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**CHAPTERS 4 AND 6 FOR  
FIFRA SCIENTIFIC ADVISORY PANEL REVIEW**

## ***4 EXPOSURE ASSESSMENT AND CHARACTERIZATION***

### ***4.1 INTRODUCTION***

This chapter will discuss the methodology for conducting a cumulative exposure assessment. It will describe the conditions necessary for conducting such an exposure assessment and the available sources of chemical specific data, the use of surrogate data, and the assumptions used in the cumulative exposure assessment process. The discussion will focus primarily on pesticide chemicals although the principles involved would, in most cases, be applicable to all chemical substances.

As discussed in Chapter 3, the hazard assessment/characterization describes the biological characteristics and mechanism of the common toxic effect that will be used in developing the cumulative exposure profile. The hazard and exposure analyses processes should 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* (EPA, 1999b) will be drawn upon to develop this chapter. This chapter will focus on those aspects of cumulative exposure that differ from the aggregate exposure assessment and risk assessment processes.

### ***4.2 CONDITIONS NECESSARY FOR CONDUCTING CUMULATIVE EXPOSURE ASSESSMENT***

After the members of a Common Mechanism Group <sup>1</sup>(CMG) have been identified, the next step in developing a cumulative risk assessment is to identify the uses and potential exposure scenarios for each member compound. This process is described in detail in the *Guidance for Performing*

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<sup>1</sup>**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).

*Aggregate Exposure and Risk Assessment* (EPA, 1999b). EPA will determine whether the combination of exposure scenarios identified present any likelihood of overlapping exposures to multiple chemicals in the CMG. Exposures are considered to overlap if chemicals are likely to be encountered from more than one source or pathway within the time frame in which the common mechanism effect is still operative from previous exposures to other chemicals in the CMG. The pathways of exposure for a chemical in the CMG may be such that overlapping exposure to another chemical will never occur. Where overlap is not anticipated, a cumulative risk assessment for that chemical is not warranted.

#### **4.2.1 GENERAL PRINCIPLES**

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

Three key pathways of exposure to pesticides are: dietary (food), dietary (drinking water), and residential and other nonoccupational exposures. An initial step in developing cumulative exposure scenarios is to identify the demographic profile of a sub-population(s) upon which the assessment will focus. The age, gender and geographic location of the group included in the investigation of the food exposure pathway may also be linked with exposure scenarios in the other two pathways of exposure. The individual consumption records in the database linking the demographic and other descriptors would be used to simulate the consumption patterns of the population or sub-population of interest. The likelihood and frequency assumption for residential scenarios would be used to superimpose a pattern of residential exposures that would reasonably be expected to occur throughout the year for an individual in the population.

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

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

The aggregate assessments will provide the assessor with information needed to define the parameters of the cumulative exposure assessment. Examination of aggregate exposure assessments for the members of the CMG will provide important information for directing the decision making process as to whether a particular pesticide-source and/or pathway combination should be included or deleted. Particular attention should be given to identifying and including

those sources of exposure that are likely to contribute significantly to the final exposure estimate. At the same time, deferring consideration of components of the assessment that are minor contributors to the final risk estimate prior to beginning cumulative quantification of the exposure is critical to bounding the scope of the cumulative exposure assessment and, ultimately, the cumulative risk assessment.

Initial cumulative assessments should not attempt to quantify risk resulting from minor exposure pathways. Exposures from minor pathways should in the first instance be considered qualitatively.

By carefully removing scenarios in which exposure is very low or non-existent, the resulting cumulative risk assessment will be more focused on exposures that are likely to be risk drivers and that may require mitigation actions. This will be especially important in identifying the important sources of exposure for the CMG, accounting for uncertainties in the data inputs, evaluating the impact of any assumptions used, and explaining the outcomes of the assessment to risk managers and the public.

The exclusionary criteria, or bases for elimination of a pathway or use from the quantitative exposure assessment, should be clearly described in the exposure characterization. This step will prevent the erroneous omission of exposures to a chemical that may contribute significantly to a common toxic effect. Examples of exclusionary criteria under consideration are:

- ❑ a particular pathway for a specific chemical in the CMG is likely to contribute less than 1.0% of the total exposure in the most refined analysis performed. The pesticide-pathway combination should be noted in the exposure characterization as extant but not included in the quantitative exposure assessment. For example, a granular formulation of a pesticide that is soil incorporated would most likely not contribute significantly (<1%) to inhalation exposure. This pathway would be noted in the exposure characterization, but not included in the quantitative exposure assessment.
- ❑ a specific pesticide-pathway combination makes a negligible (<1%) contribution to the exposure assessment because of limited use or low consumption of a treated commodity. The uses should be noted in the exposure characterization, but not included in the quantitative exposure assessment. For example, a pesticide that is used only once per season on one low consumption food crop or during a period of dormancy would be expected to make a negligible contribution to the dietary exposure **for that crop**.
- ❑ the common toxicity of interest for a pesticide by a particular route of exposure is low. The route should be noted in the exposure characterization, but not included in the quantitative exposure assessment. For example, if a pesticide and/or its formulation is shown to have negligible (<1%) dermal absorption, this information should be noted in the

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exposure characterization, but dermal exposure should not be included in the exposure assessment.

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

The rationale for excluding a pesticide-pathway combination from the quantitative cumulative exposure assessment should be clearly presented and carefully evaluated.

Data availability and quality may also play a role in the determination of whether or not to combine exposures by multiple pathways.

Where data are limited in quantity, there are difficulties with combining exposures from multiple sources because of the uncertainty that may be introduced into the assessment. For example, ample data exist to provide an estimate of exposure through food to several pesticides. However, data may be scarce or non-existent for residential exposure to the same pesticides, and the use of default values would be necessary to provide a quantitative estimation of the exposure. In such a case, the uncertainties for the default values would be far in excess of the uncertainties for the dietary (food) exposure, and combining the two pathways would be problematic. Similarly, where data sets differ in quality, i.e., how well they represent real world concentrations, combining exposure assessments may produce misleading results. The difference in quality can be illustrated by the following: Pesticide A has high quality dietary (food) residue values and a well defined residential exposure; Pesticide B has limited PDP data, limited anticipated residue data, and no chemical specific data defining the residential exposure. Combining Pesticide A and Pesticide B exposures across the residential and dietary (food) pathways would result in very misleading exposure estimates. Although the dietary (food) data sets for the two pesticides are of differing quality introducing uncertainty into the dietary (food) assessment, this difference can be evaluated and the impact discussed. However, the residential datasets are also very different in quality. The mixing of two major sources of uncertainty in a highly complex exposure assessment would make it extremely difficult, if not impossible, to evaluate the source of any apparent exceedance of acceptable exposure levels. Where issues of data quality or quantity indicate that combining pesticide exposures across multiple routes would result in unacceptable uncertainties, exposures

that are pathway-specific should be combined and the implications considered qualitatively in the risk characterization.

#### **4.2.2 ESTIMATING SOURCES OF EXPOSURE TO PESTICIDE CHEMICALS**

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

##### **4.2.2.1 DIETARY (FOOD)**

The body of information for the dietary (food) pathway is generally 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. In addition, data defining the consumption patterns for the U.S. population have been collected in a number of surveys. Current OPP dietary (food) risk assessments rely upon the food consumption data collected by USDA in the *Continuing Survey of Food Intakes by Individuals* (CSFII). Cumulative exposure assessments for residues of pesticides in foods can be performed for each hypothetical individual used to estimate the distribution of anticipated exposures. Using detailed, individual consumption records such as those provided by the CSFII, a refined estimate can be developed 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 (food) 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

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

Ordinarily, OPP will limit the residue data used in cumulative exposure assessment to monitoring data that reflects actual measurements of pesticide co-occurrence. The occurrence of residues from multiple chemicals in a single food item cannot be considered to be totally independent in the cumulative exposure assessment because of the production of mixtures of pesticides and the possible rotation of uses of multiple pesticides within a single growing season. Therefore, the use of monitoring data in which co-occurrence was measured may provide the only basis for conducting a cumulative dietary (food) exposure assessment that describes co-occurrence with any degree of certainty.

At this time, EPA does not have the methodology to incorporate residue field trial data into cumulative assessments. Such data is routinely used in aggregate risk assessments for individual pesticides. However, several factors suggest that use of such data in cumulative risk assessments would yield results with unacceptably high uncertainty. First, use of residue field trial data presents a conservative picture (i.e., an estimate that errs on the side of overstating exposure and risk) of residue levels because use of such data is premised on the assumption that all uses of the pesticide occurred at maximum label rates. This conservatism is compounded by the aggregation of these conservative values. Second, and more important, EPA currently lacks a reasonable, defensible methodology for estimating overlapping pesticide residue occurrence. Such methodology would have to extrapolate from data on use areas, use rates, season of application and many other factors. The combination of these conservative residue values with a highly speculative approach on co-occurrence would introduce sufficient uncertainty as to make the cumulative risk assessment unreliable for regulatory purposes.

#### **4.2.2.2 DIETARY (DRINKING WATER)**

Monitoring data for pesticides in water have been generated by many organizations including federal, state, and local agencies, universities, chemical companies, and others. Water samples can be either "ambient", which means they are collected from streams, lakes, or wells prior to being treated, or "finished", which means samples are collected after the water has been treated for distribution as drinking water.

For cumulative exposure assessments, residues of pesticides in "tap water" are preferred. Tap water refers to drinking water collected at the homeowner's tap. At the present time, monitoring data for residues of pesticides in tap water are available for only a limited number of pesticides from a limited number of monitoring activities. Even the USEPA's drinking water monitoring program under the SDWA relies on samples taken from points of distribution (post-treatment) within a community water system, not samples taken from the individual homeowner's tap. In spite of this limitation, concentrations of pesticides in drinking water are available for some pesticides from monitoring conducted at community water supplies required by EPA's Safe Drinking Water Act, private rural wells in EPA's *National Well Water Survey* (EPA, 1990) and state-initiated ground-water monitoring activities. In addition, there have been industry-sponsored studies such as the Novartis Rural Well Survey, Monsanto's National Alachlor Well Water Survey, and the Acetochlor Registration Partnership State Monitoring Programs. Although there are limitations with these data (finished water versus tap water, the number of pesticides and degradation products analyzed is limited, and, in some cases, high method detection limits used), these studies provide a strong basis to estimate pesticide residue levels in drinking water for those chemicals that were analyzed. Where these data are available, it may be possible to perform combined dietary (food + drinking water) cumulative assessments specific to those areas and applicable to similar sites across the U.S.

Additionally, ambient monitoring data which have been collected from surface or ground water, some of which are potential sources of drinking water, are available through the U.S. Geological Survey (USGS) National Water Quality Assessment (NAWQA) program. This program provides a source of ambient monitoring data which are high quality and on a national scale. However, although NAWQA contains some data on rural drinking water wells, it largely consists of data on pesticide residues in ambient surface water sources, not tap water. These data may become useful for future cumulative assessments as information on the efficiency of water treatment, mixing, dilution, and aging of residues in ambient water become available to use in conjunction with residue data in source water. Data on pesticide residues in tap water, or a close approximation, such as, finished drinking water or residue data from source water adjusted for the effects of mixing, dilution, and any available treatment, are needed to reliably estimate cumulative exposure. Other sources of ambient data are reconnaissance surveys conducted by the USGS Toxic Substances Hydrology Program, and monitoring from state agencies and regional water authorities, such as the Great Lakes Commission.

Evidence of co-occurrence of pesticides within a water source for a CMG is critical piece of information needed prior to making the decision to conduct a cumulative exposure assessment for drinking water. Data defining potential co-occurrence of pesticides in tap water are rarely available. The USGS National Water Quality Assessment Program (NAWQA) database does contain information on the co-occurrence of a wide variety of pesticides in ambient surface water, and some registrant-sponsored studies provide co-occurrence data for specific compounds in drinking water. In general, however, the determination of the likelihood of co-occurrence will depend heavily upon understanding the distribution of use for each pesticide within a geographic region. Once the likelihood of co-occurrence has been established through use pattern information, monitoring data can be used to support the hypothesis of co-occurrence. Because drinking water assessments are inherently local in nature, this process will require a detailed understanding of the marketing and use patterns for each pesticide for a given region.

Pesticide exposures in drinking water to individuals in a population should be incorporated into cumulative exposure assessments on a local basis. Factoring drinking water exposure into the cumulative exposure assessment framework already contemplated for food-related exposures means developing a “person-by-person” approach to estimating drinking water exposure to pesticides. Because drinking water is a local or regional concern, and additionally, because the food portion of the dietary exposure assessment is being done on an individual basis, each hypothetical person included in a cumulative risk assessment should be assigned to a location and a particular drinking water source. Databases of public drinking water supplies are available. People on private wells can be assigned to particular counties, or possible, different recharge zones.

Once an individual has been associated with a representative drinking water source, the pesticides that could potentially be present in drinking water at each of these locations should be identified. A determination as to whether pesticides within a CMG/CAG co-occur within the representative drinking water source is needed. GIS tools, and cropping and pesticide usage data combined with monitoring data may be useful to this end. Initially, it may be assumed that a person can only be exposed to those pesticides that are used in the recharge area above an aquifer for ground water or in a particular watershed.

Ultimately an estimation of pesticide concentration levels in drinking water at representative locations over the time period being considered in the exposure assessment would be needed. This requires that a credible distribution of concentrations for all pesticides in the CMG/CAG be available for representative drinking water sources included in the assessment. However, localized data sets are applicable only for the locality in which they were collected and for other very similar localities. For example, drinking water concentrations of products used in the corn belt would not be assumed to be appropriate for all individuals across the entire country, but only for individuals who may potentially be exposed in that or similar locations.

For pesticides with minimal monitoring data, concentrations could be estimated using modeling once credible, validated models become available to estimate pesticide concentrations in drinking water. Available drinking water monitoring data should be used to validate estimated concentrations derived through modeling. At the present time, screening-level models that estimate pesticide concentrations in small bodies of surface water and shallow groundwater are available for use in human health risk assessments. These models do not take into account any effects of dilution, distribution, or treatment for tap water. A major shortcoming of incorporating this approach into cumulative risk assessment is the combining of upper bound exposure estimates for multiple chemicals. Such a process is likely to result in a substantial overestimate of the potential to exceed an acceptable exposure level, and are not appropriate for inclusion in cumulative exposure assessments. More robust models validated against actual drinking water monitoring data should be developed to reliably estimate drinking water exposure in the absence of chemical-specific monitoring data.

The use of computer modeling combined with an evaluation of monitoring data for similar compounds (and estimates of treatment effectiveness) is another approach to estimate pesticide concentrations in drinking water. Modeling tools are especially valuable when monitoring data are scarce or not available. This is often the case for pesticide degradates and always the case for pesticides pending registration. Importantly, it is extremely difficult to accurately characterize peak exposures based on monitoring data for pesticides that have acute toxicologic endpoints of concern. Using validated, predictive models along with monitoring data on similar compounds, OPP could estimate a distribution of pesticide concentrations in water as a result of normal label use at different locations and apply treatment factors where appropriate in order to estimate pesticide concentrations in drinking water. However, any use of ambient monitoring data should be carefully characterized as to how representative of actual drinking water the monitoring data are. For example, if water quality monitoring data representing ambient water sources too small to be considered realistic drinking water sources are the only available monitoring data, these data would have to be characterized as such. If these data were used in a cumulative exposure assessment, the results would be considered preliminary only.

Pesticide impacts on drinking water are often seasonal in nature and are driven by time of application and the weather conditions present during or shortly after application. Therefore, temporal variation in pesticide concentrations in drinking water should be considered in any individual-based, cumulative exposure assessment for drinking water.

#### ***4.2.2.3 RESIDENTIAL AND OTHER INSTITUTIONAL SOURCES***

Applications of pesticides made in and around homes, schools, offices and other public areas may result in potential exposure via the oral, dermal and inhalation routes. Co-occurrence and linkage of uses are particularly important for residential uses. Linked uses are those in which two products are used in combination, such as dipping a pet and treating the carpet of a flea infested home. 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, the understanding of patterns of use is limited although the Agency is aware of efforts to conduct surveys describing the use habits of the U.S. public. Current exposure assessments for residential and other nonoccupational sources will most commonly be conducted using the *Residential Standard Operating Procedures* (EPA, 1999). The Residential SOPs provide the basis for a screening level assessment of exposure and may not provide estimates of exposure that can be accumulated across chemicals.

Sources of information for the estimation of residential exposure include:

- Residential Standard Operating Procedures,*
- Guidance for Performing Aggregate Exposure and Risk Assessment*
- Product labels
- Exposure Factors Handbook
- Monte Carlo Guidance Document
- National Home and Garden Use Survey*

OPP is aware that additional data that will increase the ability to estimate residential and institutional exposures are being developed by the Residential Exposure Joint Venture, the Outdoor Residential Exposure Task Force and the National Pest Control Operators.

The factors for consideration in developing reasonable exposure scenarios for residential, nonoccupational and institutional exposures are described in detail in a previous EPA document (EPA, 1999b). As described in that document, the patterns of use for pesticides in residential, nonoccupational and institutional settings are highly dependent upon location, season, dwelling type and a myriad of other factors that impact the behavior of a potential pesticide user. An assessor should attempt to make a connection between these residential pesticide use preferences and a particular type of individual, based on data, when performing cumulative exposure assessments. Where data are limited in quantity or are of poor quality, the Residential SOPs should serve as the basis for initial estimates of exposure. The Residential SOPs are by nature designed to produce screening level assessments that are intentionally conservative in nature. Combining exposures for the members of the CAG based on this screening level assessment should be approached with caution because of the potential for compounding conservative assumptions. As better data become available, residential assessments can be refined to reflect distributions of exposure based upon residue decline, probabilities of product use, variable use rates, and likelihood of use of multiple or mixed products.

Age/gender/pathway considerations play a role in cumulative assessments related to the behavior of the individual. Young children may be exposed to more pesticide residues For a variety of reasons. For example, young children engage in more hand-to-mouth activity (non-dietary

ingestion) than adults. Some national surveys of home and garden pesticide usage suggest that more males than females treat lawns while females are more likely to treat the interior of the house. Consideration of data of this type will aid in developing reasonable and realistic aggregate exposure and risk assessment scenarios.

To the extent possible, the assessment of residential, nonoccupational and institutional use patterns should characterize seasonal and geographic variations. Although not as highly localized as drinking water data, these types of uses cannot be assumed to track with the large regional breakouts currently used in the dietary (food) assessment arena. For instance, a regional dietary (food) assessment will cover the entire Pacific Northwest region of the U.S. However, the coastal regions of Washington and Oregon are more humid and have a milder temperature regime than would be found in Idaho. Residential uses of pesticides would likely differ considerably between these two areas because of differences in pest pressure even though they are within the same "region." Cumulative risk assessments should reflect use patterns and practices on a scale sufficient to capture the variability in pesticide use. In addition, a natural overlay of market share by region may help to direct the risk assessor in determining the scope of the CAG to combine on a geographic basis. An example of the incorporation of this type of data into the assessment is the very localized use of temephos for mosquito control in parts of southern Florida. This pesticide should have only limited consideration in the assessment of other organophosphate pesticides including those used for mosquito control.

#### ***4.3 ASSESSMENT OF THE EXPOSED POPULATION***

As stated previously, demographic information available from the food consumption and residue data base can be used to characterize potentially exposed subpopulations. Each assessment will focus on a single subpopulation for which the demographic characteristics have been carefully defined. The age, gender and geographic location of the group included in the investigation of the food exposure pathway can be linked with exposure scenarios in the other two pathways of exposure. The individual consumption records in the database linking the demographic and other descriptors will be used to simulate the consumption patterns of the population or sub-population of interest. The likelihood and frequency assumptions for residential scenarios would be used to superimpose a pattern of residential exposures that would reasonably be expected to occur throughout the year for that individual in the population.

The population subgroups that are most commonly of concern to OPP can be defined by a number of factors, including demographics, geographic location, and time. Demographic considerations would include age, gender, ethnicity and any other considerations that may be important in evaluating subpopulations with potential, special susceptibilities. The geographic location of the exposed population will be needed to help match geographically-based exposure data 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 should be estimated where possible. The estimates of percentiles of exposure and associated risk should be factored against the target population size to determine the magnitude of the risk. The following examples may serve to more fully illustrate these concepts:

Example A: Insecticide A has been determined to have detectable residues on wheat, which is used in commercial bread production, and a number of fresh and canned vegetables. The insecticide is also used in home gardens both on food crops and in general on lawns and flower gardens in the spring and summer primarily in the eastern United States. The pesticide has also been detected in several major rivers in the eastern United States which are used for drinking water by numerous communities of medium and small sizes. These community water systems have only the basic water treatment facilities which are known not to remove Pesticide A from the water. The dietary consumption data identifies children six to twelve and adult males as large consumers of commercial bread, and children one to six of being large consumers of green beans, one of the vegetables treated with the pesticide. In this scenario, the population of interest for a single pathway or where multiple pathways converge can be identified by matching the pesticide use information with the demographic data from the dietary (food) consumption data in several ways: by consumption only; by ethnicity and consumption; by ethnicity, consumption and geographic location. The latter may be the most appropriate since the home garden use may be a more important scenario in medium and small communities than in large urban areas. Time considerations would also be a factor since home use of the pesticide would be seasonal. In this example, the population of concern could be a six year old child in a northeastern city consuming food and drinking water containing Pesticide A, and playing in a garden treated with pesticide A in the spring.

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

the use period of Herbicide B would vary with use region based upon climate. The period of the year upon which the assessment would focus would vary depending upon location.

Example C: Insecticide C is used on a number of food crops and has been detected by PDP in 90% of these crops. It is also used in and around the home and lawn for ant, roach, and flying insect control as well as in pet collars. There are no monitoring data for surface water, but modeling data suggest that it may be present at levels of concern. Usage data indicate that home use of this insecticide is greatest in the Eastern United States, with heaviest usage in the Southeastern United States for ant and termite control. Given the prevalence of Insecticide C in dietary (food) monitoring, the outcome of the dietary (food) risk assessment would give an indication of the likely subpopulations of concern.

Note that none of the example scenarios leads to a high detailed, multipathway quantitative cumulative risk assessment. They do indicate subpopulations of potential concern. However, additional exposure data would be needed to confidently estimate multipathway cumulative risk.

#### ***4.4 DETERMINATION OF TIME FRAMES FOR THE ASSESSMENT***

The time frame over which an exposure occurs is a key criterion for defining scenarios of interest. For example, depending upon the nature of the common toxic effect and the use patterns for a pesticide, the assessment may focus on the day an item of food is consumed, or extend the time of evaluation over several days following a home pesticide use. The time frame will determine how exposures from different pathways and routes will be evaluated. This step depends heavily upon examination of the toxicity data, but requires the concurrent 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. The consideration of time frame from the toxicity study should include an evaluation of time to onset of effect, impact of dose on time to onset, and time required for reversal of the effect (if the effect is reversible) following cessation of exposure. Where exposure scenarios are found to be of insufficient duration to trigger the common toxic effect, 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 cumulative risk 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.

Until adequate data are available, conducting single pathway assessments for multiple chemicals may be prudent. The single pathway assessments can be considered in concert to provide a qualitative estimate of total cumulative risk. In developing a detailed exposure assessment for multiple pesticides with a variety of use patterns, estimated cumulative exposure would consist ideally of the exposure from each pesticide by each pathway on a day by day basis. Components of

exposure should be matched to a route specific toxicity endpoint. These considerations are discussed more fully in the Aggregate Assessment Document (EPA, 1999b). However, at this time the understanding of use patterns for pesticides in residential settings is limited. Similarly, little data reflecting potential overlap of pesticides in tap water and the duration and timing of pesticide occurrence in tap water are available. Obtaining these data will be critical to developing detailed, multipathway analyses and providing accurate risk estimates for cumulative exposures to pesticides in the CAG. 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.

In performing cumulative risk assessments, an assessor may first consider the relevant toxicological information for each route (and then pathway) of an individual's exposure. An individual's dose should be matched against relevant toxicological doses in terms of one of the approaches that are outlined in Chapter 5 of this document.

#### ***4.5 EXPOSURE CHARACTERIZATION***

The exposure characterization is a description of data inputs to the assessment, key analyses, assumptions (and their potential impact on the outcome of the cumulative risk assessment), the assessment results and the conclusions drawn. The characterization provides a statement of purpose, scope, level of detail, and approach used in the assessment, identifying 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, 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, e.g., use of screening-level methods versus monitoring data reflective of residues close to the point of consumption or contact. The exposure characterization routinely includes the following, as appropriate, for the data available:

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

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## **6 ESTIMATION AND CHARACTERIZATION OF CUMULATIVE RISK**

### **6.1 INTRODUCTION**

This chapter describes how the cumulative risk assessment can be conducted once sufficient information has been gathered to define potential exposures and hazard for each member of the cumulative assessment group<sup>2</sup> (CAG). The route and duration of exposures should be reconciled with the temporal and route specific characteristics of the toxicological data; and the magnitude, frequency, and duration of exposures as well as co-occurrences should be established for developing exposure scenarios (Chapter 4). The points of departure for the toxicological common endpoint and a method for combining the common toxicity have been identified (Chapter 5).

Cumulative risk is estimated while maintaining the appropriate spatial (e.g., location and type of home; urbanization, watershed or aquifer characteristics), temporal (e.g., duration, frequency, and seasonality of exposure, frequency of residential pest control), and demographic (e.g., age, gender, reproductive status, ethnicity, behaviors) linkages of exposure and toxicology data for the CAG. As in aggregate risk assessment (see EPA, 1999b), cumulative risk assessment proceeds by establishing reasonable exposure scenarios for a hypothetical individual over a specific interval of time. The scenarios help to identify populations of concern, and to define critical windows of time and routes of exposure that should be appropriately linked to the common toxic effect. In the case of cumulative risk assessment, the potential for overlapping exposure to multiple chemicals by multiple pathways of exposure **should** be established. There will be different linkages and co-variances in cumulative risk assessment that should be conserved, but which may not have been considered in previous single chemical, aggregate analyses (i.e., one can not simply sum the aggregate risk estimates for the group of chemicals shown to have a common mechanism of toxicity).

Particular attention should be paid to the following factors in conducting a cumulative risk assessment:

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<sup>2</sup>**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.

- ❑ An individual's exposure should be matched with the relevant toxicological characteristics of the CAG in terms of route and duration of exposure.
- ❑ If data permit, exposures from a variety of potential routes should be combined over comparable time frames, defining a range of possible exposures.
- ❑ The integrity of the exposure concerning the hypothetical individual should be maintained throughout the cumulative risk assessment (i.e., same individual at the same time, in the same setting, under the same geographic conditions). Maintaining a consistent pattern of demographics and geographic location will permit better estimation of overlapping exposures from varying sources. A full quantitative, cumulative risk assessment should include consideration of the following major issues defining the potential exposure to the hypothetical individual:
  - ✓ Uses among products and product types are linked and should be considered in appropriate combination to reflect the linkages,
  - ✓ Relationship of the exposures by routes should 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 should also be maintained.

At this time, data will rarely be available to permit evaluation of these all critical parameters. The integration of these factors, if available, and their significance in the risk assessment process will be discussed below.

In summary, the basic concept underlying cumulative risk assessment is that exposure occurs to a hypothetical exposed individual. The integrity of the data concerning this exposed individual should be consistently maintained throughout the cumulative risk assessment. Each of the individual, "sub-assessments" should be linked back to the same person and the intake should reflect the dietary (food), drinking water, and residential intakes that are for the same individual at the same time, in the same place, and under the same demographic conditions. In other words, the cumulative exposure to the CAG should agree in time, place, and demographic characteristics (adapted from ILSI, 1998a).

## **6.2 CALCULATING CUMULATIVE RISK**

The ultimate goals of the cumulative risk assessment are as follows: 1) to define likely exposure patterns for the population of interest; 2) to identify the major sources of exposure and chemicals that are driving the associated risk; and 3) to assist in the development of mitigation strategies to improve the overall risk profile. To support these goals, the assessor will need to provide the

exposure and risk estimates for a variety of subsets of data. Data should be provided as a distribution of exposure by each route (oral, dermal inhalation), and by each major pathway (dietary (food), dietary (drinking water), residential) as possible based upon available data. In addition, the total exposure and associated risk should be presented. Within each pathway, route and total distribution, the relative contribution of each chemical contributor should also be discernible.

It is important to keep in mind that a cumulative risk assessment differs from the single chemical, aggregate risk assessment both in focus and purpose. Because of the incorporation of input data describing the potential exposure to several chemicals simultaneously, the cumulative risk assessment will tend to become increasingly complex, especially when describing exposures to a CAG containing many chemicals. As discussed in Chapter 4, it will be necessary to focus exposure estimation activities on identifying those use/pesticide combinations comprising the largest and most important sources of risk from the use of the CAG members. Exclusionary criteria (as discussed in 6.2.2) should be used as appropriate to limit the focus of the quantitative assessment in order to provide risk estimates that are meaningful and useful.

In addition, because of the great complexity and potential for uncertainty in the cumulative assessment, the cumulative risk and evaluation of risk drivers will of necessity be an **estimate** of risk to a much greater extent than the results of the single chemical, aggregate assessment. The cumulative risk assessment will serve to identify the magnitude of likely exceedance of a cumulative acceptable exposure level, but only in a qualitative sense (i.e., because of uncertainty and lack of precision). The outcome will serve as a focus for returning to the detailed, quantitative single chemical assessments to pursue any necessary risk mitigation activities. In other words, the cumulative risk assessment can be envisioned as a barometric reading, suggesting only a broad scale directional change to be used in conjunction with the highly sophisticated "weather forecast" of the aggregate assessment which will provide a specific measure of the risk for individual pesticides.

### ***6.2.1 PREPARATORY STEPS***

Single chemical aggregate assessments should be conducted for each pesticide under consideration for inclusion in the CAG before initiating a cumulative risk assessment. The single pesticide aggregate assessments will be used to inform the risk assessor in designing the cumulative risk assessment and for identifying negligible pesticide/use combinations that may be initially excluded from quantitative analysis. However, a multi-pesticide cumulative risk assessment generally cannot be performed by summing single pesticide, aggregate assessments. The cumulative risk assessment should reflect linkages and co-occurrences of use between competing pesticides. These factors generally cannot be established from single chemical aggregate assessments because they were not included for consideration. In addition, some of the underlying assumptions regarding the use of

the toxicity data for a single chemical may differ markedly from those for a CAG, and factors relating to typical versus high end use data will differ depending upon whether the assessment focuses on multiple pesticides or a single pesticide. The cumulative risk assessment should be conducted beginning from the base data and cannot be reconstituted from preexisting single pesticide aggregate assessments.

### ***6.2.2 SELECTING CHEMICALS FOR CONSIDERATION IN THE CUMULATIVE RISK ASSESSMENT***

As indicated in Chapter 3, not all chemicals included in the CMG will be included in the CAG. The hazard and exposure data compiled as described in Chapters 3 and 4 will serve as a basis for determining which members of the CMG should be retained in the CAG. The exposure and use data can be evaluated to identify pesticides that have uses that are limited in nature and unlikely to result in overlapping exposures with other pesticides. For example, if a pesticide's uses are limited to contained methods of application such as bait boxes or gels designed for injection behind base boards, essentially no exposure is anticipated and the pesticide would not be included in the CAG. Factors relating to pharmacokinetics of the chemical in the body may also result in exclusion from the CMG.

### ***6.2.3 IMPACT OF DATA QUALITY ON DESIGNING THE ASSESSMENT***

Ideally, cumulative risk should be assessed for multiple chemicals by multiple pathways simultaneously. Currently, availability of exposure data for some chemicals may limit OPP's ability to conduct multipathway and multiroute assessments. Raised previously in Section 4 of this document, this consideration is the major driver in selecting the approach to cumulative exposure and risk assessment. Only exposure datasets of similar quality should be combined because of the uncertainty and loss of precision that would be introduced into the assessment by combining datasets of disparate quality. For example, highly refined estimates of dietary (food) exposure could appropriately be combined with estimates of dietary (water) based upon monitoring of tap water in which pesticide co-occurrence were measured. Both sets of data reflect closely the likely exposure to the members of the CAG. An example of disparate data quality would be where highly refined dietary (food) data are available, but only screening level estimates are available from residential SOPs. In this case, the precision of the two exposure estimates are very different and normally they would be treated separately for purposes of quantitative assessment. Given the current state of available data, the three major pathways of exposure may be assessed quantitatively in separate steps because the disparate nature of the data available may obscure important patterns of exposure and source contribution that can be determined from the cumulative exposure and risk assessments. If such a separate quantitative assessment is done, a qualitative assessment of the combined pathways should be performed.

The ability to reliably conduct a detailed dietary (food) cumulative assessment for multiple chemicals is possible for at least some subset of food/chemical combinations for which multianalyte monitoring data have been performed. An example of this is data 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 multiresidue monitoring data that are available.

It is anticipated that inclusion of exposure to pesticides in drinking water in quantitative cumulative assessments will be limited for the near future. This is because dietary (drinking water) assessments frequently rely upon back calculation from a predetermined acceptable exposure level and an estimate of the amount of the acceptable exposure already taken by dietary (food) and residential sources of exposure. The back-calculated value, the 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 multichemical assessment. Combination of screening level values such as those used in the DWLOC process will result in the compounding of conservative assumptions and produce estimates of risk from exposure to pesticides in drinking water with very high levels of uncertainty. However, for chemicals that have a common mechanism of toxicity and have been shown to co-occur in surveys such as NAWQA, combining of patterns of co-occurrence with a group of high-end water residue estimates in a cumulative dietary (drinking water) risk assessment may be used qualitatively to provide focus for targeting future data collection activities, refinements of existing risk estimates and risk mitigation activities. EPA is aware of ongoing survey efforts to obtain good quality monitoring data on pesticides in drinking water. As these data become available, it will become possible to conduct of more refined cumulative risk assessments that more accurately reflect real world drinking water exposures.

Because most residential and other nonoccupational assessments rely upon screening level methodologies at this time and little information is currently available on actual use patterns and application rates by the consumer, multichemical assessments for this pathway should also be approached with caution. The outcome of such an assessment is anticipated to be qualitatively different from the dietary (food) assessment and, therefore, ordinarily would not be combined with it. Sufficient data and screening level assessment tools are available to support performance of a cumulative residential exposure and risk assessment at a screening level in order to prioritize further risk assessment refinements. Such an assessment also may be useful in identifying use patterns of concern and identifying potential areas for risk mitigation. However, the outcome of these assessments is anticipated to be highly conservative in nature.

### **6.3 PARAMETER DEFINITION**

Once the exposure data are gathered and use and exposure scenarios are determined for each member of the CMG, 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 exposures will occur? To continue with the example above, a mosquito treatment in the Southeast should be matched with other potential exposures during the spring and summer and only in the Southeast. The cumulative exposure assessment should be carefully structured to avoid mismatches of exposures such as spraying for black flies in Minnesota in the summer with a termiticide treatment in Georgia in the fall.

### ***6.3.1 TIME FRAME***

A cumulative risk assessment should be conducted using a single time frame selected considering the time to onset of the common mechanism effect and also the time for reversibility of the effect (if it is reversible). As described in Chapter 4, a major determinant in the selection of the time frame(s) for evaluation is the defined conditions of expression for the common toxicity by duration and route. However, use patterns and likely patterns of exposure will also provide input into selection of the appropriate time frame. OPP will assume that pesticides that have food uses have the potential to cause chronic exposures. Such an assumption is generally appropriate given the nature of food distribution and storage in the U.S. unless a particular use is highly seasonal in nature and the commodity in question is only consumed fresh. However, for products with no food uses, the time frames for consideration can also be bounded by the period of time over which a likely exposure (probably residential or institutional) is anticipated to occur. In practice, the assessment should be conducted one time frame at a time, using a rolling time period over the calendar year. In other words, if the critical time frame for consideration is one week, a cumulative assessment should be performed sequentially for individuals on days 1 to 7 of the likely exposure window, then days 2 to 8, days 3 to 9, and so forth. This approach is described in greater detail in a previous document (EPA, 1999b).

### ***6.3.2 GEOGRAPHIC SCALE***

The outcome of a cumulative risk assessment will be a family of geographically oriented assessments rather than a single, national level assessment as is commonly conducted for single chemical dietary (food) risk assessments. The construction of a multichemical, multipathway assessment can be envisioned as assembling a series of clear plastic overlays in different combinations depending upon the geographic variability and scale of each component of the risk assessment. Each overlay would contain a map unit of different scale depending upon whether a highly localized area (a single watershed) or a much larger area (defining residential lawn care

uses) were represented. The dietary(food) risk assessment is a national assessment that assumes even distribution of treated commodities across the entire U.S., with the potential for breakout by region and subpopulation to permit accommodation of differences in consumption patterns that may be observed. This assessment can be envisioned as the base over which smaller scale risk assessments for residential and water may be superimposed. Residential risk assessments vary by geographic location because of differences in climate and pest pressure that occur across the U.S. The differences in climate will reflect temperature zones and seasonality differences encountered throughout the country, resulting in geographic areas ranging from a few states to whole regions in size. For example, Maine, Vermont, New Hampshire and Massachusetts might exhibit similar use patterns for residential lawn care products, with a relatively short period of application in the late spring to early summer. This use area could be overlaid upon a grosser scale regional dietary (food) risk to give a detailed smaller scale use area. Examination of the range of residential uses across different geographic regions would provide a mechanism to pursue the identification of a regional breakout for residential uses. Finally, the source of drinking water could further be superimposed to focus the risk assessment. Water source is anticipated to produce a much more localized type of assessment, varying from a large urban area drawing water from a variety of sources to highly localized sources such as single water sheds or wells. Conceptually, one way of implementing this type of assessment would be to use a Geographic Information System (GIS) approaches in conjunction with adequate definition of the distribution of residues in drinking water and sufficient understanding of the regional component of residential and institutional pesticide use and the nature of the resulting residues. The output of such an approach would consist of a series of risk assessments reflecting the collection of uses and potential exposures unique to that geographic area and similar areas for which it may serve as surrogate.

Currently, OPP's ability to perform detailed, geographically descriptive assessments as described above is constrained by the limited availability of data. Many local level exposure assessments for drinking water may be performed on an individual-by-individual basis and combined into a population-based exposure assessment. These estimates of exposure can then be combined with individually correlated exposures determined for foods. Existing dietary (food) exposure models could be used for different regions to incorporate the local distribution of pesticide concentrations in drinking water. The quality of the local exposure assessments for drinking water is dependent on the quality and availability of local data sets for estimating pesticides residue levels in tap water. Using local drinking water data, an assessor could link a food consumption record from a respondent from a certain region of the country with an appropriate drinking water data value or distribution from a water shed or locality within the region. As mentioned in Chapter 4, sufficient data may exist to permit the estimation of a distribution of some pesticides based upon surveys. In these cases, it may be possible to combine distributions of residues in drinking water for particular geographic areas with distributions of food residues for the same region to develop a localized dietary (food + water) assessment.

Situations may exist where specific sub-populations have a different potential for exposure through drinking water to a pesticide than the rest of the population. These situations may exist where a pesticide's use pattern is very narrow, e.g., application to a specific ornamental plant in one county. In this situation, only the population potentially affected, (i.e., living in the county), should be considered as exposed to that particular member of the CAG in the cumulative risk assessment. The rest of the population would be handled in a separate cumulative risk assessment that does not include that pesticide.

A pesticide with a broader use pattern may require a drinking water exposure assessment that includes multiple counties, states, even a geographic region. Such an assessment could be conducted by combining residue data from various drinking water sources if the data are judged to be sufficiently similar through appropriate statistical tests. However, pesticide use usually impacts different drinking water sources to different degrees. This should be taken into account in the exposure assessment. For example, a particularly vulnerable water source (community water system) would be suitable for use in estimating the potential drinking water exposure for individuals who drink from that community water system, but should not be the basis for an exposure assessment for individuals living nearby, and drinking from another, less vulnerable source of drinking water. In situations where residue data from several drinking water sources may be combined into one distribution of residue data, it is desirable to know the population associated with any specific drinking water source included in the exposure assessment. Knowing the size of the population served by a specific drinking water source allows for population-weighted exposure assessments. A population-weighted exposure assessment accounts for the probability that a specific portion of the population considered in the assessment may be more highly exposed than the majority of the population considered. Depending on the quality of the data chosen for the assessment, i.e., how representative they are of actual drinking water concentrations, a dietary (drinking water) assessment for the members of the CAG could be produced to permit the focus of further risk assessment efforts on areas of greatest concern or to estimate to estimate drinking water exposure and risk. If, however, a screening level assessment is all that is available, it should not be combined with a highly refined dietary (food) risk assessment because of the previously stated concern of obscuring results with increased uncertainty.

### ***6.3.3 SUBPOPULATIONS OF CONCERN***

Cumulative risk assessments should characterize multiple subpopulations depending upon the nature of the common toxicity, and the geographic distribution of use and attendant exposure. The nature of the common toxic effect will determine what portions of the population are susceptible to experiencing the common toxic effect in question. For example, males are not a reasonable target population for experiencing adverse effects related to pregnancy. For a common toxic effect that is limited in its applicability, the cumulative assessment should be tailored to focus on those groups that are susceptible. Similarly, if the use of a chemical is limited to a specific geographic locale, the

subpopulation of concern should be selected with appropriate consideration of: potential for exposure in drinking water; matching of residential and institutional use patterns that are reflective of the region under consideration; and any peculiarities of food consumption patterns or residue distributions that might impact the assessment result.

#### **6.4 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 drivers 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.

##### **6.4.1 INTERPRETATION OF RISK VALUES**

The outcome of a cumulative risk assessment usually 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 the NOAEL for an index chemical. Cumulative risk values should be expressed only as whole numbers and not as fractional values so as not to imply greater precision than actually exists. The interpretation of a cumulative risk outcome will of necessity be different than for a single pesticide 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). A cumulative MOE or cumulative %PoD should be carefully interpreted in the context of the supporting information, attendant uncertainties, and consideration of the regulatory health endpoints upon which the aggregate or pesticide specific assessments are based.

#### **6.4.2 APPLICATION OF POLICY-BASED GROUP SAFETY AND UNCERTAINTY FACTORS**

When conducting a cumulative risk assessment, the traditional five uncertainty factors applied in single chemical noncancer risk assessment are applied (see Table 6-1). Essentially the same uncertainty factors are taken into account in a cumulative hazard assessment but 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. As discussed in Chapter 5.2, two of the traditional uncertainty factors -- extrapolation from a LOAEL to NOAEL and from a subchronic to chronic exposure -- are applied before accumulating risk as adjustments on specific chemical members to insure that the doses representing points of comparison for relative potencies are uniform. These chemical specific adjustments tend to be more data driven decisions. The uncertainty factors discussed below tend to be more policy driven than data driven and are applied as a group composite factor.

**Human Inter-Individual Variation:** Given that the cumulative assessment is focused on a common effect (versus a chemical per se) that arises via a common mechanism, the factor used to account for human (intraspecies) variability should pertain to the CAG as a whole. When accounting for intraspecies differences, a factor of 10-fold is employed as a science policy default for the entire CAG.

**Interspecies Differences:** The cumulative assessment is constrained by use of PoD based on a common toxic response derived from a similar species/strain/sex and duration of exposure to achieve a uniform measure of relative potency. It is unlikely that human data on all chemicals in the CAG will be available or sufficient for quantitative use in cumulative assessment. Given that the same laboratory test species will be used, the uncertainty factor used to account for inter-species differences will pertain to the CAG as a whole, and thus is to be applied at the end of the cumulative assessment process. 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).

**Data Completeness and Quality:** 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 human risk concerns. 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 factor to be applied after accumulating risk.

**TABLE 6-1. Uncertainty Factors in Noncancer Chemical Specific Risk Assessment versus Cumulative Risk Assessment<sup>3</sup>**

FACTOR	RfD/RfC Approach for Chemical Specific Assessments	Proposed Approach for Cumulative Assessments
<b>LOAEL to NOAEL (UF<sub>L</sub>)</b>	≤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 <b>applied before accumulating</b> the hazard (see Section 5.2).
<b>Subchronic to Chronic (UF<sub>s</sub>)</b>	≤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 <b>applied before accumulating</b> the hazard (see section 5.2).
<b>Interhuman Variation (or intraspecies) (UF<sub>H</sub>)</b>	≤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 <b>applied as a group factor after accumulating</b> the hazard (see section 5.3).
<b>Experimental Animal to Human (interspecies) (UF<sub>A</sub>)</b>	≤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 <b>applied as a group factor after accumulating</b> the hazard (see section 5.3).
<b>Incomplete Data Base to Complete Data Base (UF<sub>D</sub>)</b>	≤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 <b>applied as a group factor after accumulating</b> the hazard (see section 5.3).
<b>FQPA Safety Factor</b>	≤10-fold factor that may be retained or revised in the risk	The FQPA safety factor is <b>applied in the risk characterization step</b> . It is applied only if it

<sup>3</sup>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.

The policy based factors should be applied after the cumulative risk assessment has been performed and are applied to the CAG, not to the individual chemicals. As such, these factors will be the same for all chemicals across the assessment. This approach is consistent with the presumption that the adverse effect that is the basis for the POD results from the operation of a common mechanism within the organism. That is, if a the common mechanism upon which the POD is based causes particular concern for children, and is truly common to all members of the CAG, application of the FQPA safety factor should be consistent based upon **that mechanism**, and is not chemical specific.

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, should be revisited 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, situations may arise where a FQPA safety factor was retained for some but not all pesticides in a CAG based on a finding of special sensitivity in the young. The data on each of the pesticides should be considered together to evaluate whether to retain the FQPA factor as applied to the CAG or not. Particular attention should be paid to whether the increased sensitivity in the young is related to the end point that reflects the common mechanism. 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 provided on the considerations to be addressed when making judgements about the FQPA safety factor.

Similarly, if one member of the CAG is lacking data relevant to defining the nature and potency of the adverse effect mediated by the common mechanism of toxicity for the CAG, it is reasonable to assume that the missing data can be extrapolated from the more complete data bases for the other members of the CAG. The characteristics of the dose response and nature of the effect should be consistent across the CAG if the adverse effect is mediated by a common mechanism. Therefore, the uncertainty factor for the CAG related to database quality should reasonably be applied to the CAG as a whole and not individually to each chemical member. For example, assume that the adverse effect upon which the POD is a developmental effect mediated by the binding of a

metabolite of the chemical to a receptor. In the case of all members but of the CAG except Chemical A, data are available that permit estimation of the relationship between metabolite production and the dose related expression of the adverse effect. For one chemical, adequate metabolism data are lacking for comparison to the dose response data from a developmental toxicity study. On a single chemical basis, the POD for Chemical A might contain an additional 10-fold uncertainty factor to allow for the missing data.. However, when considered with the other members of the CAG the additional 10-fold uncertainty factor may not be required because the missing data can be extrapolated based upon the data for the other members of the CAG.

### **6.4.3 CHARACTERIZING THE UNCERTAINTIES**

Uncertainties are generally encountered in any risk assessment process. In the case of cumulative risk assessment, uncertainties for the CAG can be appreciable depending upon the nature, amount, and quality of data. Thus, the risk characterization should include a discussion of what data are missing or poorly understood, in order to convey a clear sense of the degree of confidence in the resulting risk values (or range of values).

The risk characterization is a necessary part of generating any Agency report on cumulative risk assessment, whether the report is preliminary to support allocation of resources toward further study or comprehensive to support regulatory decisions. In the former case, the detail and sophistication of the characterization are appropriately small in scale; in the latter case, appropriately extensive. Also, on the continuum from simple to more sophisticated assessments, assumptions are used at almost every stage. The use of assumptions is predominant at screening stages and they are used less as more data are gathered and incorporated. The risk characterization should carefully delineate which issues in a particular assessment are most important.

The values supported by a risk characterization throughout the process are *transparency* in environmental decision-making, *clarity* in communication, *consistency* in core assumptions and science policies from case to case, and *reasonableness*. While it is appropriate to err on the side of protection of health and the environment in the face of scientific uncertainty, common sense and reasonable application of assumptions and policies are essential to avoid unrealistic estimates of risk (USEPA, 1995). Both integrative analyses and the risk characterization summary present an integrated and balanced picture of the analysis of the hazard, dose response, and exposure. The risk characterization should summarize the evidence and results, and describe the quality of available data, the relevance of the data to actual exposures, and the degree of confidence to be placed in the risk estimates. Important features include the constraints of available data and the state of knowledge, significant scientific issues, and significant science and science policy choices that were made when alternative interpretations of data existed (USEPA, 1995). Choices made

about using assumptions or data in the assessment are explicitly discussed in the course of analysis, and if a choice is a significant issue, it is highlighted in the summary.

The risk characterization process includes an integrative analysis followed by a risk characterization summary detailing the major results of the risk assessment. The integrative analysis brings together the assessments of hazard, dose response, and exposure to make risk estimates for the exposure scenarios of interest. The integrative analysis typically identifies the element of the aggregate analysis which most affects the exposure and risk conclusion for use in decision making. It is an appraisal of the science that supports the risk manager in making public health decisions. Risk characterization reports also indicate where the greatest opportunities for data or methodological improvements exist.

#### ***6.4.4 CONTENT OF CUMULATIVE RISK CHARACTERIZATION SUMMARY***

Overall, the risk characterization routinely includes the following 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 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 chemicals or similar scenarios by another organization.

## **APPENDIX A: Case Study on Cumulative Risks**

### **Note to Reader:**

The Food Quality Protection Act (FQPA) of 1996 directs EPA to conduct cumulative risk assessments on pesticides that share a common mechanism of toxicity. In order to solicit scientific peer review on the principles and approaches for conducting cumulative risk assessments, the Agency is submitting this case study to the Scientific Advisory Panel (SAP) for review.

It is important to note that the analysis, especially the exposure calculations, in this study do not reflect real-world conditions. The calculations are only for a limited number of pesticides, a limited number of uses, and do not reflect the most current use patterns. The case study is only for the purposes of illustrating a scientific methodology, and it would be inappropriate to draw any regulatory conclusions based on this case study.

This is a significant early step as the Agency proceeds to develop a sound and scientifically credible process for conducting cumulative risk assessments as part of the mandate under FQPA to protect public health and the environment. EPA intends to use the SAP's findings, as well as public comments received through a public comment period to begin in early 2000, to further refine this approach.

## ***Appendix A***

### ***Case Study: Inhibition of Cholinesterase and Cholinergic Effects***

#### ***1 INTRODUCTION***

The following case study demonstrates the application of the principles for conducting a cumulative dietary (food) risk assessment. In this case study, three pesticides that exert their toxic effects by a common mechanism are evaluated. The selection of endpoint, normalization of the hazard from each and assessment of exposure and risk are demonstrated. Pesticide residue data in foods are taken from the Pesticide Data Program (PDP) in which co-occurrence of the pesticides in this example was measured. The example does not extrapolate from existing data. A number of departures from normal practice in using monitoring data have been taken in order to simplify the example and facilitate discussion of process and demonstrate results. The conclusions presented in this case study should not be considered as an expression of regulatory intent. This example of a hypothetical cumulative risk assessment is limited to the dietary exposure of four U.S. population groups to three organophosphate pesticides from consumption of apples, pears, and peaches. This assessment does not address the additional exposures that potentially occur from these and other pesticides with a similar mode of toxicity on many other foods and water. It also does not address the exposures that potentially occur from dermal or inhalation absorption of these chemicals.

#### ***2 TOXICITY PROFILES OF ORGANOPHOSPHORUS CHEMICALS A, B, and C***

For the purposes of this assessment, data from three pesticides have been evaluated to develop the basis for normalizing the toxic response (acetyl cholinesterase inhibition) to permit the development of a cumulative risk assessment. In this section, the logic used in selecting endpoints for an acute dietary (food) assessment and for selection of an index chemical for use in a relative potency factor (RPF) approach is presented. The selection of endpoints, points of departure, and application of adjustment and uncertainty factors for use in an acute dietary cumulative assessment are components of the hazard identification process in the cumulative risk assessment process.

##### ***2.1 COMMON MECHANISM OF TOXICITY***

The Agency has recently announced its conclusion that organophosphorus pesticides act by a common mechanism of toxicity (*A Common Mechanism of Toxicity : The Organophosphorus Pesticides*, Health Effects Division, 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 (Miles 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.

In the example case studies that follow, cholinesterase inhibition (ChEI) is consistently the most sensitive, common 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. Thus, 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 effect for a cumulative risk assessment. The toxicity profiles presented below present hazard characteristics on each of the chemicals that need to be considered before selecting specific endpoints to be used in a cumulative risk assessment. Adjustment factors that may need to be applied to the common effect are also presented. The case studies 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.

Not all data pertaining to an individual chemical included in the case study are presented since, normally, a cumulative hazard and exposure assessment will rely on information provided in peer review reports issued by the Health Effects Division. Thus, some information presented in the case study is a summary of conclusions stated in peer review reports. Complete details would be found in the peer review reports.

## 2.2 CHEMICAL A

### 2.2.1 SELECTION OF SENSITIVE SPECIES AND SEX FOR CHEMICAL A

Table 1A lists NOAELs and LOAELs for the pattern of effects from key studies with rats and dogs treated with Chemical A. The data in table 1A reflect the accumulated data defining the ChEI from available studies.

**Table 1A: Comparison of blood, RBC, and brain cholinesterase inhibition and signs of neurotoxicity in rats and dogs administered Chemical A**

STUDY	RBC NOAEL/LOAEL mg/kg/day	PLASMA NOAEL/LOAEL mg/kg/day	BRAIN NOAEL/LOAEL mg/kg/day	SIGNS
Acute Rat Neurotoxicity	10/100 (M)* 2.5/25 (F)	1.0/10.0 (M) 0.25/2.5 (F)	100/500 25/250 (F)	100/500 (M) 25/250 (F)
28-Day Rat Feeding	0.02/2.4 (M&F)	0.02/2.4 (M&F)	2.3/22.5 (M&F)	2.3/22.5 (M&F)
90-Day Rat Feeding	0.3/15 (M) 0.04/0.4 (F)	0.03/0.3 (M) 0.04/0.4 (F)	15/168 (M) 0.4/9.0 (F)	168/>168 (M&F)
90-Day Rat Neurotox. Feeding	0.02/1.7 (M) 0.02/1.9 (F)	0.02/1.7 (M) 0.02/1.9 (F)	1.7/17 (M) 1.9/19 (F)	17/177 (M) 19/196 (F)
90-Day Dog Feeding	0.02/5.9 (M) 0.02/5.6 (F)	0.02/5.9 (M) 0.02/5.6 (F)	0.02/5.9 (M) 0.02/5.6 (F)	0.02/5.9 (M) 0.02/5.6 (F)

\*M=male; F=female

The results reported for the acute and 90-day feeding studies conducted with Chemical A indicate that female rats show responses below those observed in male rats. Data from a 90-day study with dogs show that NOAELs for male and female dogs are equivalent. Based on consideration of the results of studies of the same duration in rats and dogs, the 90-day neurotoxicity study in rats and the 90-day feeding study in dogs, there are no apparent difference in NOAELs for plasma and RBC cholinesterase inhibition between the two species. Based on the increased sensitivity shown for female rats, the species and sex for which most of the data are available on the toxicity of Chemical

A, the female rat appears to be the species and sex of choice for selecting acute endpoints for use in an acute risk assessment.

### **2.2.2 SELECTION OF A CRITICAL EFFECT FOR CHEMICAL A**

With one exception, the 90-day feeding study in dogs, blood ChEI was reported to occur at doses well below those that led to an inhibition of brain cholinesterase or doses leading to frank cholinergic signs.

In 1 of the 5 studies (Table 1A), plasma cholinesterase inhibition in female rats was found at doses lower than RBC ChEI. In the acute neurotoxicity study with Chemical A, plasma cholinesterase inhibition occurred at a dose 10-fold below that which inhibited RBC cholinesterase in female rats. In the other 4 studies, NOAEL's for plasma and RBC ChEI are equivalent. According to the Hazard Identification and Assessment Review Committee, the methodology used for RBC ChEI measurements in the acute neurotoxicity study was judged to be flawed. (HIARC report, September 21, 1999). The HIARC evaluation of the methodology used in the acute neurotoxicity study when considered in conjunction with results of other studies with Chemical A that show similar inhibition in plasma and RBC's support a recommendation that if RBC ChEI is found to be the critical, common endpoint for chemicals A, B, and C the NOAEL for RBC cholinesterase inhibition in the acute neurotoxicity study for Chemical A should be adjusted to account for uncertainty regarding the reliability of the RBC ChEI measurements. If plasma cholinesterase is determined to be the critical, common endpoint for the three chemicals under review, no adjustment to the NOAEL is recommended.

### **2.2.3 DOSE-RESPONSE CORRELATIONS**

As shown in Table 2A, dose-response data for Chemical A may be adequate for calculation of ED values if data on plasma ChEI in female rats are used since there is a dose-related increase in ChEI at the two higher doses.

**Table 2A. Dose response for effects on RBC and plasma ChEI in rats treated with Chemical A.**

Dose (mg/kg/day)
------------------

<b>Cholinesterase Inhibition (% of Control)</b>	<b>1.0 (M) 0.25 (F)</b>	<b>2.5 (M) 2.5 (F)</b>	<b>150 (M) 150 (F)</b>	<b>300 (M) 300 (F)</b>
<b>RBC</b>	+2 (M) -8 (F)	-7 (M) -4 (F)	-82* (M) -76 (F)	-83 (M) -77 (F)
<b>Plasma</b>	+2 (M) -14 (F)	-27* (M) -53* (F)	-76* (M) -84* (F)	-76* (M) -85* (F)

#### **2.2.4 INCREASED SENSITIVITY ASSOCIATED WITH PRE- AND POSTNATAL EXPOSURES**

The Hazard Identification and Assessment Committee evaluated data that provided information on potential differential sensitivities between fetal and neonatal animals. Conclusions reached by the committee and presented in the committee's report are summarized below.

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. No data on ChEI in fetuses or neonates is available. Body weight gain decreases have often been shown to accompany depressions of cholinesterase activity in adult animals. In a developmental toxicity study 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 to Chemical A when compared with adult animals.

#### **2.2.5 OTHER CONSIDERATIONS**

**Pharmacokinetic/dynamic Interactions** - There are no data available to evaluate PK/PD interactions between Chemical A and any other cholinesterase-inhibiting chemical.

**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 to 100-fold greater than exposures which resulted in blood ChEI, neurotoxicity is not expected to result if exposures to Chemicals A, B, and C are limited to levels which do not result in blood or brain ChEI.

### ***2.2.6 WEIGHT-OF-THE-EVIDENCE***

Data on cholinesterase inhibition are extensive and support a conclusion that cholinesterase inhibition does not occur at a dose-level below 0.25 mg/kg/day in adult animals administered Chemical A acutely by the oral route. Data from the 90-day rat neurotoxicity study show that repeated dosing with 0.4 mg/kg/day (females) or 0.3 mg/kg/day (males) of Chemical A is required to inhibit plasma cholinesterase. Therefore, it would not be expected that the dose that would lead to peak plasma ChEI would be less than 0.25 mg/kg/day following an acute exposure. 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 can reasonable be assumed that young animals or animals exposed *in utero* are not more sensitive than adults to the effects of Chemical A.

## ***2.3 CHEMICAL B***

### ***2.3.1 SELECTION OF SPECIES AND SEX***

Table 1B lists NOAELs and LOAELs for ChEI and signs in different species and sexes reported from key studies involving acute and repeated exposure durations with Chemical B.

**Table 1B: Cholinesterase inhibition and cholinergic signs in rats, mice, dogs, and rabbits administered Chemical B in the diet.**

STUDY	RBC NOAEL/LOAEL (mg/kg/day)	PLASMA NOAEL/LOAEL (mg/kg/day)	BRAIN NOAEL/LOAEL (mg/kg/day)	SIGNS (mg/kg/day)
ACUTE RAT NEUROTOXICITY	<2/2 (M) <1/1 (F)	<2/2 (M) <1/1 (F)	<2/2 (M) <1/1 (F)	2/6 (M) 1/3 (F)
90-Day RAT NEUROTOXICITY	<0.91/0.91 (M) <1.05/1.05 (F)	0.91/2.81 (M) 1.05/3.23 (F)	0.91/2.81 (M) 1.05/3.23 (F)	2.81/7.87 (M) 1.05/3.23 (F)
2 YEAR RAT	0.75/2.33 (M) 0.31/0.96 (F)	0.25/0.75 (M) 0.31/0.96 (F)	0.75/2.33 (M) 0.31/0.96 (F)	NONE
1 YEAR DOG	0.69/3.84 (M) 0.78/4.33 (F)	0.15/0.69 (M) 0.16/0.78 (F)	0.69/3.84 (M) 0.78/4.33 (F)	0.15/0.69 (M) 0.78/4.33 (F)
18 MONTH MOUSE	Not measured	0.79/3.49 (M) 0.98/4.12 (F)	0.79/3.49 (M) 0.98/4.12 (F)	Not Reported
RABBIT DEV.*	1/2.5 (F)	1/2.5 (F)	2.5/6.0 (F)	2.5/6.0 (F)
RAT DEV.	Not measured	0.5/1 (F)	0.5/1 (F)	Not reported

\*DEV=developmental

Results reported for RBC and plasma ChEI inhibition in the acute and 90-day studies in rats with Chemical B do not suggest a differential sensitivity for male and female animals. The NOAELs listed in Table 1B for these endpoints in males and females, although different in some cases, reflect differences in dose selection as well as variability in ChEI measurements and do not necessarily reflect actual differences in sensitivities. Results reported for brain ChEI are not consistent. The NOAEL reported for brain ChEI in the 2-year rat study is lower for female rats than for male rats but other studies show brain ChEI inhibition occurs at similar doses in males and females when dose selection is taken into account. Regarding the reporting of signs, effects were noted at a lower dose for females in the 90-day neurotoxicity study in rats but signs were reported to occur at a lower dose in male dogs in the 1-year dog study. Considered overall, the data do not support a conclusion that one sex is more sensitive than the other to the effects of Chemical B administration.

Because the rat seems to be as sensitive or more sensitive than other species to the effects of Chemical B, and because the data on the ChEI effects are more extensive for the rat, the rat data should be used for conducting a cumulative risk assessment.

### 2.3.2 SELECTION OF CRITICAL ENDPOINT FOR CHEMICAL B

Based on results reported for treatment of rats with Chemical B, RBC and plasma ChEI appear to be equally sensitive endpoints ( Table 1B). Results of all studies performed with Chemicals A, B, and C indicate RBC or plasma ChEI occur at doses below those eliciting brain ChEI or clinical

signs. Either RBC or plasma ChEI may be selected as common endpoints for a cumulative risk assessment involving Chemical B.

### 2.3.3 DOSE-RESPONSE CORRELATIONS

Data provided from the acute neurotoxicity study performed with Chemical B appear to be adequate for calculations of an ED or BMD value based on either RBC or plasma ChEI in male rats or RBC ChEI in female rats. Use of data from female rats would not be appropriate since the low dose was within the range of control cholinesterase activity. No measurements were made in high dose female rats.

**Table 2B: Dose-response data for the inhibition of RBC and plasma cholinesterase in rats treated acutely with Chemical B.**

Cholinesterase Inhibition (% of Control)	Dose (mg/kg/day)		
	2.0 (M) 1.0 (F)	6.0 (M) 3.0 (F)	12.0 (M) 6.0 (F)
RBC	-33 (M)* -17 (F)**	-67 (M) -65 (F)	-63 (M) Not measured (F)
Plasma	-32 (M) -11 (F)	-57 (M) -36 (F)	-50 (M) Not measured (F)

\*M=male; \*\*F=female.

### 2.3.4 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.

### **2.3.5 OTHER CONSIDERATIONS**

**Pharmacokinetic/dynamic Interactions** - There are no data available that would allow an evaluation of interactions between Chemical B and any other cholinesterase inhibiting chemical.

**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. Because the NOAEL recommended for use in an acute dietary cumulative risk assessment involving Chemical B is 10X lower than dosages which result in clinical or neurobehavioral effects, limiting exposures to levels that do not result in plasma or RBC ChEI will also preclude the potential for neurotoxicity.

### **2.3.6 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 cumulative risks of Chemical B. 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 good quality. There are no major data gaps or deficiencies apparent, with one exception, that would reduce confidence that the NOAEL or endpoint selected for an acute cumulative risk assessment with Chemical B is appropriate. The one deficiency found was that a NOAEL was not identified for RBC, plasma, or brain ChEI in the acute neurotoxicity study. If a 3X adjustment factor is applied to the LOAEL for the ChEI endpoints in the acute neurotoxicity study, the resulting extrapolated NOAELs would approximate or equal the NOAELs identified in the 2-year rat study. Such an adjustment to the acute NOAELs would lead to identification of extrapolated NOAELs that would not be expected to be higher than the actual NOAELs for the chemical.

## **2.4 CHEMICAL C**

### **2.4.1 SELECTION OF SENSITIVE SPECIES AND SEX**

Table 1C provides data on effects reported following treatment of rats, mice, and dogs with Chemical C.

**Table 1C: Oral NOAELs and LOAELs for cholinesterase inhibition and cholinergic signs in various species and in males and females for chemical C**

STUDY	RBC NOAEL/LOAEL mg/kg/day	PLASMA NOAEL/LOAEL mg/kg/day	BRAIN NOAEL/LOAEL mg/kg/day	SIGNS mg/kg/day
acute rat neurotoxicity	0.025/7.5 (M) 0.025/7.5 (F)	0.025/7.5 (M) 0.025/7.5 (F)	0.025/7.5 (M) 0.025/7.5 (F)	0.025/7.5 (M) 0.025/7.5 (F)
13-week rat neurotoxicity	0.295/3.02 (M) 0.365/3.96 (F)	0.029/0.295 (M) 0.0365/0.365 (F)	0.29/0.295 (M) 0.365/3.96 (F)	0.295/3.02 (M) 0.365/3.96 (F)
1-year rat neurotoxicity	0.11/0.53 (M) 0.14/0.70 (F)	0.11/0.53 (M) 0.14/0.70 (F)	0.11/0.53 (M) 0.14/0.70 (F)	0.11/0.53 (M)* 0.14/0.70 (F)*
2-year rat	0.02/0.21 (M) 0.29/3.34 (F)	0.21/2.21 (M) 0.29/3.34 (F)	0.21/2.21 (M&F) 0.29/3.34 (F)	.02/.21 (M) .03/.29 (F)**
13-week dog feeding	0.3/3.0 (M & F)	0.3/3.0 (M & F)	0.3/3.0 (M & F)	None
1-year dog feeding	<0.03/0.3 (M & F)	0.1/0.3 (M) 0.3/>0.3 (F)	0.1/0.3 (M) 0.3/>0.3 (F)	None
2-year mouse	1.69/9.2 (M) 2.1/13.7 (F)	0.2/1.6 (M) 0.3/2.1 (F)	0.2/1.6 (M) 0.3/2.1 (F)	Not reported
Developmental toxicity, rabbit	1/3 (F)	1/3 (F)	>3 (F)	1/3 (F)

\*=neuropathology at LOAEL; \*\*=neuropathology at highest dose tested

In bioassays of varying treatment duration with Chemical C, RBC and/or plasma ChEI were reported to occur at or below doses that resulted in brain ChEI or cholinergic signs. Therefore, comparisons of results for blood ChEI are appropriate for identifying the species and sex that is most sensitive to the effects of Chemical C.

Data are insufficient to allow a comparison of the effects of Chemical C in mice with other species. A comparison of results reported for 13-week studies in rats and dogs show the lowest NOAELs for plasma ChEI were 0.029 mg/kg/day (13-week rat neurotoxicity), and 0.3 mg/kg/day (13-week dog feeding study).

In 1-year rat and dog bioassays, plasma ChEI NOAELs were 0.11mg/kg/day and 0.10 mg/kg/day, respectively. Comparisons of plasma ChEI effect levels (LOAELs) show a LOAEL of 0.30 mg/kg/day (rats, 13-week neurotoxicity study) and a LOAEL of 3.0 mg/kg/day (13-week dog). Effect levels reported in 1-year bioassays for plasma ChEI were 0.53 mg/kg/day and 0.30 mg/kg/day, for rats and dogs, respectively. NOAELs for RBC ChEI were 0.30 and 0.30 mg/kg/day and LOAELs were 3.02 and 3.0 mg/kg/day (13-week rat neurotoxicity and 13-week dog, respectively). In 1-year studies, NOAELs were 0.01 mg/kg/day and <0.03 mg/kg/day and LOAELs were 0.53 mg/kg/day and 0.3 mg/kg/day, for rats and dogs, respectively.

It is recommended that the rat be selected as the species of choice. In general, NOAELs/LOAELs are comparable between the two species, rat and dog, but there are some exceptions that support use of the rat data (e.g., an identified LOAEL 0.3 mg/kg/day versus 3.0 mg/kg/day, 13-week neurotoxicity rat study and 13-week dog study, respectively). Where LOAELs for effects in dogs were reported to be lower (e.g., plasma ChEI in the 1-year rat neurotoxicity study and the 1-year dog study) the difference was minimal and could be accounted for by differences dose selection intervals or variability in ChEI measurements. Finally, more reliance can be placed on the rat data because there are more data available for evaluations of the effects of Chemical C.

#### ***2.4.2 SELECTION OF ENDPOINT***

Results of the acute neurotoxicity, 90-day neurotoxicity and 1-year neurotoxicity studies in rats show no differences in NOAELs or LOAELs for RBC and plasma ChEI for male and female rats when differences in dose selection between the sexes is taken into account. There is a suggestion from the 2-year rat study that male rats are more sensitive to the RBC ChEI effects of Chemical C than are female rats but the data from all other measures do not support a difference in sensitivity between the two sexes. For the exposure period of interest, an acute dietary cumulative assessment, the appropriate study for selection of an endpoint is the acute rat neurotoxicity study. The acute neurotoxicity provided data showing that there are no differences between responses in male and female rats for any of the parameters measured when dose selection is taken into account. Thus, selection of a specific endpoint (RBC or plasma ChEI, brain ChEI, or cholinergic signs) should be based on the sex and endpoint common to Chemical's A and B.

#### ***2.4.3 DOSE RESPONSE CORRELATIONS***

Data reported for plasma cholinesterase inhibition in female rats in an acute rat neurotoxicity study performed with Chemical C are inadequate for calculation of an ED using a benchmark dose analysis value since cholinesterase inhibition appears to have reached maximum inhibition at both the mid and high dose levels. If male rats were selected as the species of choice and plasma ChEI was selected as the common endpoint, the dose-related increases in ChEI would be adequate for calculation of an ED value.

**Table 2C: Dose response for RBC and plasma ChEI in rats treated acutely with Chemical C.**

Cholinesterase Inhibition (% of Control)	Dose (mg/kg/day)		
	.025 (M) .025 (F)	7.5 (M) 7.5 (F)	10 (M) 15 (F)
RBC	+2 (M) ±0 (F)	-56* (M) -57* (F)	-56* (M) -58* (F)
Plasma	-25 (M) -9 (F)	-67* (M) -71* (F)	-77* (M) -76* (F)

#### **2.4.4 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 (MTD 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.

#### **2.4.5 OTHER CONSIDERATIONS**

**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 ChEI chemical.

**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. In a 1-year rat neurotoxicity bioassay, neuropathic effects were observed in both males and females at the same dose level that resulted in blood and brain ChEI. Based on these data, it appears that dose levels required to produce neuropathology and/or clinical signs are approximately equal to the doses which lead to blood or brain ChEI.

#### ***2.4.6 WEIGHT-OF-THE-EVIDENCE***

The key studies performed using Chemical C and evaluated for data pertinent for an acute dietary cumulative risk assessment are of a good 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 confidence that the species, sex, endpoints, and dose-levels selected for use in cumulative risk assessments are sound.

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 may occur at dose levels equivalent to those that produce ChEI.

#### ***2.5 SELECTION OF THE SPECIES, SEX AND ENDPOINT COMMON TO CHEMICALS A, B, AND C.***

Data obtained in rat bioassays were identified as the most appropriate for use in cumulative risk assessments for Chemicals A, B, and C. Data from studies with Chemicals A and B indicate that female rats should be considered to be the more sensitive sex. In the acute neurotoxicity study with Chemical A, effect levels for either RBC ChEI or plasma ChEI in female rats were four times below effect levels reported for male animals; dose-response data for Chemical B show that approximately the same ChE inhibition occurred in female animals treated with 3 mg/kg/day of Chemical B as was reported for male animals treated with 6 mg/kg/day. Furthermore, at a dose level of 6 mg/kg/day, female mortality was so high as to preclude measurements of ChEI whereas sufficient numbers of animals survived at a dose-level of 12 mg/kg/day to allow measurements of ChEI activity.

Generally, the NOAELs for the two indicators of nervous tissue ChEI are equivalent. In particular, for the exposure period of interest, NOAELs for RBC and plasma ChEI are identical. However, for

Chemical A, the NOAEL for plasma ChEI is substantially below that for RBC ChEI in female rats. Since the Hazard Identification and Assessment Review Committee identified methodological deficiencies in the RBC ChEI measurements, use of the plasma data are preferred. Since Chemical A is the only chemical of the three chemicals under review showing that utilization of data from plasma measurements would affect the selection of NOAELs and since the results from the plasma measurements on Chemical A are preferred data, plasma ChEI is recommended as the endpoint to be used in assessments involving Chemicals A, B, and C.

In summary, the female rat is the species and sex of choice for an acute cumulative risk assessment on Chemicals A, B, and C. The recommended endpoint to use in an acute cumulative risk assessment with these chemicals is plasma ChEI.

## ***2.6 SELECTION OF POINTS OF DEPARTURE***

Because adequate dose-response data are not available for each chemical comprising the common assessment group of chemicals, it is recommended that NOAELs for plasma ChEI be used as PoDs.

**Chemical A** - The NOAEL of 0.25 mg/kg/day reported for plasma ChEI in female rats in the acute neurotoxicity study is recommended as the PoD for Chemical A. No adjustments to the NOAEL for Chemical A are needed.

**Chemical B** - The LOAEL (1 mg/kg/day in female rats) for the acute neurotoxicity study should be reduced by a factor of 3-fold to account for the lack of a NOAEL. The 3-fold reduction is justified because longer duration treatment (up to 2 years) yielded a NOAEL of 0.31 mg/kg/day in female rats.

**Chemical C** - There was a 300-fold difference in the doses that were used for the selection of NOAELs and LOAELs in the acute neurotoxicity study. Upon review of all the ChEI data on Chemical C, the HIARC determined that the 1-year neurotoxicity study provides data that would allow an adjustment of the NOAEL identified for acute exposures because it would not be expected that long-term exposure would yield a NOAEL higher than that of an acute exposure. Thus, the NOAEL of 0.14 mg/kg/day reported for plasma ChEI in female rats in the 1-year neurotoxicity study should be used as a point of departure.

## ***2.7 COMPARISON OF THE PODs SELECTED FOR CUMULATIVE RISK ASSESSMENTS WITH THE NOAELS USED TO ESTABLISH THE ACUTE RFDs FOR CHEMICALS A, B, AND C***

The NOAEL used to establish the acute RfD for Chemical A is the same as the NOAEL identified for use in cumulative risk assessments involving Chemical A (0.25 mg/kg/day).

The NOAEL selected for use in an acute dietary cumulative risk assessments (0.33 mg/kg/day) is the same NOAEL used to establish the acute dietary RfD for Chemical B.

The oral NOAEL used to establish an RfD for Chemical C (0.11 mg/kg/day established from the NOAEL for plasma or RBC ChEI in male rats in a 1-year neurotoxicity study) is approximately the same as the NOAEL recommended for the PoD (0.14 mg/kg/day for RBC or plasma ChEI in female rats in the same study). Because the PoDs selected for Chemical's A, B, and C are equal or close to the NOAELs used to establish acute RfDs for the chemicals, no concerns are raised that the PoDs selected will lead to underestimate of potential cumulative risks.

## ***2.8 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 confidence that the species, sex, endpoints, and other toxicity aspects of the chemicals selected for a cumulative risk assessment reasonably 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 from chemical to chemical
- direct (e.g., blood, brain ChEI) or indirect data (signs or mortality) 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 with confidence for each member of the common mechanism group even though a NOAEL had to be extrapolated from a LOAEL for Chemical B
- the endpoint selected for use in a cumulative risk assessment, inhibition of plasma 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 plasma cholinesterase
- 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 has been shown to be neuropathic. A developmental neurotoxicity study has been recommended for the chemical
- adequate dose-response data are not available for Chemical B and C in female rats for the exposure period being assessed and comparisons of relative potency of this chemical with the other member of the group is confined to single point comparisons

Quantifying potential acute cumulative risks using ED estimates is not recommended because adequate dose-response data are not available for plasma ChEI in female rats for Chemicals B and C. The PoD values (based on selection of the appropriate and representative NOAEL for each chemical) that should be used for quantifying potential acute dietary cumulative risks are listed in the next section.

### ***2.9. RECOMMENDED PODs FOR CHEMICALS A, B, AND C AND RECOMMENDED UNCERTAINTY FACTORS THAT SHOULD BE APPLIED TO THE COMMON MECHANISM GROUP OF CHEMICALS***

Table 3 lists the PoDs (NOAELs) that are recommended for use in acute dietary risk assessments involving chemicals A, B, and C. Section 2.3 provides the bases for selection of the PoDs.

#### **Table 3: Oral PODs (Adjusted) for Chemicals A, B, and C**

Study	PoD		
	Chemical A	Chemical B	Chemical C
Acute Oral Neurotoxicity	0.25 mg/kg/day	0.33 mg/kg/day*	N.A.**
1-Year Rat Neurotoxicity***	N.A.	N.A.	0.14 mg/kg/day

\* a 3-fold adjustment was applied to the LOAEL to account for the lack of a NOAEL; \*\* Not applicable; \*\*\* Used in lieu of acute neurotoxicity study due to spacing of dosing in acute study.

The standard factors, 10-fold (interspecies) and 10-fold (intraspecies) should be applied to Chemicals A, B, and C when evaluated as a single, common mechanism group in an acute cumulative risk assessment to account for pharmacokinetic and pharmacodynamic differences between species and to account for differential sensitivities/susceptibilities among the adult human population. No other uncertainty factors (e.g., to account for poor quality of the data base or major data gaps) are recommended. Chemical C has been shown to be neuropathic but this effect is confined to Chemical C and it is not an effect common to Chemicals A and B. If the effect was common to all three chemicals, that might indicate the need for an additional uncertainty factor.

### ***3 EXAMPLE OF A CUMULATIVE ASSESSMENT OF DIETARY EXPOSURE TO ORGANOPHOSPHATE PESTICIDES USING RELATIVE POTENCY FACTORS***

The exposure assumptions for these assessments, which are described in the following discussion, are for the most part not commonly used by the Agency in estimating dietary risk for single chemicals. The input assumptions used in this example preserve few of the conservative assumptions commonly encountered in dietary assessments. These assessments are intended as a conceptual basis for deliberations and are not to be interpreted as representing the Agency's recommended procedure for conducting cumulative assessments or as demonstrating a dietary risk assessment intended for regulatory purposes.

#### ***3.1 METHOD OF ESTIMATION OF CUMULATIVE DIETARY RISK***

Dietary exposure was estimated using the Dietary Exposure Evaluation Model (DEEM™) software. A joint distributional (Monte Carlo) analysis was conducted by combining representative data on concentrations of Chemicals A, B, and C on foods with distributions of anticipated consumption of these foods by different segments of the U.S. population. The primary advantage

of a joint distribution analysis is that the results are in the form of a simultaneous analysis (i.e., a distribution) of exposures that demonstrate both best-case and worst-case scenarios of exposure. The typical level of regulation for single chemical dietary exposures has been at the 99.9th percentile of exposure.

**3.2 DIETARY (FOOD) RESIDUE INPUT DATA FOR DIETARY RISK ASSESSMENT**

Anticipated concentrations of Chemicals A, B and C in foods were based on residue monitoring data collected by USDA through the Pesticide Data Program. These data are summarized in Table 4. The foods of interest for a dietary exposure assessment on apples, pears and peaches are the fresh fruits, dried fruits, and fruit juices (Table 4a). PDP does not monitor dried fruits; therefore, it was assumed that residues would concentrate in dried fruits in direct proportion to loss of mass on drying. Residues for all food forms of dried fruits were estimated using fresh fruit data and an appropriate adjustment factor to account for loss of water but retention of all of the residue. This is a conservative assumption that the Agency routinely uses for estimating concentrations in dried fruits in the absence of processing data. PDP also does not monitor for residues in peach or pear juice; therefore, for this example residues were assumed to be zero in these processed foods. This is not standard practice in Agency dietary risk assessments and has the potential to underestimate the risk from uses on these fruits. Residues on all cooked and uncooked forms of apples and pears were estimated from the fresh fruit data. This is standard Agency practice if data are not available on the residues in various cooked or processed forms. The potential for overestimation of residue exists for these forms as some pesticide residues are reduced on foods as they are cooked or processed.

**Table 4. PDP MONITORING DATA USED FOR Chemicals A, B and C**

	Chemical A	Chemical B	Chemical C
<b>APPLES (1996)</b>			
Samples Analyzed	530	530	530
Total Detects	1	289	30
Percent Detects	0.2	54.5	5.7
Average of Detects (ppm)	0.022	0.056	0.019
Maximum Detect (ppm)	0.022	0.44	0.21
<b>APPLE JUICE (1997)</b>			
Samples Analyzed	683	683	683
Total Detects	0	43	2
Percent Detects	0	6.3	0.3
Average of Detects (ppm)	-	0.022	0.003
Maximum Detect	ND	0.062	0.003
<b>PEARS (1997)</b>			

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	<b>Chemical A</b>	<b>Chemical B</b>	<b>Chemical C</b>
Samples Analyzed	708	702	708
Total Detects	24	479	37
Percent Detects	3.4	68.2	5.2
Average of Detects (ppm)	0.014	0.085	0.018
Maximum Detect (ppm)	0.094	0.00	0.079
<b>PEACHES, FRESH (1995-96)</b>			
Samples Analyzed	691	691	691
Total Detects	35	210	186
Percent Detects	5.1	30.4	26.9
Average of Detects (ppm)	0.020	0.0678	0.0586
Maximum Detect (ppm)	0.16	0.41	0.5
<b>PEACHES, CANNED (1997)</b>			
Samples Analyzed	754	754	756
Total Detects	0	1	0
Percent Detects	0	0.1	0
Average of Detects (ppm)	-	0.053	-
Maximum Detect (ppm)	ND	0.053	ND

**Table 4a. Residue Inputs for DEEM Acute Analysis for chemicals A, B & C (Cumulative)**

RDF indices and file names for Monte Carlo Analysis

- 1 Apple.rdf
- 2 AppleJuice.rdf
- 3 Pear.rdf
- 4 Peach\_fresh.rdf
- 5 Peach\_canned.rdf

Food Code	Crop Grp	Food Name	RDF #	Adj. Factor #1
52	11	Apples		
		11- Uncooked	1	1.0
		12- Cooked: NFS	1	1.0
		13- Baked	1	1.0
		14- Boiled	1	1.0
		15- Fried	1	1.0
		18- Dried	1	1.0
		31- Canned: NFS	1	1.0
		32- Canned: Cooked	1	1.0
		33- Canned: Baked	1	1.0
		34- Canned: Boiled	1	1.0
		42- Frozen: Cooked	1	1.0
53	11	Apples- dried		
		13- Baked	1	8.0
		14- Boiled	1	8.0
		18- Dried	1	8.0
		42- Frozen: Cooked	1	8.0
54	11	Apples-juice/cider		
		11- Uncooked	2	1.0
		12- Cooked: NFS	2	1.0
		14- Boiled	2	1.0
		31- Canned: NFS	2	1.0
		41- Frozen: NFS	2	1.0
377	11	Apples-juice-concentrate		
		12- Cooked: NFS	2	3.0
		13- Baked	2	3.0
		31- Canned: NFS	2	3.0
		41- Frozen: NFS	2	3.0
56	11	Pears		
		11- Uncooked	3	1.0
		12- Cooked: NFS	3	1.0
		13- Baked	3	1.0
		14- Boiled	3	1.0
		31- Canned: NFS	3	1.0
57	11	Pears- dried		
		13- Baked	3	6.25
		14- Boiled	3	6.25
		18- Dried	3	6.25
65	12	Peaches		

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	11- Uncooked	4	1.0
	12- Cooked: NFS	4	1.0
	13- Baked	4	1.0
	14- Boiled	4	1.0
	31- Canned: NFS	5	1.0
	41- Frozen: NFS	5	1.0
66 12	Peaches- dried		
	14- Boiled	4	7.0
	18- Dried	4	7.0

### **3.3 MANIPULATION OF RESIDUE DATA FOR EXPOSURE ASSESSMENT**

To determine a given one-day cumulative exposure to Chemicals A, B and C, each chemical's exposure by pathway is multiplied by its RPF to express it as an Index Equivalent Exposure.

$$\text{Exposure}_{IE}(\text{pathway}) = \text{Exposure}_n \times \text{RPF}_{\text{route}}$$

**Exposure pathways** of interest are via food, drinking water and non-occupational exposure; the **routes of entry** may be by ingestion, inhalation or dermal absorption. In this example we are limiting our consideration to the oral intake route and restricting the pathway of exposure to a limited selection of foods. So expressing exposure in terms of the index chemical, the expression becomes:

$$\text{Exposure}_{IE}(\text{food}) = (\text{Exposure}_{IEA} + \text{Exposure}_{IEB} + \text{Exposure}_{IEC})$$

In practice this leads to summing of residues reported for individual foods in pesticide monitoring data, which have been adjusted to index chemical equivalents using RPFs, on a sample-by-sample basis.

For this example individual residue concentrations reported by PDP were multiplied by the appropriate RPFs to convert concentrations to **Chemical A Equivalents**. Chemical A equivalents were then summed on a sample-by-sample basis and the resultant distribution was input as a residue distribution file in the DEEM™ software.

This means of summing of residues relied on the PDP sampling procedures to adequately capture the temporal and geographic variations in uses of pesticides. This procedure assumed that the PDP sampling protocols were designed in such a way as to reflect the foods available to the public for consumption in different regions of the country and throughout the year. The potential for co-occurrences of similar pesticides on the same serving of food was captured, subject to the sensitivity of the analytical procedures used and uncertainty involved in composite sampling procedures. Table 5 summarizes the relative distributions and co-occurrences of Chemicals A, B and C in the PDP data used for this assessment.

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**Table 5. Frequency of Co-occurrence of Chemicals A, B, and C in Apple, Pear, and Peach Commodities Monitored by PDP.**

Commodity (year)	No. of Samples Analyzed	Percent of Samples with Detectable Residues of A, B, or C	Detects per Sample			
			0	1	2	3
Apples (96)	530	58	225	290	15 <sup>1</sup>	0
Apple Juice (97)	683	6.4	639	43	1 <sup>2</sup>	0
Pears (97)	708	71	207	462	39 <sup>3</sup>	0
Peaches, fresh (95-96)	691	56	303	345	43 <sup>4</sup>	0
Peaches, canned (97)	754	0.1	753	1	0	0

1. All 15 co-occurrences involved A and B.
2. A and B were both present in one sample.
3. Seventeen co-occurrences of A and B; 22 co-occurrences of B and C.
4. Twenty-three co-occurrences of A and B; 18 co-occurrences of B and C; 2 co-occurrences of A and C.

There are two major assumptions incorporated in the present treatment of residue monitoring data that contribute to uncertainty in the outcome of an acute cumulative risk assessment. In both cases the greater likelihood is that these assumptions would underestimate the actual level of a single-day dietary exposure. These assumptions are as follows:

1. **PDP analyses on composite samples were used for residue inputs for single serving foods.** PDP analyses are performed on aliquots of food homogenates derived from several pounds of the product, i.e., it represents an average residue on several servings of a food. This sampling procedure has the potential to underestimate the actual residue levels that may occur on some of the multiple single servings of the food commodity that went into the homogenized composite sample. For purposes of the present example, it is assumed that residues reported on composite homogenates adequately reflect the residues in any given single serving contained in that homogenate. Therefore, no attempt was made to “decomposite” residue values, as is normal Agency policy, to simulate residues that might be present in the single servings contained in the PDP composite sample.

**2. Residues reported as non-detectable by PDP were assigned a value of zero in this assessment.** All residue analyses are subject to the limitations of the sensitivity of the analytical methods. Many of the samples analyzed are reported as being below the limit of reliable detection of the analytical method. It is usual practice in Agency assessments to assume that residues in nondetectable samples are present at ½ the limit of detection (LOD) of the analytical method in samples that were potentially harvested from treated fields. Thus, for purposes of estimating residues in samples reported as <LOD, a proportion of the samples equal to the estimated percent crop treated is assigned a residue level of ½ the LOD and the remaining samples, which are assumed to come from untreated crops, are assigned a residue value of zero. This procedure becomes problematic for a cumulative assessment. It is not enough to simply estimate the percent crop treated for each of the pesticides in the cumulative assessment; it is also important to consider the potential for co-occurrence of residues of multiple residues on the same crop. A strength of the present example is that it accounts for co-occurrences in single samples if they are detectable. No attempt was made in this assessment to simulate possible residue levels in the samples reported as non-detectable; they were all assumed to be zero.

### ***3.4 FOOD CONSUMPTION DATA***

Food consumption data were taken from the USDA Continuing Surveys of Food Intake by Individuals (CSFII) conducted between April, 1989 and March, 1992. These data were based on 3-day surveys collected from households throughout the contiguous 48 states, and representing information provides by 15,128 individuals of all ages. The food consumption data are translated into ingredients within the DEEM™ software using a proprietary ingredient translation database. In this example assessments were based on the consumption patterns representative of the U.S. Population, all infants less than one year old, children one to six years old, and children seven to twelve years old.

### ***3.5 ESTIMATION OF ACUTE EXPOSURE USING DEEM™ SOFTWARE***

The residue distribution files for apples, pears, and peaches were input in the DEEM™ software for a Monte Carlo analysis.

The Monte Carlo analysis was conducted by an iterative process of multiplication of residue concentrations on foods, expressed in Chemical A equivalents, by one-day consumption of these foods, as reported by all individuals in CSFII. This process used all individuals reporting in the consumption survey for all three days of the survey and the exposures were calculated as mg/kg body wt./day.

For a given population the exposure estimates were derived as follows:

- ❑ Consumption of food 1 (for example, fresh uncooked pear) by individual 1 was multiplied by a randomly selected residue value from the residue distribution file for food 1 (i.e., from the Chemical A equivalents derived from PDP monitoring data).
- ❑ Step 1 was repeated for all food forms of apples, pears, and peaches consumed by individual 1 on day 1 of the CSFII survey.
- ❑ The exposure estimates for all food forms of apples, pears, and peaches consumed by individual 1 on day 1 were summed to estimate the total cumulative dietary exposure (from apples, pear, and peaches) for individual 1 on day 1.
- ❑ Steps 1 through 3 were repeated 1000 times, still using the consumption data for individual 1 on day 1.
- ❑ The 1000 cumulative exposures for person 1 on day 1 were stored as frequencies in exposure intervals.
- ❑ Steps 1 through 5 were repeated for individual 1 on days 2 and 3.
- ❑ Steps 1 through 6 were repeated for all individuals in the population of concern.
- ❑ The frequency distribution of the exposure estimates for all individuals on all three days was used to describe the distribution of cumulative exposure among the population of concern from consumption of all foods derived from apples, pears, and peaches.

### 3.6 RESULTS

Table 6 summarizes the results of this dietary exposure assessment for Chemicals A, B, and C on food commodities of apples, pears, and peaches. The summary results are provided for three points in the distribution of exposures estimated for four populations, i.e., at the 95<sup>th</sup> percentile, 99<sup>th</sup> percentile, and 99.9<sup>th</sup> percentile of exposure. These exposure values are expressed in terms of Chemical A and any evaluation of the risk from these levels of exposure should be compared to the PoD for Chemical A. It bears repeating here also that this assessment involves only dietary exposure to three chemicals from their use on three fruits. A cumulative dietary assessment for regulatory purposes would also include the exposure from ingestion of all other foods on which these three chemicals and all other chemicals of identical mechanism of toxicity are registered for use. This dietary exposure must also be combined with all exposure from ingestion of water contaminated with these chemicals, and the non-occupational exposure incurred for all similar chemicals through the dermal, oral, and inhalation routes of exposure.

### 3.7 SUMMARY

The cumulative dietary risk due to the use of Chemicals A, B and C on apples, pears and peaches was assessed using residue monitoring data collected by USDA through the Pesticide Data

Program. The acute NOAELs for plasma cholinesterase inhibition in rats were chosen as the Toxicological Points of Departure (PoDs) for this assessment. Chemical A served as the index chemical. The residue values for Chemicals B and C were converted to Chemical A equivalents by a Relative Potency Factor ( $RPF = \text{PoD}_{[\text{index chemical}]} / \text{PoD}_{[\text{chemical n}]}$ ) approach. The resultant distribution of cumulative residues, summed on a sample-by-sample basis, was combined with a distribution of daily food consumption values (USDA Continuing Surveys of Food Intake by Individuals, 1989-1992) *via* a probabilistic procedure to produce a distribution of potential exposures for the U. S. population and three subpopulations (infants less than 1 year old, children 1 to 6 years old, and children 7 to 12 years old). The results of this assessment are shown in Table 6.

**Table 6. Summary of Probabilistic Analysis of Distribution of the Cumulative Dietary Exposures Among Four Populations from Use of Chemicals A, B and C on Apples, Pears, and Peaches.**

	95 <sup>th</sup> Percentile		99 <sup>th</sup> Percentile		99.9 <sup>th</sup> Percentile	
	Exposure (mg/kg body wt/day)	MOE	Exposure (mg/kg body wt/day)	MOE	Exposure (mg/kg body wt/day)	MOE
U.S. population - all seasons	0.000124	2000	0.000441	570	0.001532	160
All Infants (<1 yr)	0.000425	590	0.001393	180	0.004584	50
Children (1-6 years)	0.000363	690	0.001154	220	0.003403	70
Children (7-12 years)	0.000241	1040	0.000735	340	0.002081	120

1. MOEs based on acute NOAEL of Chemical A (0.25 mg/kg body-wt/day).