of concern and for reaching conclusions regarding the likelihood of hazard to the human population. The weight-of-the-evidence evaluation is a collective evaluation of all pertinent information so that the full impact of biological plausibility and coherence are considered (US EPA, 1999d). In a cumulative hazard assessment, a weight-of-the-evidence analysis requires an initial discussion of the characteristics of the data on each chemical comprising a common mechanism of toxicity grouping and how the strengths and weaknesses of data on each chemical influence confidence in the hazard identified for the grouping as a whole. Listed below in Table 3-1 are features of hazard assessment and evaluation that strengthen one's confidence that the hazard assessment is of high quality, accurately reflects potential hazards, and forms a solid basis for other aspects of the risk assessment (e.g., dose response assessment, quantification of risk). Those features that weaken one's confidence in the cumulative hazard assessment are also listed.

It is important to recognize that a hazard data base on a *CAG* will span a broad continuum ranging from a weak data base that make estimates of cumulative risks very uncertain to a robust one that provides a wealth of

[8]Available on the internet: http://www.epa.gov/children/rulewr

information.

**Table 3-1. Data Considerations in Determining the Level of Confidence for Hazard Assessment of a Cumulative Effect**

**Higher Confidence**

- ❑ Robust data are available to show that a common mechanism of toxicity is operative for all members of *CAG*
- ❑ Route specific data for toxicity endpoints selected for the cumulative risk assessment are available for all members of *CAG* and are of high quality
- ❑ Data are available on all members of *CAG* and are suitable for comparisons of relative potencies and for calculations of points of departures that reflect a uniform effect level.
- ❑ Data are available that allow insights regarding potential increased sensitivities of susceptible populations
- ❑ Pharmacokinetic data are available to show how exposure relates to dose in the target tissue over a given time frame.

**Lower Confidence**

- ❑ Mechanism of toxicity of some individual members of common mechanism grouping inferred from limited data.
- ❑ Other mechanisms are plausible for expression of specific toxicity and can not be discounted
- ❑ Route-to-route extrapolations used to infer dose-levels required to produce common effect
- ❑ Chemicals likely to have a common mechanism of toxicity eliminated from grouping due to incomplete or low quality data base
- ❑ Adequate dose-response data lacking for many members of group
- ❑ NOAEL's not identified in studies that serve as the basis for quantification of risk (important if cumulative risk assessment must be based on use of NOAEL's as points of departure)
- ❑ Some chemicals in the *CAG* do not have consistent endpoint data. Data not derived from same species, strain, or sex.

## 3.6 CHARACTERIZATION OF OVERALL DATABASE ON CHEMICALS OF COMMON MECHANISM

Hazard characterization has two functions. First, it presents results of the hazard assessment and an explanation of how the weight-of-the-evidence conclusion was reached. It explains the potential for human hazard, expected manifestations of the hazard, and mechanism of action considerations for dose-response extrapolation. Secondly, it contains the information needed for eventual incorporation into a risk characterization that would be consistent with EPA guidance on risk characterization (US EPA, 1999c). Hazard characterizations involve discussions of the quality of the data base; a description of species and strain differences in responses; and discussions of species and strain sensitivities to the same response, route-to-route extrapolation issues, statistical significance of findings, preciseness of dose response data, relevance of hazards to humans, and of potentially sensitive or susceptible populations.

Table 3-2 is a summary of factors that should be addressed when characterizing the quality of the hazard data available for chemicals that are grouped based on a common mechanism of toxicity and that produce a common toxic effect. It should be noted that the factors pertaining to common toxic effects (e.g., route specificity, duration of the toxic effect, and time to peak effect) depend on the pharmacokinetic characteristics of the chemicals. These characteristics are important to incorporate in the cumulative risk assessment in order to guide the quantification of risk and to determine the likelihood that effects will cumulate. For example, if recovery is rapid, the accumulation of toxicity is not likely to occur if exposures and duration of effects are temporally separated.

**Table 3-2. Factors to Address in Characterizing the Potential Cumulative Toxicity of Chemicals Sharing a Common Mechanism of Toxicity**

**Factors Pertaining to Common Toxic Effects**

- ❑ route specificity
- ❑ species, strain, or sex differences
- ❑ time-course for onset, duration, and reversibility of effects
- ❑ site and nature of the effect
- ❑ duration, frequency, and level of exposure required to cause the effect

**Factors Pertaining to Pharmacokinetics**

absorption, distribution, metabolism, and excretion

- ❑ biological half-life
- ❑ pharmacokinetic interactions among substances

**Factors Pertaining to Pharmacodynamics**

- ❑ dose-response relationships
- ❑ toxic efficacy of each substance
- ❑ relative toxic efficacy among substances
- ❑ pharmacodynamic interactions among substances

**Factors Pertaining to Potentially Exposed Individuals**

- ❑ anticipated susceptibility and sensitivity of exposed individuals/subpopulations, especially infants and children and in utero exposure

### 3.6.1 Weight-of-the-Evidence Narrative

The hazard assessment for a CMG of chemicals concludes with a narrative that briefly describes the conditions of expression and the potential for a common mechanism group of chemicals to produce cumulative effects in humans (by route and duration of exposure). The conditions of expression for the common toxicity helps guide the exposure assessment of biologically relevant exposure scenarios by route and duration. The narrative should include a summary of a) the mechanism of toxicity identified for the CMG, b) the key data on the common endpoint of toxicity expressed as a result of a common mechanism, and c) a recommendation of the toxicological endpoint(s), species, and sex for which the dose-response analyses should be conducted ( described in Chapter 5). The weight-of-evidence narrative also should note whether other toxic effects are expressed by members of the CMG and whether a mechanism of toxicity can be identified for the other toxic effects. This information will allow risk assessors and risk managers to make decisions regarding which group of chemicals should undergo a cumulative risk assessment first. For example, if among a group of 10 chemicals that have been identified as having a common mechanism of toxicity for an effect A, five of those chemicals also produce a common effect B risk assessors may want to perform a cumulative risk assessment on Group B and then on Group A if the mechanism of toxicity for effect B is understood and the toxic response is one of major concern.

At this point in the cumulative risk assessment, the hazard evaluation also should be considered in conjunction with the exposure assessment and characterization (Chapter 4) and a decision reached on which members of the CMG should be excluded from further consideration in the cumulative risk assessment. Reasons for exclusion of a chemical from the *CAG* in the final cumulative risk assessment may include absence of exposure potential, insufficient weight-of-the-evidence support for inclusion of a chemical in the group, lack of data showing a chemical produces an effect common to the other members of the group by a particular route of exposure, or other exposure or hazard data that show a particular chemical is unlikely to contribute to the cumulative toxicity of the other members of the group.

# 4 EXPOSURE ASSESSMENT AND CHARACTERIZATION [TO BE COMPLETED]

**[PLEASE NOTE THAT THE EXPOSURE COMPONENT OF THE CUMULATIVE RISK ASSESSMENT PROCESS IS STILL BEING DEVELOPED. A BRIEF DISCUSSION IS PROVIDED BELOW FOR WHAT THIS CHAPTER WILL COVER.]**

As discussed in Chapter 3, the hazard assessment and characterization describes features of the biological characteristics and mechanism for the common toxic effect that has implications for the cumulative exposure and risk assessment (e.g., routes of concern, time of onset and duration of effects, differential effects by sex, potential susceptible subpopulations). The hazard and exposure analyses of the cumulative risk assessment process must be interactive in order to identify the interrelationships between exposure patterns and conditions of expression for the common toxic end point. Thus, information needs to be gathered defining exposure scenarios of concern, and frequencies, durations, and magnitude of exposure for those scenarios. **It should be noted that many of the principles and tools presented in the *Guidance for Performing Aggregate Exposure and Risk Assessment (USEPA, 1996b, Draft)* will be drawn on to develop this Chapter. Thus, this chapter will focus on those aspects of cumulative exposure assessment that differ from the aggregate exposure and risk assessment processes.**

This Chapter will discuss briefly how the potential pathways, routes, and time frames of human exposure and the populations (including subgroups such as children and geographic groups) at risk are defined and considered for analysis to aid in developing the appropriate scenarios for estimating cumulative risk. It will describe the available sources of chemical specific data and use of surrogate data, and how pesticide exposures will be estimated. The assumptions used in conducting the cumulative exposure analysis also will be discussed. The contents of this chapter will be limited to exposure to pesticide chemicals. Although exposure to toxicologically similar chemicals from other sources may occur, assessment of those exposures is beyond the current scope of this document.

## 4.1 VERIFICATION OF THE NEED TO CONDUCT A CUMULATIVE RISK ASSESSMENT

Prior to initiating a full quantitative cumulative risk assessment it should be determined whether the combination of exposure scenarios identified present any likelihood of multiple, overlapping exposures. The pathways of exposure for the chemicals in the identified group may be such that exposure to more than one chemical will never be encountered at the same time. This preliminary step of eliminating unnecessary components of the assessment prior to beginning cumulative quantification of exposure and risk is critical to bounding the scope of

the cumulative risk assessment. By removing scenarios in which exposure is non-existent or negligible in magnitude the resulting assessment will be more focused on exposures of concern. This will be especially important in identifying the important sources of exposure for the common mechanism group, or *CMG*, accounting for the uncertainties, and explaining the outcomes of the assessment to risk managers and the public. The rationale with which a pesticide use can be stated to present a negligible exposure should be clearly evaluated and presented. This will prevent the erroneous omission of exposures to a chemical that may contribute to a common toxic effect. Subsequent drafts of this document will describe exclusionary criteria that have been developed to guide the exposure and risk assessor in bounding the scope of cumulative assessments.

Data availability and quality may also play an important role in the determination of whether or not to combine exposures by multiple pathways. Where data are limited in quantity, it may be inappropriate to attempt to combine exposures from multiple sources because of the uncertainty that may be introduced into the assessment. Similarly, where datasets differ in quality, combining exposure assessments may produce misleading results that are characterized by high uncertainty and low confidence. Where issues of data quality or quantity indicate that combining pesticide exposures across multiple routes is inappropriate, pathway specific cumulative exposures should be conducted. The results of the pathway specific assessments should be discussed qualitatively in the risk characterization.

### 4.1.1 Exposure to Pesticide Chemicals

Three key pathways of exposure to pesticides are: dietary (food), dietary (drinking water), and residential and other nonoccupational exposures. How and when people are exposed to chemicals within a common mechanism grouping depends largely on the ways in which the chemicals are used. By evaluating a pesticide's life cycle including its registered uses, a profile for each chemical from the common mechanism group can be developed to establish the potential routes, durations, frequencies, and magnitude of exposure.

#### 4.1.1.1 Dietary (Food)

One of the more important exposure pathways that will be evaluated for cumulative risk will be dietary exposure. The body of information for this pathway is much greater than that available for the other pathways. 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 (i.e., close to the point of consumption). In addition, data defining the consumption patterns for the US population have been collected in a number of surveys. Cumulative exposure assessments for residues of pesticides in foods can be performed on an individual by individual basis, with a detailed estimation of the likelihood of consuming foods containing 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 nationally distributed unless there is evidence to the contrary. Some of the types of data and their sources that can be used in assessing dietary exposure to pesticides are:

- ❏ Continuing Survey of Food Intakes by Individuals (CSFII) (1989-1991)
- ❏ Field Trial Data (studies submitted to EPA that are required for registration or re-registration).
- ❏ Monitoring Data:
  USDA's Pesticide Data Program
  FDA's Surveillance Monitoring Data
- ❏ Market Basket Data

#### 4.1.1.2 Dietary (Drinking Water)

For cumulative human health risk assessments, residues of pesticides in finished drinking water are preferred. At the present time, monitoring data for residues of pesticides in finished drinking water are available for only a limited number of pesticides from monitoring activities under the Agency's Safe Drinking Water Act (SDWA) and the National Well Survey (EPA 1990), registrant-sponsored studies such as the Acetochlor Registration Partnership (ARP), and the Novartis Rural Well Survey and Voluntary Monitoring programs. State agencies and community water suppliers may also have data for specific compounds; however, these data are not organized and readily available at this time. The USGS National Water Quality Assessment Program (NAWQA) database contains some data on rural drinking water wells, but largely consists of data on pesticide residues in ambient surface water sources, not finished drinking water. Data on pesticide residues in finished drinking water are needed to reliably estimate

cumulative exposure and models need to be developed to reliably estimate finished drinking water exposure in the absence of chemical-specific monitoring data.

Data defining potential co-occurrence of pesticides in finished drinking water is rarely available; however, the NAWQA data do provide some co-occurrence data for a wide variety of pesticides in raw surface water sources, and some registrant-sponsored studies provide co-occurrence data for specific compounds. The determination of the likelihood of co-occurrence will depend heavily upon understanding the distribution of use for each pesticide within a geographic region. Because drinking water assessments are inherently regional in nature, this process will require a detailed understanding of the marketing and use patterns for each pesticide for a given region.

At the present time, screening-level models that estimate pesticide concentrations in small bodies of surface water and shallow ground water are available for use in cumulative human health risk assessments. These models do not take into account any effects of dilution, distribution, or treatment on finished drinking water. A major short-coming of this approach is the combining of upper bound exposure estimates. Such a process is likely to substantially overestimate the potential for exceeding an acceptable exposure level in cumulative exposure and risk assessments.

#### 4.1.1.3 Residential and Other Nonoccupational Sources

Potential exposure via the oral, dermal and inhalation routes to pesticides results from applications made in and around the home and in institutional settings. Co-occurrence and linkage of uses are particularly important for residential and institutional uses. The maintenance of these linkages will be critical in developing reasonable estimates of exposures to a hypothetical individual with defined demographic characteristics. At this time, there is a limited understanding of use patterns for pesticide products in and around the home and in institutional settings. The Agency is aware of efforts to conduct surveys describing the use habits of the US public. Current exposure assessments for residential and other nonoccupational sources will most commonly be conducted using the Residential SOPs.

The Residential SOPs provide a screening level assessment of exposure and may not provide estimates of exposure that can be accumulated across chemicals. Sources of information on the estimation of residential exposure are:

- ❏ Residential SOPs,
- ❏ Guidance for Performing Aggregate Exposure and Risk Assessment
- ❏ Exposure Factors Handbook
- ❏ Monte Carlo Guidance Document
- ❏ National Home and Garden Use Survey

## 4.2 PARAMETER DEFINITION

Once the exposure data are gathered, and profiles are determined for each common mechanism chemical, the assessment should be planned with the following questions in mind: Who is exposed? To which chemicals and how much? 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 exposure will occur? The integration of the data in the assessment must be carefully planned such that the relevant linkages of exposure data are made. An example might be the matching of a mosquito treatment with other exposures during the spring and summer in the appropriate region of the US. In addition, the relative quality of the data available for each pathway and chemical should be assessed to determine whether or not combining of the exposure pathways will result in meaningful assessments or will reflect the compounding of conservative exposure estimates and uncertainties in one or more of the pathways at the expense of interpretation of the results.

## 4.3 CHARACTERIZATION OF THE EXPOSED POPULATION

The population subgroups that are most commonly of concern can be defined by a number of factors, including demographics, geographic location, and time of the year of interest. Demographic considerations would include age, gender, ethnicity and any other considerations that may be important in evaluating subpopulations with potential special susceptibilities. Determination of the geographic location of the exposed population will be necessary to help

match geographically based exposure data 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 of concern may suggest very different strategies for risk mitigation than exposures that are widely disseminated. The size of the subpopulation exposed 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.

## 4.4 DETERMINATION OF TIME FRAMES

The time frame over which an exposure occurs is a key criterion of defining scenarios of interest. 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 assessment of what scenarios will be represented in the assessment. The nature of the adverse effect from the toxicity data will determine the time course over which exposure should be assessed. Where exposure scenarios are found to be of insufficient duration to trigger the adverse effect cautious consideration may be given to eliminating some of the scenarios from the assessment. This factor alone, however, cannot be considered as an exclusionary criterion because the final exposure which is analyzed in the assessment will be the accumulation of exposures from many pathways. Several exposures of short duration may overlap to produce a cumulative exposure that exceeds an acceptable level.

In developing a detailed exposure assessment for multiple chemicals with a variety of use patterns, estimated cumulative exposure would consist ideally of the exposure from each chemical by each pathway. However, in reality the understanding of use patterns for pesticides in residential settings is limited. Similarly, little data reflecting potential overlap of pesticides in finished drinking water and the duration and timing of pesticide occurrence in finished drinking water are available. Obtaining these data will be critical to developing detailed, multipathway analyses. Until adequate data are available, conducting single pathway assessments for multiple chemicals as dictated by the availability, quantity and quality of exposure data may be prudent. For pathway specific exposure assessments, matching of the critical time frame from the toxicology data with the appropriate exposure scenarios may be possible. A variety of data are needed to permit an understanding of the interrelationship of exposures to multiple chemicals from multiple sources. These data will be outlined in subsequent drafts of this document.

## 4.5 EXPOSURE CHARACTERIZATION

The exposure characterization is a description of the data inputs used to estimate exposure, key analyses, the assessment results and the conclusions drawn. The characterization provides a statement of purpose, scope, level of detail, and approach used in the assessment and identifies the exposure scenario(s) covered. It estimates the distribution of exposures among members of the exposed population as the data permit. It identifies and compares the contribution of different sources and routes and pathways of exposure. Estimates of the magnitude, duration, and frequency of exposure are included as available monitoring or modeling results or other reasonable methods permit. The strengths, limitations, and uncertainties of the data and methods of estimation are made clear. The exposure characterization routinely includes the following, as appropriate for the data available:

- ❏ identification of the kinds of data available,
- ❏ results of assessment as above,
- ❏ explanation of analyses in terms of quality of data available
- ❏ apportionment of exposure sources (dietary - food, dietary - drinking water, residential and other nonoccupational sources)
- ❏ uncertainty analyses as discussed in Exposure Assessment Guidelines (USEPA, 1991b)
- ❏ explanation of derivation of estimators of "high end" or central tendency of exposure and their appropriate use.

# 5 DOSE-RESPONSE ASSESSMENT AND CHARACTERIZATION

A dose-response assessment evaluates the extent and magnitude of a potential adverse response in humans at exposure levels of interest for a single chemical or a group of chemicals. The evaluation first covers the relationship of the dose[9] to the degree of response in the dose range of observation in animal laboratory or human studies. This evaluation is then followed if necessary by extrapolation to estimate response at lower environmental exposure levels. In general, three extrapolations may be made: from high to low doses, from animal to human responses, and from one route of exposure to another. In this discussion, "response" data may include measures of key events (i.e., events considered integral to the mechanism of toxicity and the toxic effect), in addition to the frank toxicological outcome of a mechanism (e.g., incidence of tumors or developmental malformations).

The Agency evaluates potential human risks for non-cancer effects along two lines. The first is derivation of a chronic reference dose (RfD) for oral or dermal exposures or a reference concentration (RfC) for inhalation exposures. An RfD or an RfC represent "an estimate, with uncertainty spanning perhaps an order of magnitude, of a daily exposure to the human population, including sensitive subgroups, that is likely to be without appreciable risk of deleterious effects during a lifetime" (Barnes and Dourson, 1988; USEPA, 1994). RfDs or RfCs also have been developed for shorter time frames. An RfD or an RfC is a dose operationally calculated by dividing the NOAEL (or in some cases a LOAEL) or a modeled benchmark dose, typically derived from an animal study for a critical effect, by various uncertainty factors (UFs) and a modifying factor. These factors are usually 3- or 10-fold for each, and are applied to the NOAEL to account for intra- and inter-species differences and various types and quality of data used (see Table 5-1).

Although many of the principles that are currently used to derive an RfD or an RfC in single chemical assessments apply to a cumulative risk assessment of multiple chemicals sharing a common mechanism of toxicity, there are notable differences. As discussed in Chapter 3, chemicals that have been grouped via a common toxic effect and mechanism may produce other toxicities not associated with the common mechanism. Thus, in a cumulative assessment, selection of an endpoint that

[9]For this discussion, "exposure" means contact of an agent with the outer boundary of an organism, and dose can mean either "applied dose"(i.e., the amount of an agent presented to an absorption barrier and available for absorption), "internal dose"(i.e, the amount crossing an absorption barrier such as the exchange boundaries of skin, lung, and digestive tract, through uptake processes, or "delivered dose" (i.e., the amount available for interaction with that organ or cell (U.S. EPA, 1991b).

represents the common mechanism for a group of chemicals may or may not be the same endpoint that the RfD or RfC is based on for each specific member. Furthermore, the UFs incorporated in the RfD or RfC approach for a chemical member may or may not be relevant to the uncertainty surrounding the chemicals grouped via a common mechanism (see section 5.3). For example, the lack of a developmental toxicity study may justify applying a database UF when deriving an RfD or an RfC for an individual assessment of a member of the group, but may not be relevant to the common toxic effect and the common mechanism of toxicity for the group.

Another way of evaluating noncancer risks for a single chemical is to calculate a Margin of Exposure (MOE). An MOE is the ratio of a point of departure (e.g., NOAEL or benchmark dose) pertaining to a toxic effect to the expected or measured human exposure level. The larger the ratio, the less likely an agent poses a risk to humans; the smaller the ratio, the greater the chance of risk.

Eq. 5.1

$$MOE = \frac{PoD}{Exposure}$$

In the assessment of cancer risk, the Agency traditionally has applied a low-dose linear extrapolation model (i.e., the linearized multistage model) as a default (USEPA, 1986b). With the publication of revisions to the EPA's 1986 cancer risk guidelines and, consistent with those 1986 guidelines, it is proposed that the MOE approach be applied to those carcinogens that act by a mode of action consistent with a nonlinear dose-response relationship (USEPA, 1999d Draft).

Once the chemicals from the common mechanism group have been selected for inclusion in the cumulative risk assessment based on the common toxic response (Chapter 3) and the pertinent exposure scenarios identified (Chapter 4), the following must be established as part of the dose-response analysis before cumulative risk can be estimated. Thus, this chapter will cover:

- ***Selection of a uniform point of departure*** (e.g., effective dose levels or NOAELs) for all chemicals in the cumulative assessment group,or *CAG*
  *Objective*: To determine a point (estimated or measured) on each chemical's dose-response curve for the common response that is close to or within the background (or baseline) level of response as seen in the control groups.

- ***Normalization of the point of departure.***
  *Objective*: To make necessary adjustments to the dose-response data in order to establish a uniform point of departure (e.g., conversion of

LOAELs to NOAELS) across the *CAG*.

- ***Selection of a method for combining doses or exposures,*** such as the *Cumulative Margin-of-Exposure* or *Relative Potency Factor* approach, so as to normalize differences in toxic potencies among the chemicals in the *CAG*.
  *Objective*: To select a method that is best able to quantify the risk and combine point of departure data (i.e., dose-response data) for the *CAG*.

- ***Determination of a group uncertainty factor (UF).***
  *Objective*: To account for uncertainties that are common and inherent to the *CAG*, such as intra- and inter-species differences, as well as to reflect the remaining uncertainty concerning the overall quality of the database that pertains to the *CAG* as a whole.

Appendix A includes a case study illustrating the above process.

### 5.1 IDENTIFICATION OF A POINT OF DEPARTURE

A **point of departure (PoD)** is generally defined as a point estimate of the dose or exposure level that is used to depart from the observed range of empirical response (or incidence) data for purpose the of extrapolating risk to the human population (USEPA, 1999d Draft). In the case of a cumulative assessment, a dose reflecting a uniform response for the common toxic effect is needed for each chemical. This is needed to normalize and combine the different toxic potencies among the chemicals in the *CAG*. This dose corresponding to the uniform measure of response is represented by a point of departure. The PoD serves either as an observed dose or an estimated dose on each chemical's dose-response curve that is close or within the control background level of response. Depending upon the kinds of data available, different types of PoDs can be used for cumulating the exposure for a common effect. As described below, a PoD may be a designated effective dose or an interpolated no-observed-adverse-effect-level (NOAEL).

- ***Effective Dose (ED):*** The effective dose is a measured or estimated dose level associated with some designated level or percent of response relative to the control or baseline level of response. This is the preferred PoD. The ED is essentially the as a benchmark dose (BMD) (USEPA1995b, 1996d). It is determined by using a curve-fitting procedure that is applied to the dose-response data for a chemical.[10] As discussed below, the Agency prefers to use the lower confidence limit on the ED (i.e., LED) for single chemical assessments.

  The advantage of using an ED derived value over a NOAEL is that unlike the NOAEL, which represents a single arbitrary selected dose, an ED embodies responses observed at all doses tested (i.e, it takes into account each dose-response curve). It is especially useful in accumulating the hazard because it provides a more uniform measure of response across the *CAG*, and is not as constrained by study dose selection (ILSI, 1999).

  Adopting a 10% effect level ($ED_{10}$) as the standard default point of departure should accommodate most data sets without departing from the range of observation.[11] For example, in study protocols for developmental toxicities, the response levels range from about 5% to 30% (Faustman et al., 1994). A 10% level is at or just below the limit of sensitivity for discerning a statistically significant tumor increase in most long-term rodent studies (Haseman, 1983). For some *CAGs*, a choice of a point of departure other than the $ED_{10}$ may be appropriate for cumulating toxicity. For example, if the observed responses for the individual chemicals are lower than the 10% level of response, then a lower point of departure (e.g., an $ED_{5 \text{ or } 1}$) may be more appropriate for the *CAG*. The choice of an ED and the justification for that choice will be provided on a case-by-case basis.

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[10]For tumor incidence information, the Agency will apply a standard curve-fitting procedure. This procedure models incidence, adjusted for background, as an increasing function of dose; it will be available to the public on EPA's web site (http\www.epa.ncea) for use or for downloading when the revisions to the cancer risk assessment guidelines are finalized. The procedure will identify situations in which the standard algorithm fails to yield a reliable point of departure, signaling the need for additional judgment and an alternative analysis. Draft benchmark software for nontumor endpoints is currently available at http\www.epa.gov\ncea\bmds.

[11]The Agency is nearing a final position on adopting the lower limit on dose (LED) at 10% as a standard point of departure for both tumor and nontumor endpoints in the revision of the guidelines for carcinogen assessment, and for the benchmark methodology for noncancer assessment.

For risk assessments involving single chemicals, the lower limit on dose (LED), which is the 95% upper confidence limit, has been preferred by the Agency over the central estimate (ED) when extrapolating the risk. This is because the LED takes experimental variability into account. Use of the LED is also the approach proposed in the revisions to the Agency's Guidelines for Carcinogen Risk Assessment (USEPA, 1999d Draft). For cumulative risk assessment of multiple chemicals, however, use of the lower limit on dose is considered inappropriate when summing the doses for multiple chemicals which are being normalized to a common scale. Although the error in the simple addition of chemical members' upper bounds may be small with a few chemicals, but as the number of chemicals increase combining the lower 95% confidence limits on dose of multiple chemicals may result in compounding the conservatism in a multiplicative manner and may exaggerate the risk. Experimental variability is a factor to be dealt with when determining the need for a group uncertainty factor to account for limitations in the overall database as discussed in section 5.3. If experimental variability is considered unacceptable for the chemical group as a whole, then applying a benchmark type of modeling technique to response data may not be appropriate. For purposes of cumulative risk assessment, further methodology development is needed to account for the variability among a group of chemicals quantitatively.

Although an ED is less dependent on the selection of treatment doses in a study than a NOAEL, certain requirements of the benchmark approach might make the application of NOAELs more practical. For an ED analysis to be meaningful, rigorous data requirements for the *CAG* should be met (e.g., similar study designs, potentially more dose levels tested, and spacing of dose levels that encompass a range of responses on the dose-response curve). Although application of a benchmark analysis to quantal data (such as tumors or structural malformations) is fairly well defined, derivation of an ED from continuous or graded measures of response data (such as changes in organ weight, hormonal or enzyme levels) is not as well defined or established. To apply an ED or benchmark dose type of analysis to continuous data, thus requires more professional judgment to define some absolute change in response that is biologically significant.

Given the issues discussed above, there may be few opportunities to use this approach in the near term. Currently, the Agency is developing procedures for benchmark dose analysis of both quantal and continuous data. For interim guidance, the risk assessor should refer to the Agency's benchmark dose guidance (USEPA 1995b; 1996d).

- ***No-Observed-Adverse-Effect-Level (NOAEL) Approach***: While an ED is preferred as the PoD for each chemical, for the reasons discussed above, it is anticipated that in many situations in the near term, data for the *CAG* will not be amenable to curve-fitting estimation due to insufficient or inadequate dose-response information. In such situations, NOAEL's will be used in establishing PoDs for estimating cumulative risk. Currently, NOAELs are the PoDs most commonly used in single chemical risk assessments. A disadvantage of using NOAELs for cumulative risk assessment is that they are single point estimates, and do not reflect the relationship between dose and response for a given chemical nor 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 due to 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.

## 5.2 NORMALIZATION OF RESPONSE DATA

After a PoD is determined (EDs or NOAELs), a PoD for individual chemicals in the group may have to be adjusted to normalize the response data across the *CAG*. For example:

***Adjustment of LOAELs to NOAELs***: When an ED can not be determined, NOAELs will be used to combine the endpoint data. If NOAELs are not available, use of a LOAEL will have to be considered. In this case, the analysis must account for use of LOAELs for a specific chemical(s) in the group of interest. The LOAEL may be used if adjusted to approximate a NOAEL. Adjustments can be made in the following ways:

- A dose-response analysis of the common toxic effect for a specific chemical member can be performed in order to interpolate a NOAEL from the effective doses for that chemical.

- Evaluation of data on other related studies on the common toxicity involving the same species and strain for a specific chemical may reveal a pattern so that a NOAEL can be derived for the common toxic endpoint for that chemical.

- If a LOAEL for a specific member is used because it is not possible to establish a NOAEL by using the above adjustment approaches, it should be divided by a factor of 3- or 10-fold as a default adjustment to estimate

the NOAEL.

***Adjustments to Account for Most Sensitive Species**:* In estimating cumulative risk, response data from the same species, strain and sex for all the chemicals in the *CAG* is preferred. If it can be demonstrated that there are no, or minimal, species (strain or sex) differences among the test animals or subjects, then response data from different species (strain or sex) on the individual chemicals may be used to estimate cumulative risk. When there are clear and pronounced species (strain or sex) differences and it is unknown which test species responds most like humans to the test substance, data from the most sensitive test animal should be used to determine cumulative risk. In situations where response data in the most sensitive species are not available for all the chemicals in the *CAG*, then adjustments of those chemical's PoDs will be necessary to account for the most sensitive species response. This may be accomplished by comparing doses between the most sensitive species and the species from which EDs or NOAELs are selected for the individual chemical members to determine the magnitude of the difference in response between experimental species (strain or sex). Comparisons of doses should be based on the same endpoint and on effect levels (e.g., $ED_{10}$) rather than NOAELs, if possible. The above approach is based on using shared characteristics or comparative data for the group as a whole as a means to estimate the missing data for a member of the *CAG*.

## 5.3 DEVELOPMENT OF A GROUP UNCERTAINTY FACTOR

When conducting a cumulative risk assessment**,** the traditional uncertainty factors intended to account for interspecies and intraspecies differences, an incomplete chemical specific data base, extrapolation from subchronic to chronic data, and use of LOAELs rather than NOAELs, must be revisited in the cumulative assessment. As shown in Table 5-1, some of the traditional UFs are applied as adjustment factors on each chemical before cumulative risk is estimated (as discussed above in Section 5.2), and other UFs are applied at the end of the process as uncertainty factors that pertain to the chemicals in the *CAG* as a whole (discussed below).

Traditionally in single chemical risk assessments, uncertainty factors are applied during the hazard assessment phase to account for the uncertainty for a specific chemical assessment. In a cumulative hazard assessment, the procedure to determine and apply appropriate uncertainty factors depends not only on the attributes of individual chemicals of a common mechanism group, but on the characteristics of all the chemicals as a whole. Of the factors stated above, the two which account for extrapolation of LOAELs to NOAELs and of NOAELs from subchronic studies to chronic studies, are applied before cumulating hazard. In other words, these two factors applied as adjustment

factors to an individual chemical member (as discussed above in section 5.2).

The uncertainty factors to account for intra- and inter-species differences are considered to pertain to the *CAG* as a whole, and thus are to be applied at the end of the cumulative assessment process. For human (intraspecies) variability, if sufficient information is available to identify the variability in response, it is used, and if not, a factor of 10-fold is employed as a science policy default for the entire group to account for human variability. For interspecies variability, a factor of 10-fold is applied as a default assumption for the *CAG* to account for differences in sensitivity between species when animal data are used to assess human risk. When data indicate that humans are less sensitive than animals, the interspecies group uncertainty factor of 10-fold may be reduced. For example, the Agency policy for rat thyroid disruption as a mechanism that leads to follicular cell cancer is that a factor of unity is used instead of the traditional 10-fold factor (USEPA, 1998b).

A weak data base for a specific chemical in the *CAG* may be strengthened by rich data bases for the other members in the group. Thus, a science policy default factor of 3- or 10-fold is applied to account for deficiencies in or incompleteness of a database for the group as a whole and not on specific chemical members. A data gap requiring application of traditional uncertainty factor to a specific chemical may involve a study that has no bearing on the endpoint selected for *CAG* according to the common mechanism of toxicity. For example, the lack of a chronic toxicity study has no bearing on a cumulative risk assessment addressing a toxic effect that occurs from short-term exposure. Application of a 10-fold uncertainty factor because a chronic endpoint is extrapolated from a subchronic endpoint may not be justified if a chronic NOAEL can be estimated with reasonable confidence by comparing dose-response curves among chemicals, with subsequent extrapolation of a NOAEL (as discussed in section 5.2). A group uncertainty factor represents uncertainties that pertain to the *CAG* as a whole is based on the answers to questions such as-- Are the key studies used in the assessment available for most, if not all, members of the group?, or Are there concerns regarding potential interactions, but data are inadequate to establish the magnitude of interactions?

Only after the characteristics of the overall chemical grouping are considered should additional group uncertainty factors be applied to account for reliance on extrapolation and estimations and concerns about susceptible populations (e.g., infants and children; **see Chapter 6 for discussion of FQPA factor**). Exposure patterns must also be considered (populations affected, route and duration of exposure, and concurrence of exposure to multiple chemicals) before reaching a decision on an appropriate group uncertainty factor to be applied after accumulating risk.

**TABLE 5-1. Uncertainty Factors in Noncancer Risk Assessment: Shift in Traditional RfD/RfC Paradigm**[12]

| FACTOR | RfD/RfC Approach for Chemical Specific Assessments | Proposed Approach for Cumulative Assessments |
|---|---|---|
| **LOAEL to NOAEL ($UF_L$)** | ≤10-fold UF intended to account for uncertainty in identifying a (sub)threshold dose from an LOAEL, rather than a NOAEL. | ≤10-fold adjustment factor (AF) is used to estimate a NOAEL from a LOAEL for a specific chemical's PoD. This adjustment is **applied before accumulating** the hazard (see Section 5.2). |
| **Subchronic to Chronic ($UF_S$)** | ≤10-fold UF intended to account for uncertainty in extrapolating a NOAEL or LOAEL data from a less than chronic study to derive a lifetime hazard value. | ≤10-fold adjustment factor (AF) is used to estimate a chronic point of departure from a less than chronic data for a specific chemical's PoD. This adjustment is **applied before accumulating** the hazard (see section 5.2). |
| **Interhuman Variation (or intraspecies) ($UF_H$)** | ≤10-fold UF intended to account for variation in sensitivity among humans, and is considered to include toxicokinetic/dynamic processes. | 10-fold UF, intent is similar to single chemical assessment but is **applied as a group factor after accumulating** the hazard (see section 5.3). |
| **Experimental Animal to Human (interspecies) ($UF_A$)** | ≤10-fold UF intended to account for uncertainty in extrapolating data from laboratory animals to project human risk, considered to include toxicokinetic/dynamic processes. | 10-fold UF, intent is similar to single chemical assessment but is **applied as a group factor after accumulating** the hazard (see section 5.3). |
| **Incomplete Data Base to Complete Data Base ($UF_D$)** | ≤10-fold UF intended to account for the inability of any single study to adequately address all possible adverse outcomes. | ≤10-fold intended to account for any uncertainties surrounding the data base as a whole for the chemicals of interest. This factor is **applied as a group factor after accumulating** the hazard (see section 5.3). |
| **FQPA Safety Factor** | ≤10-fold factor that may be retained or revised in the risk characterization step and intended to provide sufficient | The FQPA safety factor is **applied in the risk characterization step**. It is applied only if it pertains to the common toxic effect and common mechanism of toxicity (see Chapter |

[12]In single chemical risk assessments, the NOAEL or benchmark dose for a critical effect is divided by uncertainty factors (UFs) to derive a RfD (for oral exposure) or RfC (for inhalation exposure). These factors are applied to account for the completeness of the entire data base in evaluating all potential endpoints at various critical life stages. In a cumulative risk assessment, these factors are applied differently or not at all based on the nature of the common toxic effect and common mechanism of toxicity as well as the exposure scenarios of interest.

## 5.4 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 pharmacokinetic (PBPK) models. This approach for dose extrapolation between species is not possible for most chemicals since the use of PBPK models requires extensive comparative metabolism and pharmacokinetic data which rarely exist. In the absence these data, estimates of human equivalent dose are based on science policy defaults. Currently, the derivation of an oral RfD, it is assumed that the dose administered orally is proportional to the delivered dose as well as to the biologically effective dose, and is equivalent across species on a body weight basis ($BW^1$). Thus, when dose is given in terms of dose per body weight, a 10-fold factor then is used as a default to account for the uncertainties in interspecies differences of pharmacokinetic and pharmacodynamic processes. In the RfC approach for exposure to gases and vapors, a dosimetric adjustment using the regional gas dose ratio (RGDR) is applied, and for particles, a regional deposited dose ratio (RDDR) is used as described in US EPA, 1994. The default 10-fold factor for interspecies differences is replaced by a factor of 3 with the RGDR or RDDR dosimetric adjustments.

To derive a human equivalent oral chronic dose for carcinogens from animal data, the default procedure has been to scale the lifetime average daily dose by 2/3 power of body weight ($W^{0.67}$) as a measure of differences in body surface area (USEPA, 1986b). The Agency has proposed in the cancer risk assessment guidelines to scale daily applied doses experienced for a lifetime in proportion to body weight raised to the 0.75 power ($W^{0.75}$), which reduces the interspecies default factor of 10 to a factor of 3 (USEPA, 1999d Draft). A discussion of the rationale and data supporting this scaling factor in cancer risk assessment can be found in U.S. EPA (1999d Draft). The Agency is moving in the direction of using the 0.75 power scaling factor in both cancer and noncancer assessments for chronic oral exposures.

Currently, EPA's Office of Research and Development (National Center for Environmental Assessment) is sponsoring an inter-agency dosimetry project to develop parallel mechanistic dosimetry models across inhalation, oral, and dermal routes and across different durations of exposure (acute versus chronic). When these models are finalized, this cumulative risk assessment guidance will be revised to incorporate these into route-to-route extrapolation as well as for the calculation of human equivalent doses. In the interim, OPP will continue to use the default of ($BW^1$) and the interspecies factor of 10 (which will be applied as a group uncertainty factor as discussed in section 5.3) for noncancer

toxicities for all routes and durations of exposure, realizing this is not the preferred approach. For cancer endpoints, the $W^{0.75}$ adjustment for oral and dermal exposures will be used, and the inhalation dosimetric adjustment for inhalation exposures as described in those guidelines (USEPA, 1999d Draft).

## 5.5 ROUTE-TO-ROUTE EXTRAPOLATION

FQPA requires that multiple route/pathway risk assessments for single and multiple chemicals be based on data that are valid, complete, and reliable, and that describe the nature of any toxic effects [FQPA Sec. 405(2)(D)]. Our ability to reasonably do this may be limited by a general lack of exposure data and toxicology data for the common toxic effect for all routes of concern, especially for the dermal and inhalation routes.

Route-to-route extrapolations allow one route (usually oral) to serve as a surrogate for another route provided adjustments are made for pharmacokinetic differences between the routes. Extrapolations based on PBPK models may be reliable enough for use in risk assessments, but they are rarely available. Simple extrapolations based on pharmacokinetic defaults are inherently unreliable because they assume that both routes are pharmacokinetically and toxicologically similar. For example, default-based oral → inhalation extrapolations frequently understate the hazard, and they cannot predict what the portal-of-entry effects will be.

Uncertainty in a cumulative risk assessment is compounded with each chemical that lacks route-specific data, and too much uncertainty can render an assessment meaningless. A default-based extrapolation should not be included in a risk assessment unless there is a reasonable rationale for using it (e.g., it is known that absorption is similar by both routes, and there are no portal-of-entry effects). Additional guidance on route-to-route extrapolations can be found in Whalan and Pettigrew (1998).

## 5.6 METHODS FOR ESTIMATING THE CUMULATIVE TOXICITY

At this point in the analysis, PoDs have been determined for each individual chemical, as discussed in the preceding sections. Before risks associated with cumulative exposure to the *CAG* can be estimated, a method needs to be selected which will be used to accommodate the difference in relative potencies of the chemicals in the *CAG* and for combining the PoDs across each chemical, route and pathway (as discussed in Chapter 6). This section presents the assumptions and possible methods for combining the PoDs in estimating the cumulative toxicity of the chemical group.

Although a biologically-based model which incorporates specific data on the kinetics of biological processes is the most desirable approach for combining the dose response data across the chemicals of interest in a cumulative risk assessment, these models are data intensive and are not yet standard methods. Thus, in lieu of a biologically-based model, this guidance will consider dose addition component-based mixture methods that have been used to estimate the toxicity of mixtures of chemicals. The basis of these approaches is discussed in detail in the Agency's *Guidance for Conducting Health Risk Assessment of Chemical Mixtures* (USEPA, 1986d,1999e Draft). It is acknowledged that this is an area where additional method development is needed.

### 5.6.1 Dose Addition Methods

**Dose addition** is considered an appropriate approach to cumulative risk assessment because it assumes that the chemicals of interest act on similar biological systems and elicit a common response (whereas response addition applies when components act on different systems or produce effects that do not influence each other). The mathematical definition of dose-addition requires a constant proportionality between the effectiveness of the chemicals being considered (Hertzberg et al., 1999). The application of dose addition is based on the assumption that the chemicals behave similarly in terms of the primary physiologic processes (absorption, metabolism, distribution, elimination), as well as the toxicologic processes. In other words, the chemicals of interest are assumed to behave as if they were dilutions of each other. When applying dose addition methods, the Agency has generally assumed no interactions among the chemicals (i.e., simple additivity) when there is no adequate interaction information (U.S. EPA, 1986d; 1999e Draft). The recent draft EPA *Guidance for Conducting Health Risk Assessment of Chemical Mixtures* (USEPA, 1999e Draft) and Hertzberg et.al., (1999) discusses evidence supporting the assumption of addivitity. The EPA guidance for chemical mixtures proposes approaches for incorporating data on chemical interactions among the chemical components of a mixture. This guidance defers to the 1999 Draft EPA chemical mixture guidelines on this point at this time.

Each of two dose addition approaches, the **Cumulative Margin-of-Exposure (Cumulative MOE) Method** and the **Relative Potency Factor (RPF) Method**, can be used to combine the toxicity of a *CAG*. Both approaches sum the doses for the chemicals of interest which have been normalized to a common scale. In the MOE approach, scaling is based

on deriving a unitless MOE, which is a chemical's PoD divided by the measured or estimated dose for a given route. In the RPF method, the potency of each chemical is expressed in terms of the potency of a index chemical. Scaling accounts for the different potencies among the group, which is used to convert exposures for all chemicals to equivalents of the index chemical's exposure. Both of these methods are described below.

❑ **Cumulative Margin of Exposure**[13]

The Agency's Office of Pesticide Programs has traditionally relied on the margin of exposure (MOE) approach as the preferred means for evaluating potential risk associated with acute dietary, occupational, and residential exposures to a single pesticide. Furthermore, the proposed revisions to the EPA guidelines for carcinogen risk assessment advocates the MOE approach for carcinogens that have mode of action data supportive of a nonlinear dose response extrapolation (USEPA, 1999d Draft), and the Agency is considering using the MOE approach as one way to harmonize noncancer and cancer risk assessment. OPP believes that the MOE approach for assessing the risks posed by single chemicals can be extended to assessing the cumulative risks of multiple chemicals.

The Cumulative MOE method combines individual MOEs for each chemical by route for a given duration (e.g., all acutes or all chronics). The advantage of this approach is that each chemical has stand-alone route-specific MOEs that are not influenced by any other route or chemical. An illustration of the Cumulative MOE method can be found in Appendix A. The basic steps in this method are as follows:

**Step 1.** An MOE is calculated for each chemical (A, B, ... n) and exposure pathway (dietary, drinking water,

[13]Another component-based approach used in the Agency for mixtures assessment is the Hazard Index (HI), which is also based on dose addition. A hazard quotient (HQ) is calculated for each chemical and route by dividing the dose (exposure) of a chemical by the maximum acceptable dose for that compound (typically an RfD), and then the HQ's are summed to calculate the HI. The Cumulative MOE is simply the reciprocal of the HI method, and thus only the MOE is presented for consideration.

residential and other non-dietary) and route (oral, dermal, and inhalation)

**Step 2.** The individual MOEs for each chemical and pathway are then combined to yield the following three ratios:

- ❑ The **Aggregate MOE** (**$MOE_A$**) which is the ratio for a single chemical by all applicable pathways.
- ❑ The **Cumulative Pathway MOE** (**$MOE_{Pathway}$**) which is the ratio for all chemicals by an individual pathway (e.g. drinking water).
- ❑ The **Cumulative Assessment Group MOE** (**$MOE_{CAG}$**) which is the ratio for all chemicals and pathways.

Exposure by route is determined on a daily basis for each individual and for each exposure scenario of interest in the population. The $MOE_{Pathways}$ for each route are combined over time and presented as a distribution. The $MOE_{CAG}$ values are compared against the group uncertainty factor.

❑ **The Relative Potency Factor (RPF) Method**

The **RPF** approach expresses the potency of each chemical in relation to the potency of another member in the group which has been selected as the index chemical. A relative potency factor is calculated for each route and chemical. For example, if compound A is judged to be one-tenth as toxic as the index compound, the RPF for compound A is 0.1. In the RPF approach,[14] the oral, dermal, and inhalation exposures for each chemical are expressed as exposure equivalents of the index chemical (i.e., the product of

[14]It should be noted that the Toxicity Equivalency Factor (TEF) approach is a type of Relative Potency Factor approach that has been used by the Agency as an interim measure to assess the toxicity of polychlorinated dibenzo-p-dioxins and the dibenzofurans (USEPA, 1989). Use of the TEF approach will likely be limited in assessing the cumulative risk associated with multiple chemicals that cause a common effect because a key assumption of the TEF approach is that all the chemical constituents in the mixture encompass and apply to all health endpoints and all exposure routes for each chemical member. Thus, the TEF approach is conceptually a more rigorous type of relative potency factor (RPF) approach.

the exposure and RPF for each route). These exposure equivalents are summed to obtain an estimate of total exposure by pathway/route in terms of the index chemical.

The index chemical must be well characterized (qualitatively and quantitatively) because any imprecision in its data is compounded for every chemical compared against it. If, for example, the index chemical's inhalation PoD is questionable, the index-adjusted inhalation exposures for every chemical in the grouping will be similarly questionable. This problem can be avoided by using different index chemicals for the different routes of interest (depending on the quality of data for that route). The basic steps in this method are as follows:

**Step 1:** Oral, dermal, and inhalation relative potency factors (RPFs) for each chemical and route in a grouping are derived as follows (the RPF for the index chemical is always 1):

Eq.5.2 $$RPF = PoD_{[Index\ Chemical]} \div PoD_{[Chemical\ n]}$$

**Step 2:** For a given day, each chemical's exposure pathway is adjusted by its RPF to express it as an Index Equivalent (IE) exposure. The dietary pathway is used here as an example.

Eq.5.3 $$Exposure_{IE}\ (dietary) = (Exposure_{n} \times RPF_{oral})$$

**Step 3:** For each pathway, the Index Equivalent Exposures ($Exposure_{IE}$) for all chemicals in the grouping are summed.

**Step 4:** Cumulative Pathway MOEs ($MOE_{Pathway}$) are calculated for each pathway. Since the total exposure for a given pathway is an equivalent of the index chemical exposure, it is compared to the index chemical's PoD for the appropriate route to derive an $MOE_{Pathway}$.

**Step 5:** All $MOE_{Pathway}$ values are then combined to yield a $MOE_{CAG}$

#### 5.6.1.1 Selection of a method

Estimating cumulative risk as described in Chapter 6, is extremely resource intensive. Thus, before one actually estimates the cumulative risk, one method should be selected to integrate the toxicity and exposure data. The Cumulative MOE and RPF approaches described above are both considered to be valid approaches for estimating cumulative risk. This guidance does not suggest that one of these methods is preferred over the other. Rather, both methods should yield similar results if the PoDs are the same and the UFs are applied as a group factor at the end of the process (as illustrated in the Appendix A). The choice of a method may be reflected in the inherent transparency of the analysis. Each has advantages and disadvantages, and should be selected on a case-by-case basis. Below are some factors to consider when selecting one of these approaches:

- *Common Mechanism:* Both the Cumulative MOE and RPF methods can be used to estimate the hazard of noncancer effects or cancer effects caused by chemicals whose mechanism of toxicity is consistent with a nonlinear dose-response relationship. Mechanisms consistent with low dose linearity can be summed using the RPF approach. In this case, the slope of the dose-response curve of each chemical are summed.

- *Dose Response:* Because the RPF approach is based on an index chemical within the *CAG*, this approach should ideally be implemented only when good quantitative dose-response data for the route and durations of interest are available. The RPF method is more dependent than the Cumulative MOE approach on the assumption of parallel dose-response curves among the chemicals in the group. However, for groups with a well characterized index chemical and with a well supported assumption of similar mechanism, the RPF may be preferred to the Cumulative MOE approach because the common mechanism hazard can be inferred directly from the index chemical's dose-response relationship, and a qualitative index of concern is not necessary.

- *Routes of Extrapolation:* Although both approaches

(Cumulative MOE and RPF) are hindered by route-to-route extrapolations, this is considered more of a limitation in the RPF approach. If there is uncertainty about the index chemical's potency for an effect via a specific route, that uncertainty will be compounded with every chemical in the grouping. Thus, the assessment may imply a precision that is not supported by the data. (See section 5.4 for discussion of route-to-route extrapolation). In these situations, the Cumulative MOE method may be preferred because any extrapolation error is limited to one chemical's MOE for the route with the extrapolated data. If route-to-route extrapolation is the only way of providing a toxicological value, and there is reason to believe it is not sufficiently reliable, then that route should not be included in the cumulative risk assessment.

It should be emphasized that application of the Cumulative MOE method or the RPF method in the cumulative risk assessment is viewed as a work-in-progress in that the methods to estimate the cumulative toxicity need to be refined, particularly to accommodate the pharmacokinetic and temporal aspects of the data.

## 5.7 DOSE-RESPONSE CHARACTERIZATION

As with hazard and exposure characterization, the dose-response characterization serves the dual purposes of presenting a technical characterization of the dose-response analysis and supporting the overall risk characterization (as described in Chapter 6).

Dose-response characterization presents the results of analyses of the dose-response data. The dose response for the *CAG* should be characterized in sufficient detail to aid in evaluation and interpretation of the cumulative risk values and potential public health impact. Where a mechanism of toxicity or other feature of the biology has been identified that has special implications for exposure, differential effects by sex, or other concerns for sensitive subpopulations, these are explained. Uncertainty analyses, qualitative and quantitative, if possible, are highlighted in the characterization. The dose-response characterization routinely includes the following, as appropriate for the data available:

- ❑ identification of the kinds of data available for analysis of dose and response, and for dose-response assessment,

- ❑ results of assessment as above,
- ❑ explanation of analyses in terms of quality of data available,

- ❑ selection of studies/species/response and dose metrics for assessment,
- ❑ justification and rationale for combining the responses of the *CAG*,
- ❑ discussion of implications of variability in human susceptibility, including for susceptible subpopulation,
- ❑ applicability of results to varying exposure scenarios--issues of route of exposure, dose rate, frequency, and duration,
- ❑ rationale for assuming dose additivity or departure from additivity,
- ❑ discussion of the experimental variability, strengths and uncertainties, and sensitivity associated with assumptions, adjustments, and defaults related to the approach for quantifying cumulative risk.

# 6 ESTIMATING CUMULATIVE EXPOSURE AND RISK [TO BE COMPLETED] [PLEASE NOTE THAT THE EXPOSURE COMPONENT OF THE CUMULATIVE RISK ASSESSMENT PROCESS IS STILL BEING DEVELOPED. A BRIEF DISCUSSION IS PROVIDED BELOW FOR WHAT THIS CHAPTER WILL COVER.]

At this point in the cumulative risk assessment process, information has been gathered identifying potential exposures. The route and duration of exposures have been reconciled with the toxicological data; and the magnitude, frequency, and duration of exposures as well as co-occurrences have been established for developing exposure scenarios (Chapter 4). The points of departures for the toxicological common endpoint and a method for estimating the common toxicity of the *CAG* has been identified (Chapter 5).

This chapter will describe how cumulative risk is calculated by maintaining the appropriate spatial (e.g, location and type of home or institution; urbanization, watershed or aquifer characteristics), temporal (e.g., duration, frequency, and seasonality of exposure, frequency of residential or institutional pest control), and demographic (e.g., age, gender, reproductive status, ethnicity, behaviors) linkages of exposure and toxicological data for the chemical group. As in aggregate risk assessment (USEPA, 1999b), cumulative risk assessment will be based on establishing reasonable exposure scenarios for a hypothetical individual over a specific interval of time. These scenarios will help evaluate populations of concern, critical time frames, and routes of exposure that must be linked to the common toxic effect. In the case of cumulative risk assessment, characterization of the potential for concurrent exposure must be done with multiple chemicals by multiple pathways of exposure. There will be different linkages and co-variances in cumulative risk assessment that must be conserved, but which have not been considered in previous single chemical analyses (i.e., one cannot simply sum the aggregate risks for the group of chemicals). This Chapter will also discuss the interpretation and characterization of a cumulative risk assessment.

At this point in the process, particular attention to the following factors is important:

- ❏ An individual's exposure must be matched with relevant toxicological exposures (or doses) in terms of route and duration.

- ❏ If data permit, exposures from a variety of potential routes must be combined over comparable time frames, defining a range of possible exposures.

- ❑ The integrity of the exposure concerning the hypothetical individual must be maintained throughout the cumulative risk assessment (i.e., same individual at the same time, in the same place, under the same geographic conditions). This approach will permit better estimation of overlapping exposures from varying sources. At this time, data will rarely be available to permit evaluation of the following factors:

  - ✔ Uses among products and product types are linked and must be considered in appropriate combination to reflect the linkages,

  - ✔ Relationship of the exposures by routes must be maintained in order to develop as realistic a representation of a possible exposure pattern as possible.

  - ✔ Geographic and seasonal distribution of sources of exposure must also be maintained.

## 6.1 CALCULATING CUMULATIVE EXPOSURE AND RISK

Major considerations regarding the estimation of exposure to chemicals by different routes and the feasibility of combining the assessments will be described. Currently, the limiting factor to conducting multiroute exposure assessments is the availability of exposure data. Raised previously in Chapter 4 of this document, the lack of exposure data is the major driver in selecting the approach to cumulative exposure and risk assessment recommended as practicable at this time. Given the current state of available data, the three major pathways of exposure should be treated separately because the disparities in the quality and quantity of the data available may obscure patterns of exposure and source contribution that could be determined from the cumulative exposure and risk assessments.

The ability to conduct a detailed dietary - food assessment for multiple chemicals appears to be possible for at least some subset of food and chemical combinations for which multi-analyte monitoring data have been performed. An example of these data is that collected by the USDA PDP program. Data generated by this program permit identification of residues of several pesticides of a chemical class in the same sample. As a consequence, an estimate of co-occurrence of residues can be drawn directly from the samples without the need for inference from secondary data sources. The extent to which this process is practical will be limited by the amount of high quality multi-residue monitoring data that are available.

Current treatment of drinking water exposure and risk relies upon the back calculation of an acceptable pesticide concentration in drinking water from a predetermined acceptable level of exposure, and an estimate of the amount of the acceptable exposure already taken by dietary - food and residential sources of exposure. The back calculated value or Drinking Water Level of Comparison (DWLOC) is compared to the outputs of screening level models to determine if a risk concern is anticipated. This back calculation approach is problematic within the setting of a multi-chemical assessment. Combination of coarse screening level values such as those used in the current process for estimating drinking water exposures may result in the compounding of conservative assumptions that would result in an unuseful overestimate of likely exposure from drinking water. At this time, drinking water estimates should remain on a chemical-by-chemical basis. At such time as data on finished drinking water that are of comparable quality to monitoring data in foods and are reflective of regional and seasonal variation become available, combination with a cumulative dietary - food assessment may be possible.

Because most residential and other nonoccupational assessments rely upon screening level assessments at this time and little information is currently available on use patterns, multichemical assessments for this pathway must also be approached with caution. The outcome of such an assessment is anticipated to be qualitatively different (i.e., of greater uncertainty due to the use of screening level exposure estimates and limited data) from the dietary - food assessment and therefore should not be combined with it. However, some data are available to support performance of a cumulative residential exposure and risk assessment and OPP is aware of survey efforts underway to determine in detail the use patterns and habits of the US public. This information will expand the capability to conduct screening level assessments for multiple sources of chemicals by this pathway. Such an assessment may be useful in identifying use patterns of concern and identifying potential areas for risk mitigation.

The ultimate goals of the cumulative assessment are as follows: 1) to define likely exposure patterns for the population of interest; 2) to identify the major sources of exposure and drivers of the associated risk; and 3) to assist in the development of mitigation strategies to improve the overall risk profile. To support these goals, the risk assessor will need to provide the exposure and risk estimates for a variety of subsets of data, including evaluation of regional and temporal assessments. Exposure assessments should be presented as a distribution of exposure by each route (oral, dermal inhalation), and by each major pathway (dietary, residential, water) as feasible based upon available data. In addition, the total exposure and associated risk should be presented. Within each pathway, the route of exposure, the total distribution of exposures, and the relative contribution of each chemical contributor to exposure must also

be discernible.

As is evident from the discussion, a multi-chemical cumulative assessment cannot be reasonably performed by summing single chemical, aggregate assessments. The cumulative assessment must reflect linkages and co-occurrences of use between competing chemicals. These factors cannot be established between singly conducted assessments. The cumulative assessment must be conducted beginning from the base data and cannot be reconstituted from preexisting single chemical aggregate assessments. The single chemical aggregate assessments should be conducted first for each pesticide under consideration for inclusion in the cumulative exposure and risk assessments. The single chemical aggregate assessments will be used to inform the risk assessor in designing the cumulative assessment and for identifying negligible pesticide/use combinations that may be excluded. The relative availability, quantity and quality of data for estimating cumulative exposures will drive the ability to conduct cumulative risk assessments.

## 6.2 RISK CHARACTERIZATION OF THE CUMULATIVE RISK ASSESSMENT

Risk characterization is an integrative process that brings together the assessments and characterizations of hazard, dose response, and exposure to yield risk estimates for the exposure scenarios of interest and to present the major results of the risk assessment. The Risk Characterization Summary is 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, as do other decision-making analyses of economic, social, or technology issues. The integrative analysis typically should identify the chemical drivers or pathway of the cumulative risk and exposure scenarios.

Choices made about using assumptions and uncertainties and key data used in the assessment are explicitly discussed in the course of the analysis. Choices or decisions that represent significant issues should be highlighted in the summary.

### 6.2.1 Interpretation of Risk Values

The outcome of a cumulative risk assessment will **not** be a single estimate of risk. Rather, it will contain a series of estimates, some represented as ranges reflecting risk values of differing proportions of (sub)populations exposed to the possibility of adverse health effects resulting from different time scales of exposure. As presented in Chapter 5, the values will be unitless cumulative MOEs or a comparison to an

index chemical in the *CAG*. The interpretation of a cumulative risk outcome will of necessity be different than for a single chemical assessment. Implicit in the cumulative risk estimate will be the uncertainties attendant from multiple datasets. Therefore, 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 factor (section 5.3). The results of a cumulative MOE or relative potency factor approaches must be carefully interpreted in the context of the supporting information, attendant uncertainties, and consideration of the regulatory health endpoints upon which the aggregate or chemical specific assessments are based. The Agency is establishing an intra-agency workgroup to prepare interim risk management guidance for determining the acceptability of a calculated margin of exposure to compliment the EPA's new cancer risk assessment guidelines (USEPA, 1999d). The cumulative risk guidance will drawn upon that effort, as appropriate, for multiple chemicals, in aiding in the interpretation of a cumulative $MOE_{CAG}$.

### 6.2.2 FQPA Safety Factor

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....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." Current determination of the FQPA safety factor is made for individual chemicals when making a tolerance decision. The FQPA safety factor, however, must be re-visited in the cumulative assessment, where it is considered as a single composite factor applied to the group of chemicals (not individual members) in the risk characterization step as a risk management decision. The determination of the composite group FQPA safety factor is judged in light of the common toxic effect and mechanism of toxicity for that group of chemicals. It includes the

evaluation of data on induction of any potential cumulative effects after pre- or postnatal exposures compared to adult exposures. Conclusions about retention or revision of the FQPA safety factor for an individual pesticide may be different for the cumulative assessment chemical group. For example:

- ❏ An FQPA safety factor may not be retained in whole or in part for the cumulative risk chemical group in cases where extensive data on the group as a whole allow sound and reliable comparison of fetal, neonatal and adult effects (relevant to the common mechanism), although data may be limited for one or a few of the chemical members which did have an FQPA safety factor applied to their RfDs in whole or in part because the presence of increased sensitivity in the young to the end point that reflects the common mechanism.

- ❏ An FQPA factor may not have been retained in whole or in part for a specific chemical assessment because the potential for increased sensitivity associated with pre- or post- natal exposures was not apparent. However, when the evaluation was conducted for the chemical group as a whole, a number of other chemicals in the group did have the FQPA safety factor retained, in whole or in part. On balance, the decision could be made to retain the FQPA safety factor for the group.

Although guidance on *Determination of the Appropriate FQPA Safety Factor(s) for use in the Tolerance-Setting Process* (USEPA, 1999f) does not directly address the cumulative risk assessment process, useful guidance is still provided on the considerations to be addressed when making judgments about the FQPA safety factor.

### 6.2.3 Characterizing the Uncertainties

Uncertainties are generally encountered in any risk assessment process. In the case of cumulative risk assessment, uncertainties for the chemical member group can be appreciable based on the nature, amount, and quality of data. Thus, the risk characterization must include a discussion of what is missing or poorly understood, in order to convey a clear sense of the quality and degree of confidence in the resulting risk values.

### 6.2.4 Content of Cumulative Risk Characterization Summary

Overall, the risk characterization routinely includes the following, capturing the important items covered in hazard, dose response, and exposure characterization:

- ❏ primary conclusions about hazard, dose response, and exposure, including plausible alternatives,
- ❏ nature of key supporting information and analytical methods,
- ❏ risk estimates and their attendant uncertainties, including key uses of default assumptions when data are missing or uncertain,
- ❏ statement of the extent of extrapolation of risk estimates from observed data to exposure levels of interest (i.e., margin of exposure) and its implications for certainty or uncertainty in quantifying risk,
- ❏ significant strengths and limitations of the data and analyses, including any major peer reviewers' issues,
- ❏ appropriate comparison with similar EPA risk analyses or common risks with which people may be familiar, and
- ❏ comparison with assessments of the same problem by another organization.

# 7 RESEARCH NEEDS [TO BE DEVELOPED]

**[TO BE DEVELOPED]**

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## GLOSSARY [TO BE COMPLETED]

**Absorption**: the process of movement of a chemical substance from the site of exposure (gastrointestinal tract, skin, lung) into the systemic circulatory system.

**Active Ingredient:** The chemical component of a pesticide formulation or end-use product that is intended to act on the pest (i.e., the biologically active chemical agent in a pesticide product).

**Additivity:** When the "effect" of the combination is estimated by the sum of the exposure levels or the effects of the individual chemicals. The sum may be a weighted sum (see "dose addition") or a conditional sum (see "response addition").

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

**Analog(s):** Analog is a generic term used to describe substances that are chemically closely related. Structural analogs are substances that have similar or nearly identical molecular structures. Structural analogs may or may not have similar or identical biological processes.

**Antagonism:** The ability of a substance to prevent or interfere with another substance from interacting with its biological targets, thereby reducing or preventing its toxicity.

**Benchmark Dose (BMD):** A statistical lower confidence limit on the dose producing a predetermined level of change in adverse response compared with background response. BMD is derived by fitting a mathematical model to the dose-response data.

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

**Common Mechanism of Toxicity:** Common mechanism of toxicity pertains to two or more pesticide chemicals or other substances that cause a common toxic effect(s) to human health by the same, or essentially the same, sequence of major biochemical events. Hence, the underlying basis of the toxicity is the same, or essentially the same, for each chemical.

**Common Toxic Effect:** A pesticide and another substance that are known to cause the same toxic effect in or at the same anatomical or physiological site or locus (e.g., the same organ or tissue) are said to cause a common toxic effect. Thus, a toxic effect observed in studies involving animals or humans exposed to a pesticide chemical is considered common with a toxic effect caused by another chemical if there is concordance with both site and nature of the effect.

**Cumulative Dose:** The amount of multiple (two or more) substances which share a common mechanism of toxicity available for interaction with biological targets from multiple routes of exposure.

**Cumulative Exposure Assessment:** A process for developing an estimate of the extent to which a defined population is exposed to two or more chemicals which share a common mechanism of toxicity by all relevant routes and from all relevant sources.

**Cumulative Toxicity or Toxic Effect:** A cumulative toxic effect(s) is the net change in magnitude of a common toxic effect(s) resulting from exposure to two or more substances that cause the common toxic effect(s) from a common mechanism, relative to the magnitude of the common toxic effect(s) caused by exposure to any of the substances individually.

**Cumulative Risk:** For the purpose of implementation of FFDCA as amended by FQPA, cumulative risk is the likelihood for the cumulation of a common toxic effect resulting from all routes of exposure to substances sharing a common mechanism of toxicity.

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

**Dose Additivity:** When the effect of the combination is the effect expected from the equivalent dose of an index chemical. The equivalent dose is the sum of component doses scaled by their potency relative to the index chemical

**$ED_{10}$:** Central estimate on a dose associated with 10% extra risk adjusted for background.

**Exposure:** Contact of a substance with the outer boundary of an organism. Exposure is quantified as the concentration of the agent in the medium in contact integrated over the time duration of that contact.

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

**Exposure Scenario:** A combination of facts, assumptions, and inferences that define a discrete situation or activity where potential exposures may occur.

**Hazard Index:** The primary method for component-based risk assessment of noncancer toxicity is the Hazard Index (HI), which is based on dose addition, and is defined as the weighted sum of the exposure measures for the mixture component chemicals.

**Index Chemical:** The chemical selected as the basis for standardization of toxicity of components in a mixture. The index chemical must have a clearly defined dose-response relationship.

**Inhibition:** When one substance does not have a toxic effect on a certain organ system, but when added to a toxic chemical, it makes the latter less toxic.

**Key Event:** An empirically observed precursor consistent with a mechanism of toxicity.

**$LED_{10}$** : The 95% lower confidence limit on a dose associated with 10% extra risk adjusted for background.

**Margin of Exposure:** The point of departure divided by a human environmental exposure(s) of interest, actual or hypothetical.

**Mechanism of Toxicity:** Mechanism of toxicity is defined as the major steps leading to an adverse health effect following interaction of a substance with biological sites. 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 that are required in being able to describe a mechanism of toxicity.

**Pathway of Exposure:** The physical course a chemical or pollutant takes from the source to the organism exposed..

**Point of Departure:** Derived from observed data--for incidence, or for key event(s)--is estimated to mark the beginning of extrapolation. This is a point that is either a data point or an estimated point that can be considered to be in the range of observation, without significant extrapolation. Depending on the kind of data available and the purpose of the analysis, there are differing procedures for estimating the point of

departure.

**Potential Dose:** The amount of a chemical contained in material ingested, air breathed, or bulk material applied to the skin.

**Route of Exposure:** The way a chemical enters an organism after contact, e.g., ingestion, inhalation, or dermal absorption. Note that all three routes of exposure can occur within an exposure pathway. A pathway is not route specific.

**Site of Toxic Action:** The physiological site(s) where a substance interacts with its biological target(s) leading to a toxic effect(s).

**Structure-Activity Relationships:** Substances that contain or are bioactivated to the same toxophore may cause a common toxic effect by a common mechanism. The relative toxic efficacy and potency among the substances in their ability to cause the toxic effect may vary substantially. Differences in potency or efficacy are directly related to the specific or incremental structural differences between the substances and the influence these differences have on the ability of the toxophore to reach and interact with its biomolecular site of action, and on the intrinsic abilities of the substances to cause the effect. The ability of two or more structurally-related substances to cause a common toxic effect and the influence that their structural differences have on toxic efficacy and potency are referred to as structure-activity relationships.

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

**Toxic Action:** The interaction with biological targets that leads to a toxic effect.

**Toxic Effect:** An effect known (or reasonably expected) to occur in humans that results from exposure to a chemical substance and that will or can reasonably be expected to endanger or adversely affect quality of life.

**Toxic Endpoint:** A quantitative expression of a toxic effect occurring at a given level of exposure. For example, acute lethality is a toxic effect, an $LD_{50}$ value (median lethal dose) is the toxic endpoint that pertains to the effect.

**Toxic Potency:** The magnitude of the toxic effect that results from a given exposure. Relative potency refers to comparisons of individual potencies of chemicals in causing a common toxic effect at the same magnitude (e.g, $LD_{50}$, $ED_{50}$) by a common mechanism.

**Weight-of-Evidence:** Weight-of-evidence refers to a qualitative scientific evaluation of a chemical substance for a specific purpose. A weight of evidence evaluation involves a detailed analyses of several or more data elements, such as data from different toxicity tests, pharmacokinetic data, and chemistry data followed by a conclusion in which a hypotheses is developed, or selected from previous hypotheses.

# APPENDIX A: CASE STUDY: INHIBITION OF CHOLINESTERASE AND CHOLINERGIC EFFECTS

**[NOTE: This case study will be based on a short duration exposure scenario and thus the toxicity of interest will be combined in a 90-Day Risk Assessment.]**

## TOXICITY PROFILES OF ORGANPHOSPHORUS CHEMICALS A, B, and C

## 1. HAZARD AND DOSE RESPONSE ASSESSMENT AND CHARACTERIZATION

### 1.1 COMMON MECHANISM OF TOXICITY

The Agency recently concluded that organophosphorus pesticides (OPs) act by a common mechanism of toxicity (*A Common Mechanism of Toxicity: The Organophosphorus Pesticides*, Office of Pesticide Programs, USEPA, 1999). The toxicity of this class of chemicals is manifested through inhibition of acetylcholinesterase (AChE), followed sequentially by an accumulation of acetylcholine at the preganglionic or postganglionic junction. A continuation of uninterrupted neurotransmission (resulting from the inability of AChE to break down acetylcholine and terminate transmission), which is sustained results in the expression of a cholinergic response. Cholinergic responses are manifested as, for example, salivation, miosis, nausea, vomiting, frequent urination and, in the extreme, convulsions, coma, and death. Examination of the structural features of the registered organophosphorus pesticides shows that all can be expected to inhibit AChE by phosphorylation, either without further metabolism or following activation to an oxon. Despite potential differences and uncertainties regarding the toxicological characteristics (e.g., relative distribution and metabolic pathways, pattern of clinical signs, effects on specific receptor sites, disruption of the parasympathetic, sympathetic, or central nervous system), their common elicitation of cholinergic effects and inhibition of cholinesterase in blood and brain define a unity more compelling than their differences.

Although there may be differences in the pattern of toxicity elicited among the OP pesticides, an expert workgroup convened by the Risk Sciences Institute (RSI) of the International Life Sciences Institute (ILSI) concluded that a scientific basis currently did not exist for subgrouping the OP pesticides (Mileson et al., 1998). Briefly, the rationale for this conclusion was that all but a few OP pesticides require metabolic activation, evidence does not exist that some operate by a different mechanism of action nor that they are activated or deactivated by different enzymes, and available evidence does not indicate

exclusive distribution to or action on one tissue or another.

Whereas neuronal activity is associated with acetylcholinesterase activity and can be affected by binding of the enzyme to an OP pesticide, an OP pesticide may also inhibit butyl cholinesterase (BuChE), an enzyme which occurs in blood and the nervous system and for which no proven inherent physiological function is known. Although the ratio of BuChE to AChE varies among species, in general, most OP's inhibit both of these esterases.

In the example case studies that follow, cholinesterase inhibition (ChEI) is consistently the most sensitive endpoint measured in studies with Chemical A, B and C. No other effects occur in any species (rats, mice, rabbits, dogs, monkeys) at or below doses which inhibit cholinesterase. Therefore, it is appropriate to use data involving ChEI for a cumulative risk assessment on chemicals A, B, and C. Plasma and red blood cell ChEI, although in themselves are not considered adverse effects, are considered as surrogates for potential ChEI in peripheral tissues or in some cases, for brain tissue (USEPA, 1998c). Plasma and RBC ChEI, therefore, are included as effects to consider for selection of a common endpoint for a cumulative risk assessment. The toxicity profiles presented below present data on other features of the data base on each of the chemicals that need to be considered before selecting specific endpoints to be used in a cumulative risk assessment and adjustment factors that may need to be applied to the endpoints. The case studies also are intended to illustrate the elements of hazard and dose-response assessment and characterization components of the cumulative risk assessment process that should be addressed when presenting hazard information for incorporation in a cumulative risk assessment.

The evaluations presented on the chemicals A, B, and C are intended to illustrate elements of hazard assessment and characterization that should be addressed when preparing a cumulative risk assessment. The information provided does not represent an accurate or definitive review of any specific chemical.

## 1.2. CHEMICAL A

### 1.2.1. ORAL TOXICITY

#### 1.2.1.1. Endpoint/Species/Sex Selection for Cumulating Risk

Data provided in Table 1A show that plasma and RBC inhibition occurs at equivalent dose levels during a 90-day exposure period. On the other hand, brain cholinesterase activity is depressed following 90-day exposures at higher dose-levels than those required to inhibit plasma or RBC cholinesterase activity (10-100X). These data and data from additional studies with other species show that selection of either plasma or RBC cholinesterase inhibition (ChEI) is an appropriate endpoint to use when performing risk assessments. For purposes of the current assessment, data on RBC ChEI is presented for incorporation in a cumulative risk assessment since this endpoint is a common endpoint for Chemicals A, B, and C.

**Table 1A: Comparison of Blood, RBC, and Brain Cholinesterase Inhibition in Female Rats for Chemical A**

| STUDY | PLASMA NOAEL/LOAEL mg/kg/day | RBC NOAEL/LOAEL mg/kg/day | BRAIN NOAEL/LOAEL mg/kg/day |
|---|---|---|---|
| **90-Day Rat Feeding** | 0.04/0.4 | 0.04/0.4 | 0.4/9.0 |
| **90-Rat Neurotox. Feeding** | 0.019/1.9 | 0.019/1.9 | 1.9/19 |
| **28-Day Rat Feeding** | 0.02/2.4 | 0.02/2.4 | 2.4/23.1 |

Table 2A provides data generated from studies involving rats, dogs, rabbits, and monkeys. Among the species investigated for inhibition of RBC cholinesterase following exposure to Chemical A, the rat appears to be the species for selecting NOAELs, LOAELs,or $LED_{10}$s for quantiying potential cumulative risks.

**Table 2A: RBC Cholinesterase Inhibition in Various Species-Chemical A***

| STUDY | NOAEL/LOAEL (mg/kg/day) | COMMENTS |
|---|---|---|
| **90-day dog** | 0.034/.02 (M) and 0.021/5.6 (F) | |
| **90-day rat neurotoxicity** | 0.017/1.7 (M) and 0.019/1.9 (F) | |
| **Dog 1-Yr feeding** | >50/>50 (M) and <1/1 (F) | minimal inhibition at 1 mg/kg/day in females |
| **Dog 4-week feeding** | 0.0034/0.02 (M) and 0.021/5.6 (F) | minimal ChEI at 0.02 mg/kg/day in males |
| **Monkey 104-week feeding** | 0.05/0.5 (M&F) mg/kg/day | |
| **Rat 28-day feeding** | 0.02/2.3 (M&F) | |

M = males; F = females

The data on RBC ChEI reported for male and female rats (and other species) do not consistently show one sex to be more sensitive than the other when LOAELs are compared. Further analysis reveals that, although LOAELs for male and female rats may be equivalent, the magnitude of cholinesterase inhibition is markedly greater in female rats than male rats at the LOAELs. The data reported from two six-week studies also suggest that female rats may be more sensitive to the cholinesterase inhibiting properties of Chemical A since LOAELs reported for RBC AChEI are well below those reported for male rats. Finally, the 90-day neurotoxicity feeding study, an additional 90-day rat feeding study, a 6-week rat pilot feeding study, and a 28-day rat feeding study indicate that brain cholinesterase inhibition in females occurs at dose-levels substantially below those which inhibit brain acetyl cholinesterase in male rats. Since the 28-day and 6-week exposure intervals contribute to hazard potential over a 90-day period and because the magnitude of cholinesterase inhibition is greater in females than males administered comparable dosages of Chemical A, use of data from female rats is appropriate.

#### 1.2.1.2. Increased Sensitivity Associated with Pre- and Postnatal Exposures

In a 2-generation reproduction feeding study, parental toxicity (decreased body weight gain) was observed at a LOAEL of 7.63 mg/kg/day; offspring toxicity (decreased pup weight) was observed at LOAEL of 7.63 mg/kg/day.

In a developmental toxicity study (rat), maternal toxicity (decreased body weight gain) occurred at a LOAEL of 100 mg/kg/day; developmental toxicity (decreased pup weight) was observed at LOAEL of 100 mg/kg/day. Body weight gain decreases have often been shown to accompany depressions of cholinesterase activity in adult animals. It appears fetal and neonatal toxicity (body weight loss and, possibly, cholinesterase depression) occurs only at dose levels that affect maternal animals. In a developmental toxicity in rabbits, no effects on offspring were noted at a dose of 100 mg/kg/day although mortality occurred in maternal animals at this dosage. No other data are available that suggest an increase in sensitivity of animals exposed pre- or postnatally when compared with adult animals.

#### 1.2.1.3. Time to a Steady State of Inhibition

Studies of varying duration (acute, 28-day, 90-day, 2-year) using female rats show that inhibition of RBC cholinesterase reaches a plateau by 90 days or sooner. NOAELs of 0.02-0.05 mg/kg for all observable effects were reported in these studies. Other studies show that a steady state of ChEI is attained at earlier times. In a 6-week pilot feeding study, a plateau for AChEI was reached by 24-days (NOAEL/LOAEL 0.05/0.2 mg/kg/day). In a standard 6-week feeding study a plateau for AChEI was reached by 42 days (NOAEL/LOAEL 0.05/0.2 mg/kg/day). In a second 6 week feeding study ChEI was at or near a plateau by 14-15 days (NOAEL/LOAEL 0.05/0.19 mg/kg/day). Since there is evidence to support the attainment of maximum RBC AChEI after 14 days of continuous exposure to Chemical A, data generated from studies of 14 days' duration are relevant for exposures of up to 90-days or longer.

#### 1.2.1.4. Dose Response

A clear dose-response relationship can not be shown for Chemical A as illustrated in Table 3A because saturation of the cholinesterase enzyme reaches a plateau at a low dose that is the minimal dose that leads to ChEI. Data from the 28-day study (Table 3A) on RBC AChEI shows the difficulty in comparing increases in responses with increasing dosages. Other studies comprising the data base on Chemical A show inhibition reached a plateau at the lowest effective dose or only at the high-dose tested and there are no clear dose-responses.

**Table 3A: Dose-Response for RBC AChEI in Female Rats Administered Chemical A for 28-Days**

| | Dose (mg/kg/day) | | | |
|---|---|---|---|---|
| | 0.02 | 2.4 | 23.1 | 210 |
| **% ChEI** | 32 (NS)* | 81 | 94 | 96 |

*NS- not significant

#### 1.2.1.5. Selection of Oral PoD

Since the endpoint of concern (RBC AChEI) is a response representing continuous data and because adequate dose-response data are not available for applying a benchmark dose analysis, the appropriate point of departure to apply for quantification in a cumulative risk assessment is the NOAEL (0.02 mg/kg/day) selected from the studies presented in Table 4A.

Data from a 90-day neurotoxicity study and a 28-day feeding study in female rats are appropriate for use in a 90-day cumulative risk assessment. Data from the 28-day study show RBC AChEI can reach the level of inhibition noted at 90-days since NOAELs/LOAELs are comparable (Table 4A). Both are well conducted studies that contained no apparent deficiencies. Other studies (e.g., a 90-day feeding and a six week pilot study), although useful for evaluating the time period required to reach a plateau of AChEI, suggest different NOAELs or LOAELs, but the quality and reliability of the additional studies is questionable since a) LOAELs are not supported by studies of longer duration, b) purity of the chemical is unknown, c) the methodology for analyses or processing of samples is unknown, and/or d) reporting of

findings is incomplete.

**Table 4A: NOAEL's and LOAEL's for RBC AChEI Identified in Key Female Rat Studies**

| STUDY | NOAEL/LOAEL mg/kg/day |
|---|---|
| **90-Day Neurotoxicity Feeding** | 0.019/1.9 |
| **28-Day Feeding** | 0.02/2.4 |



### 1.2.2. DERMAL TOXICITY

There are potential residential dermal exposures to Chemical A, but there are no acceptable dermal toxicity studies available on Chemical A that measured ChEI. Dermal absorption is estimated to be equivalent to oral absorption since the results of a 21-day dermal study with rabbits and a developmental toxicity study with rabbits showed that 100 mg/kg/day was lethal in both studies. Thus, dermal absorption should be considered to be 100% (i.e., equivalent to oral absorption).

### 1.2.3. INHALATION TOXICITY

There are potential residential exposures to Chemical A by the inhalation route.

ChEI was measured in a 21-day inhalation study performed with male and female rats. Concentrations administered were 0.1, 1, 10, or 100 micrograms/L. At the lowest dose, RBC cholinesterase activity was depressed by 56 % in female rats. The HIARC determined that the lack of a NOAEL in the study warranted assignment of a an adjustment factor of 3X to the low concentration. Thus, the concentration to be used for quantification of aggregate or cumulative risk estimates is 0.00003 mg/L/day.

### 1.2.4. OTHER CONSIDERATIONS

#### 1.2.4.1. Pharmacokinetic/Dynamic Interactions

There are no data available to evaluate PK/PD interactions between Chemical A and any other chemical.

#### 1.2.4.2. Comparison of the PoD Selected for Cumulative Risk Assessments with the NOAEL Used to Establish the RfD for Chemical A

The NOAEL used to establish the chronic dietary RfD for Chemical A is the same as the NOAEL identified for use in cumulative risk assessments involving chemical A (0.02 mg/kg/day).

#### 1.2.4.3. Neurotoxicity Findings

In studies performed with Chemical A, clinical and/or cholinergic signs were observed only at dose levels which equaled or were greater than the dose levels that were shown to inhibit brain cholinesterase activity. Since brain ChEI was reported following exposures 10-fold - 100-fold greater than exposures which resulted in RBC AChEI, neurotoxicity is not expected to result if exposures to Chemicals A, B, and C are limited to levels which do not result in RBC or brain ChEI.

### 1.2.5. WEIGHT-OF-THE-EVIDENCE

Data on cholinesterase inhibition are extensive and produce a high level of confidence that cholinesterase inhibition does not occur at a dose level below 0.02 mg/kg/day in adult animals administered Chemical A by the oral route. No data are available regarding ChEI inhibition in fetuses or neonates but other information supports a conclusion that fetal or neonatal animals are not more sensitive to the effects of Chemical A than are adults. Neurotoxicity evaluations are limited to adult animals, but based on results of such evaluations in adult animals (neurotoxicity observed at doses well above LOAELs for ChEI) and evidence that minimal toxicity is observed in fetuses or neonates (no clinical signs of toxicity) at maternally toxic doses, it does not appear that young animals or animals exposed *in utero* are more sensitive than adults to the effects of Chemical A. Dermal toxicity data are limited for Chemical A. Use of a dermal absorption factor of 100% is used in the absence of actual absorbtion data. A reliable NOAEL for inhalation toxicity has not been established for Chemical A. Although an adjustment factor has been applied to account for the use of a LOAEL, additional studies may be warranted depending on the extent to which inhalation exposure to this

chemical can be anticipated.

## 1.3. CHEMCIAL B

### 1.3.1 ORAL TOXICITY

#### 1.3.1.1. Species/Sex/Endpoint Selection

Table 1B provides data on studies with rats, mice, dogs and rabbits. Information presented in the table provides the information needed to identify the appropriate species, sex and toxicity endpoint for cumulative risk assessments involving Chemical B. Data in Table 1B show, with the exception of the 1-year dog study, that the female rat expresses the greatest sensitivity to inhibition of cholinesterase inhibition following exposure to Chemical B. Although a lower NOAEL/LOAEL for RBC AChEI is shown for the dog, examination of the raw data for this study shows that the difference between results of the dog study and the 2-year rat study appears to be attributable to the spacing of doses and the magnitude of inhibition at the LOAEL (dog RBC AChEI - 18-20%; rat RBC AChEI - 30-40%). Regarding the selection of the most appropriate endpoint (plasma, RBC, or brain ChEI), RBC ChEI is recommended as the endpoint for use in a cumulative risk assessment since a) inhibition in this compartment in the rat 2-year study is as sensitive an endpoint as ChEI in plasma or brain, b) the study involved larger groups of animals than the dog study (10 animals versus 4), c) the rat study involved multiple determinations at varying intervals and shows that values reported after 90 days of exposure (plateau for inhibition) are reproducible, and d) there are questions about the health status of the dogs used in the 1-year dog study.

**Table 1B: Cholinesterase Inhibition in Rats, Mice Dogs, and Rabbits Administered Chemical B in the Diet.**

| STUDY | PLASMA NOAEL/LOAEL (mg/kg/day) | RBC NOAEL/LOAEL (mg/kg/day) | BRAIN NOAEL/LOAEL (mg/kg/day) |
|---|---|---|---|
| **2 YR RAT** | 0.75/2.33 (M)<br>0.31/0.96 (F) | 0.25/0.75 (M)<br>0.31/0.96 (F) | 0.75/2.33 (M)<br>0.31/0.96 (F) |
| **1 YR DOG** | 0.69/3.84 (M)<br>0.78/4.33 (F) | 0.15/0.69 (M)<br>0.16/0.78 (F) | 0.69/3.84 (M)<br>0.78/4.33 (F) |
| **18 MONTH MOUSE** | Not measured | 0.79/3.49 (M)<br>0.98/4.12 (F) | 0.79/3.49 (M)<br>0.98/4.12 (F) |
| **RABBIT DEV.** | 1/2.5 (F) | Not measured | Not measured |
| **RAT DEV.** | > 1 (F) | > 1 (F) | 0.5/1 (F) |

#### 1.3.1.2. Increased Sensitivity/Susceptibility of Young

In a developmental study using rabbits, ChEI (plasma, RBC, and brain) was measured in both maternal animals and fetuses. No plasma or RBC ChEI was found in maternal animals up to a dose level of 1 mg/kg/day. Inhibition of brain cholinesterase was noted in maternal animals (NOAEL/LOAEL 0.5/1.0 mg/kg/day). Measurement of the same parameters in fetuses revealed no inhibition of cholinesterase in any compartment at 2.0 mg/kg/day, the highest dose administered to maternal animals. Further, no developmental effects were observed at or below doses which resulted in maternal toxicity. These data indicate there is no increased sensitivity of fetuses or neonatal animals compared with adult animals following exposure to Chemical B.

#### 1.3.1.3. Time to a Steady State of Inhibition and Recovery

The 2-year rat study included determinations of ChEI at 1, 3, 6, 12, 18, and 24 months. At the LOAEL of 0.96 mg/kg/day in the females, 29% RBC ChEI was reported at 1 month. Further depression of plasma cholinesterase inhibition did not occur at that dose level during subsequent sampling intervals. Maximum RBC cholinesterase inhibition was also attained at one month at the 0.96 mg/kg/day dose-level in female rats. These results show that a plateau for cholinesterase inhibition occurs rapidly (within one month) and that data on RBC cholinesterase inhibition from short-term studies are appropriate for use in risk assessments that encompass longer-term exposures.

#### 1.3.1.4. Dose-Response

There are, as shown in Table 2B, dose-response data available from the 2-year rat study that may allow calculations of an $ED_{10}$ for quantifying potential cumulative risks.

**Table 2B: RBC ChEI in Female Rats at 1, 6, & 12 Months**

| RBC ChEI (%) | | | |
|---|---|---|---|
| **MONTH** | 0.31 mg/kg/day | 0.96 mg/kg/day | 3.11 mg/kg/day |
| **1** | 12 | 29 | 56 |
| **6** | 8 | 29 | 66 |
| **12** | 10 | 35 | 67 |

#### 1.3.1.5. Selection of Oral PoD

If it is determined that a reliable $ED_{10}$ cannot be calculated using data from Table 2B, due to the continuous nature of ChEI data, an alternative is to select an appropriate NOAEL as a POD. Table 3B lists data on key, well-conducted studies on RBC ChEI in female rats and dogs. It is recommended that, if a NOAEL is selected for a POD, the NOAEL determined from the 3-month sampling in the 2-year study is used since the data are from the most sensitive species and sex and since the results of the 90-neurotoxicity study are not consistent with the 2-year rat study or other rat studies that measured RBC cholinesterase activity.

**Table 3B: RBC ChEI in Key Studies Performed with Chemical B with Female Animals**

| STUDY | NOAEL/LOAEL (mg/kg/day) | % ChEI |
|---|---|---|
| **2-year rat** | 0.31/0.96 | 35 at 3 months |
| **90-day rat neurotoxicity** | 1.05/3.23 | 60 at 3 months |
| **1-year dog** | 0.78/4.33 | 50 at 3 months |

### 1.3.2. DERMAL TOXICITY

Dermal exposure from non-dietary sources is not anticipated with Chemical B. In the event new information or changes in use patterns show that residential dermal exposures occur, the information which follows should be incorporated into the aggregate and cumulative risk assessments.

An acceptable dermal toxicity study in which ChEI was measured is not available.

In a dermal absorption study conducted with rats, Chemical B was administered over a period of 7 days to 4 groups of male rats (4 animals per group). Dose-levels were 0, 0.056, 0.56, or 5.6 mg/kg/day. Maximum absorption, 42%, was reported in the 0.056 mg/kg/day group on day 7.

Comparisons of RBC AChEI at day 1 in the dermal absorption study with RBC ChEI in an acute oral neurotoxicity study support a dermal absorption factor of 42%. At 24 hrs in the dermal absorption study, RBC cholinesterase activity was inhibited by 17% at the 5.6 mg/kg/day dose-level. In an acute oral neurotoxicity study, RBC AChEI reached 33% at a dose-level of 2 mg/kg/day. The ratio of RBC AChEI by the two routes of exposure is 35 (LOAEL, oral/ LOAEL, dermal or 2 mg/kg/day/5.6 mg/kg/day).

When aggregating or cumulating exposures to Chemical B, a dermal absorption factor of 42% should be used.

### 1.3.3. INHALATION TOXICITY

Residential or other non-dietary inhalation exposures are not anticipated for Chemical B. In the event new information identifies inhalation exposure as a route of concern, the information that follows should be incorporated in aggregate and cumulative risk assessments.

In a 13-week inhalation toxicity test, male and female rats were administered Chemical B at concentrations of 0, 0.0002, 0.0012, or 0.0047 mg/L. Plasma and RBC cholinesterase activity were significantly depressed in both male and female rats at 0.0047 mg/L at 13 weeks. Brain cholinesterase activity was not affected. The NOAEL/LOAEL for RBC ChEI was established as 0.0012/0.0047 mg/L. Since the 13-week data are appropriate for use in assessing risks presented by the exposure duration of concern (90-days), the NOAEL established in the 13-week inhalation study should be used for aggregate and cumulative risk assessments.

### 1.3.4. OTHER CONSIDERATIONS

#### 1.3.4.1. Pharmacokinetic/Dynamic Interactions

There are no data available that would allow an evaluation of interactions between Chemical B and any other chemical.

#### 1.3.4.2. Comparison of PoD Selected for Cumulative Risk Assessments with NOAEL Used to Establish the Chronic Dietary RfD

The NOAEL selected for use in oral cumulative risk assessments (0.31 mg/kg/day) is the same NOAEL used to establish the chronic dietary RfD for Chemical B.

#### 1.3.4.3. Neurotoxicity Findings

The lowest dose at which clinical or neurobehavioral effects were noted in any study involving oral exposure to Chemical B is 3.2 mg/kg/day. Neuropathology was not detected in any study. Since the NOAEL recommended for use in aggregate and cumulative risk assessments involving Chemical B is 10-fold lower than dosages which result in clinical or neurobehavioral effects, limiting exposures to levels that do not result in RBC ChEI will also preclude the potential for neurotoxicity.

### 1.3.5. WEIGHT-OF-THE-EVIDENCE

There are sufficient data available from a variety of toxicity studies with Chemical B that allow selection of the appropriate species, sex, endpoints and relevant NOAELs/LOAELs for use in assessing potential aggregate and cumulative risks of Chemical B. Some uncertainties remain regarding the potential for Chemical B to express neurobehavioral or neuropathological effects in young animals as a reproductive or developmental neurotoxicity study has not been performed on young animals. Available data from developmental and reproductive studies provide evidence that neonatal animals (or animals exposed *in utero*) are not more sensitive than adults as clinical signs, ChEI, and other signs of toxicity occur only at maternally toxic doses or higher. As with most chemicals, there is no information available to evaluate interactions of Chemical B with other chemicals. The overall data base on Chemical B is of high quality. There are no data gaps or deficiencies apparent that would reduce confidence that the NOAEL's or endpoints selected for aggregate and cumulative risk assessments with Chemical B are

appropriate.

## 1.4. CHEMICAL C

### 1.4.1. ORAL TOXICITY

#### 1.4.1.1. Species/Sex Selection

Table 1C presents a summary of data reported from a series of intermediate and long-term studies performed with Chemical C. Among the species tested for ChEI, rats, dogs, mice and rabbits, the rat appears to be more, or at least equally, sensitive to the ChEI effects of Chemical C. With respect to differing ChEI responses in male and female rats following exposure to Chemical C, examination of LOAEL's suggests that males may be more sensitive than females. Further examination of the data in study reports shows that the apparent difference in sensitivity is a function of dose selection. Male and female animals were administered equivalent doses (ppm) in the diet. When the ppm in the diet is converted to mg/kg/day based on food consumption and body weights, the apparent dose level to which females were exposed is larger than that of male animals. Due to problems associated with estimating small differences in food consumption among different animals and sexes, it is assumed for purposes of this review that male and female animals are equally sensitive. Since female rats were the species and sex of choice for hazard evaluations of Chemicals A and B, the female rat is recommended for hazard evaluations involving Chemical C.

**Table 1C: Oral NOAEL'S and LOAEL'S for Cholinesterase Inhibition in Various Species and in Males and Females for Chemical C**

| STUDY | PLASMA NOAEL/LOAEL mg/kg/day | RBC NOAEL/LOAEL mg/kg/day | BRAIN NOAEL/LOAEL mg/kg/day |
|---|---|---|---|
| **2-year rat** | 0.21/2.21 (M)<br>0.29/3.34 (F) | 0.21/2.21 (M)<br>0.29/3.34 (F) | 0.21/2.21 (M&F)<br>0.29/3.34 (F) |
| **13-week dog** | 0.3/3.0 (M & F) | 0.3/3.0 (M & F) | 0.3/3.0 (M & F) |
| **2-year mouse** | 1.69/9.2 (M)<br>2.1/13.7 (F) | 0.2/1.6 (M)<br>0.3/2.1 (F) | 0.2/1.6 (M)<br>0.3/2.1 (F) |
| **Developmental toxicity, rabbit** | 1/3 (F) | 1/3 (F) | >3 (F) |
| **13-week rat neurotoxicity** | 0.295/3.02 (M)<br>0.365/3.96 (F) | 0.029/0.295 (M)<br>0.0365/0.365 (F) | 0.29/0.295 (M)<br>0.365/3.96 (F) |

#### 1.4.1.2. Increased Sensitivity/Susceptibility of Young

In a series of special studies conducted with adult and neonatal rats, maximal plasma, RBC, and brain ChEI was found to be similar in adults and neonates treated with Chemical C. It was also noted that following cessation of treatment, neonatal cholinesterase activity returned to baseline values more rapidly than adults. In contrast, neonatal animals were found to be more sensitive with respect to dosages that elicit acute lethality (maximum tolerated dose in adult and neonatal animals).

In developmental and reproductive studies performed with Chemical C, fetal or neonatal toxicity was observed only at dose levels that resulted in maternal toxicity.

The data from the special studies and the reproductive and developmental toxicity studies indicate that fetal and neonatal animals are not more sensitive than adult animals to the cholinesterase inhibiting properties of Chemical C at low dosages but that some increase in sensitivity (increased mortality) can be anticipated at doses approaching a maximum tolerated dose.

#### 1.4.1.3. Time to a Steady State of Inhibition

Serial sampling for cholinesterase activity was performed in a 1-year rat study, a 90-day rat neurotoxicity study, and a 90-day dog study. In each of these studies, maximum RBC AChEI occurred by the first sampling period (rats - 1 month; dog - 6 weeks).

#### 1.4.1.4. Dose Response

A 1-year feeding study with rats provides data that are amenable to dose-response analyses (Table 2C). The 1-year study is the only study available on Chemical C that demonstrates a depression in cholinesterase activity that increases with increasing dose. In all other studies, maximum ChEI occurred at the LOAEL or only at the high dose tested.

**Table 2C: Responses in RBC ChEI at Multiple Doses in Female Rats Administered Chemical C for 1 Year**

| | 0.026 | Dose (mg/kg/day) 0.138 | 0.697 | 3.088 |
|---|---|---|---|---|
| **ChE activity (%)** | +5 | -10 | -33 | -70 |

#### 1.4.1.5. Selection of Oral PoD

Data provided in the 1-year feeding study in female rats (Table 2c) are appropriate for calculations of EDs, assuming it is possible to address problems associated with the use of continuous data. If a NOAEL is used to establish a PoD, the NOAEL of 0.21 mg/kg/day reported for the 2-year rat study (Table 1c) is recommended for estimates of aggregate and cumulative risks. As discussed above, the 1-year rat study is the only study that provides suitable dose-response data for regression analysis or ED (or BMD) determinations. The 2-year rat study is the appropriate study to use for selection of a NOAEL as a PoD since the NOAEL for RBC ChEI in the study is the lowest reported for any study performed with Chemical C, data from the study are considered reliable, and, although exposure in the study encompasses a 2-year time frame, the data are suitable for use in a 90-day risk assessment since serial sampling in several other studies show that maximum RBC ChEI occurs within 4-6 weeks.

### 1.4.2. DERMAL TOXICITY

There are no residential uses for Chemical C. Therefore, dermal exposure is not an exposure route of concern for Chemical C.

### 1.4.3. INHALATION TOXICITY

There are no residential uses for Chemical C and inhalation exposure is, therefore, not a route of concern.

### 1.4.4. OTHER CONSIDERATIONS

#### 1.4.4.1. Pharmacokinetic/Dynamic Interactions

There are no data available that would allow an evaluation of PK/PD interactions that may occur between Chemical C and any other chemical.

#### 1.4.4.2. Neuropathology

In a 2-year rat study, Chemical C was shown to be neuropathic in female animals at the high dose tested, 3.34 mg/kg/day (retinal and sciatic nerve degeneration). A 90-day rat neurotoxicity study and a 1-year dog feeding study, which included examinations of nervous tissues, provided no evidence of neuropathology but clinical signs were observed at the high-dose tested (3.96 mg/kg/day) in female rats in the neurotoxicity study. Based on these data, it appears that dose-levels required to produce neuropathology and/or clinical signs are approximately 15-fold greater than doses which lead to RBC ChEI.

#### 1.4.4.3. Comparison of the PoD Selected for Cumulative Risk Assessments with the NOAEL Used to Establish the Chronic Dietary RfD for Chemical C

The oral NOAEL used to establish an RfD for chemical C (0.021 mg/kg/day) is the same NOAEL recommended for the PoD.

### 1.4.5. WEIGHT-OF-THE-EVIDENCE

The key studies performed using Chemical C and evaluated for data pertinent for an aggregate or a cumulative risk assessment are of a high quality. ChEI measurements were performed using accepted methodologies, histopathology (including neuropathology) evaluations were extensive and well reported, study designs and execution were sufficient to attain the goal of identifying hazards associated with exposures to the chemical. No data gaps are apparent that would influence the overall conclusions reached regarding the hazard potential of Chemical C. There is a high level of confidence regarding the species, sex, endpoints, and dose-levels selected for use in aggregate or cumulative risk assessments.

Some uncertainties exist despite the availability of a comprehensive data base on the chemical. Since Chemical C has been shown to be neuropathic, data from a developmental neurotoxicity study would be useful and may be warranted, depending on consideration of exposure patterns and levels of exposure encountered among the human population for Chemical C and other chemicals that may be combined with it for a cumulative risk assessment and recognizing that the neurotoxicity effects of Chemical C appear to occur at dose levels far exceeding those that produce ChEI.

## 2. CHARACTERIZATION OF THE CUMULATIVE HAZARD OF THE COMMON MECHANISM GROUP (CHEMICAL A, CHEMICAL B, AND CHEMICAL C)

The hazard data on the group of chemicals (Chemicals A, B, and C) identified as having a common mechanism of action and that are the subject of these case studies provide a high level of confidence that the species, sex, endpoints, and other toxicity aspects of the chemicals selected for a cumulative risk assessment accurately reflect the hazard potential of the components of the group for the following reasons:

- ❏ the mechanism of toxicity is well established for all members of the common mechanism grouping (inhibition of cholinesterase by phosphorylation)
- ❏ the pattern of effects (plasma, RBC, Brain ChEI and clinical and neurobehavioral signs) are consistent for all three chemicals
- ❏ data are available on each chemical that provide insights regarding sensitivities of fetal and neonatal animals compared with adult animals
- ❏ NOAELs and LOAELs for oral toxicity can be established for each member of the common mechanism group
- ❏ the endpoint selected for use in a cumulative risk assessment, inhibition of RBC cholinesterase, is a common effect and the effect occurs at or below the NOAEL for any other toxic effect for each chemical
- ❏ no data were identified in the available studies that would call into question the use of a NOAEL based on inhibition of RBC cholinesterase
- ❏ data are available on each chemical that provide information on time to a steady state of ChEI inhibition and time required for recovery following cessation of treatment
- ❏ no data gaps were identified that would lessen confidence that the species, sex, or endpoints selected for a cumulative risk assessments are appropriate
- ❏ there are, nevertheless, aspects of the hazard data that suggest additional studies on one or more members of the common mechanism group are warranted.
- ❏ no data are available that address the potential for pharmacokinetic or pharmacodynamic interactions to occur among Chemicals A, B, and C.

- ❏ developmental or reproductive neurotoxicity studies have not been conducted on any member of the group

- ❏ one member of the group (Chemical C) has been shown to be neuropathic, albeit at very high doses. It is unknown if further studies with other members of the group would reveal the potential for similar responses

- ❏ adequate dose-response data are not available for Chemical A and comparisons of relative potency of this chemical with other members of the group are confined to single point comparisons

There are certain aspects of the data base that indicate uncertainty factors should be applied to the common mechanism group when quantifying cumulative risks. First, inhalation data are available for only a single chemical in the group and for that chemical, a NOAEL was not established. An uncertainty factor of 3-fold to account for the use of a LOAEL for ChemicalA. For the Chemicals B & C, no inhalation data are available but inhalation exposures for those two chemicals are not expected. Therefore, it is recommended that the inhalation LOAEL for Chemical A be reduced by a factor of 3-fold before proceeding with quantification of potential cumulative risks of the common mechanism group.

Regarding the relative sensitivity of adults versus fetal or neonatal animals, the available evidence does not indicate there is an increase in sensitivity in any age group for any of the chemicals. However, Chemical C has been shown to be neuropathic at high doses. A developmental neurotoxicity test is recommended to be performed on Chemical C. It is not recommended that neuropathology serve as an endpoint for combining Chemicals A, B, and C in a cumulative risk assessment because the neuropathic effect is limited to Chemical C and exposure to Chemicals A and B is not expected to contribute in an additive manner to that effect. Confirmation that this is a sound conclusion would be provided by additional studies (i.e., developmental or reproductive neurotoxicity tests) that are performed with a combination of the three chemicals. Such a study(ies) would also provide data on the potential for interactions to occur among the three chemicals that might enhance or lessen toxicity compared with the additivity assumed for risk estimates.

Quantifying potential aggregate and cumulative risks using $ED_{10}$ estimates is not recommended since adequate dose-response data are not available for Chemical A and because ChEI data are continuous data. The PoD values (based on selection of the appropriate and representative NOAEL for each chemical) that should be used for quantifying potential aggregate and cumulative risks are listed below in Table 4A.

**Table 4A: Oral, dermal, and inhalation PODs for Chemicals A, B, and C**

| Route | PoD | | |
|---|---|---|---|
| | **Chemical A** | **Chemical B** | **Chemical C** |
| **Oral** | 0.02 mg/kg/day | 0.31 mg/kg/day | 0.21 mg/kg/day |
| **Dermal** | 0.02 mg/kg/day | N/A* | N/A |
| **Inhalation** | 0.00003 mg/L/day | N/A | N/A |
| Common toxic endpoint: intermediate-term inhibition of RBC ChE | | | |

*N/A - Not applicable since no exposures by this route are anticipated

## 3. QUANTIFYING THE CUMULATIVE RISK

At this point in the assessment process, information has been gathered defining exposure scenarios of concern and use patterns and usage patterns. In this case, study a theoretical scenario for a single day of exposure would be constructed where the diet is the predominant exposure pathway for all three chemicals, with some residential exposure (inhalation and dermal) for Chemical A (see Table 5A).

Exposure by pathway is determined on a daily basis for each individual and for each scenario of interest in the population. This case study represents only one day of exposure as an example of the two methods for quantifying cumulative risk. In practice, the risk data for each pathway would be combined over time and presented as a distribution.

**Table 5A: Exposure Data for Chemicals A, B, and C**

| Pathway | Chemical A | Chemical B | Chemical C |
|---|---|---|---|
| **Oral** - Dietary | 0.007 mg/kg/day | 0.016 mg/kg/day | 0.00046 mg/kg/day |
| **Oral** - Drinking Water | 0.0005 mg/kg/day | 0.0013 mg/kg/day | 0.00003 mg/kg/day |
| **Oral** - Residential - Non-dietary | N/A* | N/A | N/A |
| **Dermal** - Residential | 0.09 mg/kg/day | N/A | N/A |
| **Inhalation** - Residential | 0.0000002 mg/L/day** | N/A | N/A |

*N/A - Not applicable since no exposures by this route are anticipated
** This is a hypothetical exposure concentration. All other exposure values are measured values.

Two methods for calculating cumulative risk are illustrated below. Although both methods produce the same cumulative risk value, they do it in very different ways. The Margin-of-Exposure method uses risk addition (i.e., MOEs are combined), and the Relative Potency Factor (RPF) method uses dose exposure addition (doses are combined). The PoDs and exposure data used in these examples comes from Tables 4A and 5A, respectively.

### 3.1. MARGIN OF EXPOSURE METHOD

**Step 1:** For each chemical and exposure pathway, Margins-of-Exposure (MOEs) are calculated as follows:

Eq. 1

$$MOE = \frac{PoD}{Exposure}$$

**Table 6A: Chemical A**

| Pathway | PoD ÷ Exposure = MOE | | |
|---|---|---|---|
| | **PoD** | **Exposure** | **MOE** |
| **Oral** - Dietary | 0.02 mg/kg/day | 0.007 mg/kg/day | 2.86 |
| **Oral** - Drinking Water | 0.02 mg/kg/day | 0.0005 mg/kg/day | 40 |
| **Oral** - Residential - Non-dietary | 0.02 mg/kg/day | N/A | N/A |
| **Dermal** - Residential | 0.02 mg/kg/day | 0.09 mg/kg/day | 0.22 |
| **Inhalation** - Residential | 0.00003 mg/L/day | 0.0000002 mg/L/day | 150 |

**Table 7A: Chemical B**

| Pathway | PoD ÷ Exposure = MOE | | |
|---|---|---|---|
| | **PoD** | **Exposure** | **MOE** |
| **Oral** - Dietary | 0.31 mg/kg/day | 0.016 mg/kg/day | 19.38 |
| **Oral** - Drinking Water | 0.31 mg/kg/day | 0.0013 mg/kg/day | 238.46 |
| **Oral** - Residential - Non-dietary | 0.31 mg/kg/day | N/A | N/A |
| **Dermal** - Residential | N/A | N/A | N/A |
| **Inhalation** - Residential | N/A | N/A | N/A |

**Table 8A: Chemical C**

| Pathway | PoD ÷ Exposure = MOE | | |
|---|---|---|---|
| | **PoD** | **Exposure** | **MOE** |
| **Oral** - Dietary | 0.21 mg/kg/day | 0.00046 mg/kg/day | 456.52 |
| **Oral** - Drinking Water | 0.21 mg/kg/day | 0.00003 mg/kg/day | 7000 |
| **Oral** - Residential - Non-dietary | 0.21 mg/kg/day | N/A | N/A |
| **Dermal** - Residential | N/A | N/A | N/A |
| **Inhalation** - Residential | N/A | N/A | N/A |

**Step 2:** Individual MOEs for each chemical and pathway are tabulated (see Table 9A), and then combined to yield the following three risk values:

❑ The **Aggregate MOE** (**$MOE_A$**) expresses risk for a single chemical by all applicable pathways (e.g. the column of MOEs for Chemical B in Table 9A):

Eq. 2
$$MOE_A = \frac{1}{\frac{1}{MOE_{Diet}} + \frac{1}{MOE_{Water}} + \frac{1}{MOE_{Non-Diet}} + \frac{1}{MOE_{Dermal}} + \frac{1}{MOE_{Inhal}}}$$

❑ The **Cumulative Pathway MOE** (**$MOE_{Pathway}$**) expresses risk for all chemicals by a single pathway (e.g. the $MOE_{Pathway}$ of 34.09 for drinking water is in the far right column in Table 9A):

Eq. 3
$$MOE_{Pathway} = \frac{1}{\frac{1}{MOE_{Chemical\ A}} + \frac{1}{MOE_{Chemical\ B}} + \frac{1}{MOE_{Chemical\ C}}}$$

❑ The **Cumulative Assessment Group MOE** (**$MOE_{CAG}$**) expresses risk for all chemicals and pathways. It can be calculated in either of two ways:

✔ Combining $MOE_A$ values for all chemicals (bottom row in Table 9A):

Eq. 4

$$MOE_{CAG} = \frac{1}{\frac{1}{MOE_{A_{Chemical\ A}}} + \frac{1}{MOE_{A_{Chemical\ B}}} + \frac{1}{MOE_{A_{Chemical\ C}}}}$$

✔ Combining all $MOE_{Pathway}$ values (far right column in Table 9A):

Eq. 5

$$\boldsymbol{MOE_{CAG} = \frac{1}{\frac{1}{MOE_{Diet}} + \frac{1}{MOE_{Water}} + \frac{1}{MOE_{Non-Diet}} + \frac{1}{MOE_{Dermal}} + \frac{1}{MOE_{Inhal}}}}$$

**Table 9A: Risk Summary**

| Pathway | Chemical A MOE | Chemical B MOE | Chemical C MOE | $MOE_{Pathway}$ |
|---|---|---|---|---|
| **Oral** - Dietary | 2.86 | 19.38 | 456.52 | 2.48 |
| **Oral** - Drinking Water | 40 | 238.46 | 7000 | 34.09 |
| **Oral** - Residential - Non-dietary | N/A | N/A | N/A | N/A |
| **Dermal** - Residential | 0.22 | N/A | N/A | 0.22 |
| **Inhalation** - Residential | 150 | N/A | N/A | 150 |
| **$MOE_A$** (by chemical) | 0.20 | 17.92 | 428.57 | **$MOE_{CAG}$ = 0.20** |

**Step 3 - Interpretation:**

Table 9A summarizes all the risk values from this example. Individual MOEs for chemicals A, B, and C are presented for each exposure pathway. The **Aggregate MOEs** (**$MOE_A$**, listed in the bottom row) quantify the aggregate risk for individual chemicals by all applicable exposure pathways. The **Cumulative Pathway MOEs** (**$MOE_{Pathway}$**, listed in the far right column) quantify the cumulative risk for individual exposure pathways. The **Cumulative Asesssment Group MOE** (**$MOE_{CAG}$**, listed in the bottom right corner) quantifies the risk for all chemicals and pathways.

In this case study, the MOE, $MOE_A$, $MOE_{Pathway}$, and $MOE_{CAG}$ are compared against a group Uncertainty Factor (UF) of 100 (interspecies UF of 10, and an intraspecies sensitivity UF of 10).

Because this method uses risk values (MOEs) throughout, one can instantly see which exposure scenarios (e.g. Chemical A, dermal residential exposure), which pathways, and which chemicals pose the greatest hazard.

Exposure by pathway is determined on a daily basis for each individual and for each scenario of interest in the population. This case study represents only one day of exposure for the sake of demonstrating this method. In practice, the $MOE_{Pathway}$s are combined over time and presented as a distribution.

### 3.2. RELATIVE POTENCY FACTOR (RPF) METHOD

In this case study, chemical A has been selected as the index chemical.

**Step 1:** Oral, dermal, and inhalation relative potency factors (RPFs) for each chemical and route in a grouping are derived as follows (note that the RPF for the index chemical is always 1):

Eq. 6 $$RPF = PoD_{[Index\ Chemical]} \div PoD_{[Chemical\ n]}$$

**Table 10A: Relative Potency Factors (RPFs)**

| Route | Index PoD ÷ PoD = RpF | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Chemical A | | | Chemical B | | | Chemical C | | |
| | Index PoD | PoD | RPF | Index PoD | PoD | RPF | Index PoD | PoD | RPF |
| **Oral** (mg/kg/day) | 0.02 | 0.02 | **1** | 0.02 | 0.31 | **0.065** | 0.02 | 0.21 | **0.095** |
| **Dermal** (mg/kg/day) | 0.02 | 0.02 | **1** | N/A | N/A | **N/A** | N/A | N/A | **N/A** |
| **Inhalation** (mg/L/day) | 0.00003 | 0.00003 | **1** | N/A | N/A | **N/A** | N/A | N/A | **N/A** |

**Step 2:** For a given day, each chemical's exposure by pathway is multiplied by its RPF to express it as an Index Equivalent Exposure ($Exposure_{IE}$).

Eq. 7 $$Exposure_{IE}\ (pathway) = (Exposure_n \times RPF_{route})$$

**Table 11A: Equivalent Exposure Values - Chemical A**

| Pathway | Exposure x RPF = $Exposure_{IE}$ | | |
|---|---|---|---|
| | **Exposure** | **RPF** | **$Exposure_{IE}$** |
| **Oral** - Dietary | 0.007 mg/kg/day | 1 | 0.007 mg/kg/day |
| **Oral** - Drinking Water | 0.0005 mg/kg/day | 1 | 0.0005 mg/kg/day |
| **Oral** - Residential - Non-dietary | N/A | 1 | N/A |
| **Dermal** - Residential | 0.09 mg/kg/day | 1 | 0.09 mg/kg/day |
| **Inhalation** - Residential | 0.0000002 mg/L/day | 1 | 0.0000002 mg/L/day |

**Table 12A: Equivalent Exposure Values - Chemical B**

| Pathway | Exposure x RPF = $Exposure_{IE}$ | | |
|---|---|---|---|
| | **Exposure** | **RPF** | **$Exposure_{IE}$** |
| **Oral** - Dietary | 0.016 mg/kg/day | 0.065 | 0.001 mg/kg/day |
| **Oral** - Drinking Water | 0.0013 mg/kg/day | 0.065 | 0.00008 mg/kg/day |
| **Oral** - Residential - Non-dietary | N/A | 0.065 | N/A |
| **Dermal** - Residential | N/A | N/A | N/A |
| **Inhalation** - Residential | N/A | N/A | N/A |

**Table 13A: Equivalent Exposure Values - Chemical C**

| Pathway | Exposure x RPF = $Exposure_{IE}$ | | |
|---|---|---|---|
| | **Exposure** | **RPF** | **$Exposure_{IE}$** |
| **Oral** - Dietary | 0.00046 mg/kg/d | 0.095 | 0.000044 mg/kg/day |
| **Oral** - Drinking Water | 0.00003 mg/kg/d | 0.095 | 0.0000029 mg/kg/day |
| **Oral** - Residential - Non-dietary | N/A | 0.095 | N/A |
| **Dermal** - Residential | N/A | N/A | N/A |
| **Inhalation** - Residential | N/A | N/A | N/A |

**Step 3:** For each pathway, the Index Equivalent Exposures ($Exposure_{IE}$) for all chemicals in the grouping are summed (see Table 14A).

Eq. 8 $$Total\ Exposure_{IE}\ (pathway) = Exposure_{IE_A} + Exposure_{IE_B} + Exposure_{IE_C}$$

**Table 14A: Total Index Equivalent Exposures**

| Pathway | $Exposure_{IE}$ | | | |
|---|---|---|---|---|
| | **Chemical A** | **Chemical B** | **Chemical C** | **Total** |
| **Oral** - Dietary (mg/kg/day) | 0.007 | 0.001 | 0.000044 | **0.0080** |
| **Oral** - Drinking Water (mg/kg/day) | 0.0005 | 0.00008 | 0.0000029 | **0.00058** |
| **Oral** - Residential - Non-dietary (mg/kg/day) | N/A | N/A | N/A | **N/A** |
| **Dermal** - Residential (mg/kg/day) | 0.09 | N/A | N/A | **0.09** |
| **Inhalation** - Residential (mg/L/day) | 0.0000002 | N/A | N/A | **0.0000002** |

**Step 4:** Cumulative Pathway MOEs ($MOE_{Pathway}$) are calculated for each pathway (see Table 15A, far right column). Since the total exposure for a given pathway is an equivalent of the index chemical exposure, it is compared to the index chemical's PoD for the appropriate route to derive an $MOE_{Pathway}$:

Eq. 9 $$MOE_{Pathway} = \frac{Index\ POD}{Total\ Exposure_{IE}}$$

**Step 5:** All $MOE_{Pathway}$ values are then combined to yield a $MOE_{CAG}$:

Eq. 10 $$MOE_{CAG} = \frac{1}{\frac{1}{MOE_{Dietary}} + \frac{1}{MOE_{Water}} + \frac{1}{MOE_{Non-Dietary}} + \frac{1}{MOE_{Dermal}} + \frac{1}{MOE_{Inhal}}}$$

**Table 15A: Risk Summary**

| Pathway | Index PoD ÷ Σ $Exposure_{IE}$ = $MOE_{Pathway}$ | | |
|---|---|---|---|
| | Index PoD | Total Index Equivalent Exposure | $MOE_{Pathway}$ |
| **Oral** - Dietary | 0.02 mg/kg/day | 0.0080 | 2.50 |
| **Oral** - Drinking Water | 0.02 mg/kg/day | 0.00058 | 34.48 |
| **Oral** - Residential - Non-dietary | 0.02 mg/kg/day | N/A | N/A |
| **Dermal** - Residential | 0.02 mg/kg/day | 0.09 | 0.22 |
| **Inhalation** - Residential | 0.00003 mg/L/day | 0.0000002 | 150 |
| | | **$MOE_{CAG}$ =** | **0.20** |

**Step 6: Interpretation:**

In the Risk Summary table (Table 15A), the **Cumulative Pathway MOEs** (**$MOE_{Pathway}$**, listed in the far right column) quantify the cumulative risk for individual pathways. The **Cumulative Assessment Group MOE** (**$MOE_{CAG}$**, listed in the bottom right corner) quantifies the risk for all chemicals and pathways.

In this case study, the $MOE_{Pathway}$ values for each pathway and the $MOE_{CAG}$ are compared against a group UF of 100 (including an interspecies UF of 10 and an intraspecies sensitivity UF of 10).

This method allows one to instantly see which pathways pose the greatest hazard. Because risk values are calculated only at the end of the process, this method cannot identify which chemical or individual exposure scenario poses an unacceptable hazard.

Exposure by pathway is determined on a daily basis for each individual and for each scenario of interest in the population. This case study represents only one day of exposure for the sake of demonstrating this method. In practice, the $MOE_{Pathway}$s for each pathway are combined over time and presented as a distribution.

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