STATUS OF CUMULATIVE RISK ASSESSMENT FOR ORGANOPHOSPHATE PESTICIDES

U.S. EPA Office of Pesticide Programs

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Revised Draft

I. Introduction

A. General

This document summarizes the basic principles that underlie OPP's approach to cumulative risk assessment. It also summarizes and explains the information in the "Preliminary Organophosphorus Cumulative Risk Assessment," which was released on December 3, 2001. Other subjects presented here are discussed more fully in the documents:

- ❏ "A Common Mechanism of Action: The Organophosphate Pesticides," dated November 2, 1998;
- ❏ "Guidance for Identifying Pesticide Chemicals and Other Substances that Have a Common Mechanism of Toxicity," dated February 5, 1999;
- ❏ "General Principles for Performing Aggregate Exposure and Risk Assessments," dated November 28, 2001;
- ❏ "Proposed Guidance on Cumulative Risk Assessment of Pesticide Chemicals That Have a Common Mechanism of Toxicity," dated June 22, 2000;
- ❏ "Endpoint Selection and Determination of Relative Potency in Cumulative Hazard and Dose-Response Assessment: A Pilot Study of Organophosphorus Pesticide Chemicals," dated September 5, 2000;
- ❏ "Cumulative Risk: A Case Study of the Estimation of Risk From 24 Organophosphate Pesticides," dated November 9, 2000; and
- ❏ "Preliminary Cumulative Hazard and Dose Response Assessment for Organophosphorus Pesticides: Determination of Relative Potency and Points of Departure for Cholinesterase Inhibition," dated July 31, 2001.

This guide is designed to assist the reader by identifying and explaining the key features of the preliminary organophosphorus (OP) cumulative risk assessment. The goal is to help stakeholders better understand the assessment and the potential issues involved in the assessment and, ultimately, provide input on the conduct and conclusions of the assessments. Because the assessment is preliminary, some elements may change before release of the revised assessment. Changes are possible as a result of the public comment period on the preliminary risk assessment; review by the FIFRA Scientific Advisory Panel scheduled for February 2002; as well as continuing work by the Agency.

The preliminary cumulative risk assessment for the OPs was placed in the public docket on December 3, 2001. It is available on the internet at www.epa.gov/pesticides/cumulative. The other documents noted above are

posted on the Internet at www.epa.gov/scipoly/sap/ or www.epa.gov/trac/science. A public comment period on the preliminary risk assessment was announced following the opening of the docket. This comment period will close March 8, 2002.

B. Common Mechanism Group/Cumulative Assessment Group

OPP has determined that it is appropriate to treat the organophosphates (OPs) as sharing a common mechanism of toxicity: the inhibition of cholinesterase activity. A preliminary cumulative assessment was conducted to evaluate the combined risk from food, water, and residential/non-occupational exposure resulting from all relevant uses of OPs.

All of the OPs, which have been determined to cause a common toxic effect by the same major biochemical event, that is, inhibition of acetyl cholinesterase form the “Common Mechanism Group” or CMG for the OPs. The 40 pesticides in the CMG include the 39 OPs that are currently registered or have tolerances for import purposes plus a new pesticide fosthiazate. Fosthiazate was examined in the hazard assessment to determine its relative potency. It may be considered for registration in the future. Fosthiazate is a potential alternative to methyl bromide. The 40 members of the CMG are listed in Section II, “Common Mechanism Group/Technical Registrants.”

However, not all of these chemicals contribute meaningfully to the OP cumulative risk, for a variety of reasons. Therefore, some chemicals are not included in the assessment. The chemicals that are included in the quantification of cumulative risk are referred to as the “Cumulative Assessment Group” or CAG. The Cumulative Assessment Group for the OPs includes 31 pesticides. Section III, “Cumulative Assessment Group,” describes the decisions leading to formation of this group.

C. Relationship Between Individual Chemical and Cumulative Assessments

To fully understand the goals and methods of the cumulative OP assessment it is necessary to understand the relationship of the single chemical OP risk assessments to the multi-chemical cumulative OP risk assessment.

Comparison of Individual and Cumulative Risk Assessment

Individual Assessment	Cumulative Assessment
• Focus is on specific chemical • Goal–determine "safe" level for most sensitive endpoint • Considers all effects and exposures	• Emphasis on the effect shared by members of the common mechanism group • Considers relative potency of chemicals in the group • Must look at the likelihood of co-occurrence of exposures

In general, the individual chemical risk assessments should be done first. The aggregate assessments for the individual chemicals provide information needed to define the parameters of the cumulative exposure assessment. They permit evaluation of the strengths and weaknesses of the available data. This information is important for directing the process for deciding whether a particular pesticide source and/or pathway combination should be included in the cumulative assessment. In any case, it is necessary that both the individual and cumulative assessments be done, since they consider the risks of the chemicals in different ways.

As noted above, the cumulative risk assessment considers only the common mechanism effect. The effect identified as "common" may or may not be the effect that was used as the basis for establishing an individual chemical's endpoint. The common toxic effect may be produced at, above, or below doses that produce other toxicological effects that are not associated with the common mechanism of toxicity. For example, an OP may have an affect that is not associated with cholinesterase inhibition that may occur at a different dose level than the cholinesterase inhibition. In addition, because the emphasis is on the common effect, the endpoint selected for the cumulative assessment may be generally the same as in the individual assessment, for example the inhibition of cholinesterase, while the specific measure(s) used, for example plasma, red blood cell or brain, or specific test animal may be different for the two assessments.

Exposures are only relevant for a cumulative assessment if they have the potential to result in a cumulative risk. For example, for the OPs, potential for concurrent or overlapping exposure exists because the effects on cholinesterase may overlap given the effect can persist over several days to weeks depending on the magnitude of exposure. This is in contrast to, for example, most chronic and cancer endpoints for which the effect occurs after long-term exposure. In

that case, concurrent or overlapping exposures are not necessary for evaluation of a common mechanism effect.

To analyze the potential for concurrent exposures, the exposure assessments for the OP cumulative risk assessment must address:

- ❏ Critical window for the common mechanism effect (i.e., time from exposure to the pesticide and expression of the common mechanism effect until the effect is reversed and the individual has returned to a pre-exposed condition),

- ❏ Regional patterns in usage, which result in exposures to multiple chemicals that can be expected to occur only in a defined spatial or geographic area; and

- ❏ Temporal issues, for example, whether the pesticides are applied during the same season or time period, so that multiple exposures are possible, and the temporal relationship between exposures in food, water, and the home.

The critical window of expression for the common toxic effect and exposure duration, pattern, and frequency, therefore, become paramount in determining where there is an opportunity for an individual to be exposed to two or more pesticides concurrently. In addition, to maintain the appropriate relationship among the components of the assessment (food, water, and residential), it is necessary to maintain the appropriate demographic element of the assessment, so for example, a two-year-old's dietary exposure would not be combined with a homeowner applicator's exposure from treating his lawn. Finally, because the assessment combines many data sets into a single assessment, reducing the likelihood of compounding conservative assumptions and over-estimation bias becomes very important in constructing the cumulative risk assessment.

Developing a modeling tool that permits the assessment of co-occurrence is a necessary aspect of the development of cumulative methods. The model must be able to integrate exposure through food, water, and residential/non-occupational pathways to reflect both the probability of exposure by any given pathway and the timing of exposures through different pathways. Therefore, the model should reflect the exposure of discrete individuals/population members in which routes of exposure are linked and the estimated exposures reflect the individual's location, and other demographic characteristics of the individual/population member such as age and weight; the time of year; the individual's anticipated patterns of pesticide use (for residential exposure); and the individual's history of exposure. For example,

- ❏ if an individual's house was treated for termites today, that

exposure could continue for a period of time for that individual, but would not be randomly spread through a population

- ❏ similarly, for drinking water, the source of an individual's drinking water today is likely to be the same source tomorrow, and that spatial and temporal linkage must be preserved.

The following chart illustrates how potential exposure to an individual/population member should consider and link temporal, spatial, and demographic components for the specific individual/population member.

Illustration of Exposure Linkages for an Individual in the Population

Example(s) of Individual Characteristics	*Dimension*	*Correlation for an Individual in the Population*
▸Season of the Year	*Temporal*	▸Drinking water exposure and residential pesticide application pattern correlate with season of year
▸Location of home (Urban or rural area, region of country)	*Spatial*	▸Drinking water estimates correlate with region of country ▸Residential pesticide usage likely for region of country
▸Gender ▸Person's Age	*Demographic*	▸Reproductive status consistent with age and gender ▸Age correlates with consumption pattern, activity pattern, inhalation rate ▸Personal preferences, behaviors, and characteristics consistent with data on home pesticide usage and type of home
Individual Example: An individual who is part of a population of concern is a 1-year old female, in New England, during the winter, in a rural location without municipal water, whose food and water consumption is that reported for her in the CSFII. She encounters potential residential pesticide use consistent with a rural, New England location in the winter. She does not apply home pesticides, but may come in contact with pesticides by crawling on the floor. Body weight, height, surface area, inhalation and other biological factors are consistent with her other demographic characteristics, as recorded in the CSFII.		

The following chart summarizes the differences in the major exposure components of the risk assessments for the individual and cumulative assessments for food, water, and residential exposures and the resulting differences in the outputs of the assessments.

Differences in Individual OP Chemical And Cumulative OP Exposure Assessments

Exposure Pathways Element to Compare		*Individual Assessments*	*Cumulative Assessment*
Food	**Type of Assessment:**	Probabilistic	Probabilistic
	Input:	If an individual eats a particular food item, his probability of exposure to an individual chemical's residue is determined only by the probability of the residue being present on the food. In the individual assessments, estimates are made for all food items, and all the estimates are independently made, because it can be assumed that the probability of a single chemical being on any given item (say carrots) is unrelated to the probability of it being on any other item (say green beans) or to the probability of other chemicals being present on these items.	An individual's probability of exposure to multiple chemical residues depends not on the additive probabilities of the single chemical being present on a given food item, but on the probability of their co-occurrence on a single food item and across the multiple food items that the individual consumes. These probabilities, unlike with a single chemical, cannot be assumed to be independent of each other. Thus, for example, if a given field were treated with one OP for a particular pest, it would not be likely that it would also be treated with the other 15 OPs registered on that crop for that pest. Reliance on monitoring data and use of composite samples allows the assessment to capture co-occurrence of OPs on food.
	Output:	Distribution of exposures for population of concern on a national scale.	Distribution of exposures for population of concern on a national scale; however, these distributions will also be presented as regional distributions when integrated with the regional assessments being done for water and residential exposures.

Exposure Pathways Element to Compare		*Individual Assessments*	*Cumulative Assessment*
Water	**Type of Assessment:**	Deterministic	Probabilistic
	Input:	Generally uses a screening level conservative assessment, which uses a point estimate from a reasonable high-end exposure scenario, which is generally selected to represent all use areas for a given crop. The point estimate typically does not take into account seasonal variations in exposure concentrations. Thus, variations in exposure over time are not considered in the screening estimates. Such variation may be considered in more refined assessments, if sufficient information is available to do so, (e.g., water monitoring with frequent sample intervals). Point estimates are also used for water consumption values.	Uses a distribution of daily pesticide concentrations over multiple years rather than a single point estimate, and uses a regional approach based on geographic location, crops grown and agricultural practices as opposed to having one scenario represent all crops. Since determining the probability of co-occurrence or exposure to multiple pesticides at the same time is important to calculating total exposure for cumulative risk assessment, the timing of pesticide use, the place where the pesticide is used and the probability that it will occur in the drinking water in one or more regions are all accounted for in order to develop reasonable estimates of exposures to pesticides in drinking water. Water consumption values are taken from the CSFII
	Output:	Point estimate is compared to the residue level that could be in water and still be "safe", given the amount of residues estimated to be in food. This residue level is termed the Drinking Water Level of Comparison (DWLOC).	Distribution of exposures for populations of concern. These distributions are presented as regional/location-specific estimates designed to represent the region of concern. They are combined with exposure estimates from food, using food and water consumption data from the CSFII as the common, linking factor.
	Analysis of Modeling Results:	When model estimates exceed the DWLOC, use all available refinements. Obtain all available monitoring data and compare to modeled values.	Model estimates refined as extensively as possible and compared to available monitoring data.

Exposure Pathways Element to Compare		*Individual Assessments*	*Cumulative Assessment*
Residential	**Type of Assessment:**	Deterministic	Probabilistic
	Input:	Individual exposure scenarios are developed to represent reasonable high-end exposures from application (home-owner applicators) and post-application exposures. The scenarios are generally taken to represent all areas of the country. Timing of exposure is not generally considered (except for the duration of exposure, for example, short-term, intermediate-term, or long-term).	Individual exposures are estimated along with the probability of co-occurrence with other exposures, all of which are presented, not in the context of the individual, but as probability distributions for the population of interest. To estimate co-occurrence the temporal and spatial aspects of residential use, together with the probability of use at any given time period are incorporated in the assessments. For example, termite applications would only be considered in certain areas of the country and lawn exposures would only occur at certain times of the year for most areas of the country. To establish these relationships, assessments are done for separate regions and for specific time periods.
	Output:	Risk estimates for individuals for representative scenarios, e.g., toddlers on a treated lawn, or combined applicator and post-application exposures for adults who treat their own lawn. These risk estimates are evaluated to determine if the use is “safe” for the individual/population member exposed.	Distribution of exposures for populations of concern, rather than for a specific individual/population member subject to the exposure. These distributions are presented as regional/location-specific estimates designed to represent the region of concern and are combined with food and region-specific water exposure estimates.

In summary, it is important to see these two different assessments (individual chemical and cumulative) as distinct, in the questions they address, the methods they use, and the regulatory outcome that may be appropriate.

II. Common Mechanism Group/Technical Registrants

The following table lists the 40 OPs that are currently in the common mechanism group. This list includes the 39 OPs that are currently registered or have tolerances for import purposes, and also includes a new chemical, fosthiazate, which was examined in the hazard assessment to determine its relative potency. It may be considered for registration in the future. Fosthiazate is a potential methyl bromide alternative. The table also shows the registrant(s) primarily responsible for the data on the chemicals.

Chemical	*Registrant(s)*
Acephate	Valent
Azinphos methyl	Bayer; Mahkteshim-Agan
Bensulide	Gowan
Cadusafos	FMC
Chlorpyrifos	Dow
Chlorpyrifos methyl	Dow
Chlorethoxyfos	AMVAC
Coumaphos	Bayer
Diazinon	Syngenta; Mahkteshim-Agan
Dichlorvos	AMVAC
Dicrotophos	AMVAC
Dimethoate	Cheminova
Disulfoton	Bayer
Ethion	Cheminova
Ethoprop	Aventis
Ethyl Parathion	Cheminova
Fenamiphos	Bayer
Fenitrothion	Sumitomo
Fenthion	Bayer
Fosthiazate	ISK Biosciences
Malathion	Cheminova; Bayer
Methidathion	Gowan

Chemical	*Registrant(s)*
Methamidophos	Bayer
Methyl Parathion	Cheminova; Griffin; CerexAgri
Mevinphos	AMVAC
Naled	AMVAC
Oxydemeton Methyl (ODM)	Gowan
Phorate	BASF; Aceto
Phosalone	Aventis
Phosmet	Gowan
Phostebupirim	Bayer
Pirimiphos methyl	Agriliance
Profenofos	Syngenta
Propetamphos	Wellmark
Sulfotepp	Plant Products; Fuller
Temephos	Clark Mosquito Control
Terbufos	BASF
Tetrachlorvinphos	Boehringer Ingelheim Vetmedica; Hartz Mountain Corporation
Tribufos	Bayer
Trichlorfon	Bayer

III. Cumulative Assessment Group

Not all of the chemicals in the common mechanism group contribute meaningfully to the OP cumulative risk for a variety of reasons. Therefore, some chemicals are not included in the assessment. In addition, some chemicals and some chemical/use combinations are not evaluated quantitatively. The following summarizes which OP chemicals the Agency has excluded from the CAG, and discusses several for which only qualitative assessments were performed.

A. Excluded Chemicals

Ethion, ethyl parathion, sulfotepp, cadusafos, fenitrothion, temephos, propetamphos, and coumaphos were not included in the cumulative assessment group, for the reasons discussed below.

Ethion, ethyl parathion, and sulfotepp are not included in the cumulative assessment group because these chemicals are being phased out according to specific legal agreements with the registrants. These legal actions call for a near term removal of the uses. In addition, the result of these actions in practice is often an accelerated move away from the chemical. As a result, if the Agency chose to include the chemicals in an assessment, it would be difficult to estimate the continuing exposure contribution. Finally, the Agency believes, given that these actions have already taken place, there could be an inappropriate regulatory effect if other chemicals or uses were considered for removal from the market now, as the result of considering these phased out uses in the assessment. It should be noted that phased out *uses* of certain other chemicals will also be excluded from the assessment.

Cadusafos, fenitrothion, temephos, and propetamphos are not included in the cumulative assessment group because it was determined in each of their individual assessments that there were negligible, if any, exposures.

- ❑ **Cadusafos** is used exclusively on imported bananas. No detectable food residues are expected from this use.
- ❑ **Fenitrothion** has a tolerance for imported wheat gluten from Australia and is used in the U.S. only in containerized bait stations in child resistant packaging. Monitoring data show negligible residues for wheat gluten, and exposure resulting from the containerized bait stations in child resistant packaging is expected to be insignificant also.
- ❑ **Temephos** is used only as a mosquito larvicide. Applications are limited to brackish water areas where exposure to both bystanders and drinking water is expected to be negligible.
- ❑ **Propetamphos** is used only as a crack and crevice treatment. It is not

allowed to be used in structures children or the elderly occupy, such as or including homes, schools, day-cares, hospitals, and nursing homes with the exception of areas of food service within those structures, when food is covered or removed prior to treatment. As the result of these restrictions, exposure is expected to be negligible.

Coumaphos is used for direct application to livestock and to swine bedding. The Agency anticipates that there is not likely to be appreciable transfer to meat and milk as the result of these uses.

B. Chemicals to Be Examined Qualitatively

Three chemicals--**chlorethoxyfos, phostebupirim, and profenofos**--have no detectable residues in PDP monitoring data and are each used on a single crop However, a screening analysis for water was conducted to assess whether their contribution to water exposure is also negligible. Tetrachlorvinphos has only pet and livestock uses. The pet uses are not included in this assessment due to lack of exposure data suitable for probabilistic assessment methods. The individual chemical assessment shows risks of concern for this use. Any possible residues resulting from the livestock use are expected to be covered by the conservative residue estimate for meat commodities that is being used in the assessment. Fostiazate, the new chemical which may be considered for registration in the future, is included but has only a hazard assessment.

C. Current Status of Each Chemical

The following table summarizes the current status of the OPs in regard to their inclusion in the cumulative assessment. For included pesticides it indicates which assessments have been done (F = Food, W = Water, R = Residential) It also indicates the 11 pesticides for which residential uses are registered.

Organophosphates: Current Status

Chemical/Uses	Included: F=Food; W=Water; R=Residential	Included: Screening Assessment Only	Excluded	Residential Use Registered
Acephate	✓ (F,W,R)			✓
Azinphos methyl	✓ (F,W)			
Bensulide	✓ (W,R)			✓
Cadusafos			✓	

Chemical/Uses	Included: F=Food; W=Water; R=Residential	Included: Screening Assessment Only	Excluded	ResiRdential Use Registered
Chlorethoxyfos		✓(W)		
Chlorpyrifos	✓ (F,W)			✓ (Not included due to low risk of remaining uses)
Chlorpyrifos methyl	✓ (F)			
Coumaphos			✓	
Diazinon	✓(F,W)			
Dichlorvos	✓ (F, R) Included in Water only as a degradate of Naled			✓
Dicrotophos	✓(W)			
Dimethoate	✓ (F,W)			
Disulfoton	✓ (F,W,R)			✓
Ethion			✓	
Ethoprop	✓ (F,W)			
Ethyl parathion			✓	
Fenamiphos	✓ (F,W,R)			✓
Fenitrothion			✓	
Fenthion	✓ (R)			✓
Fosthiazate*		✓ (Hazard Only)		
Malathion	✓ (F,W,R)			✓
Methidathion	✓ (F,W)			
Methamidophos	✓(F,W)			
Methyl parathion	✓ (F,W)			
Mevinphos	✓ (F)			
Naled	✓ (F,W,R)			✓

Chemical/Uses	Included: F=Food; W=Water; R=Residential	Included: Screening Assessment Only	Excluded	Residential Use Registered
Oxydemeton methyl (ODM)	✓ (F,W)			
Phorate	✓(F,W)			
Phosalone	✓ (F)			
Phosmet	✓ (F,W)			
Phostebupirin		✓ (W)		
Pirimiphos methyl	✓ (F)			
Profenophos		✓ (W)		
Propetamphos			✓	
Sulfotepp			✓	
Temephos			✓	
Tetrachlorvinphos		✓(F,R)		✓ (No quantitative assessment due to lack of data–screening level assessment indicates risks of concern)
Terbufos	✓(F,W)			
Tribufos	✓(F,W)			
Trichlorfon	✓ (R)			✓

*A new chemical being examined to determine if it might be considered for registration in the future–it is a potential methyl bromide alternative.

IV. Endpoint Selection

A. Uncertainty Factors

1. Individual Chemical Uncertainty Factors

Chemical-specific uncertainty factors are applied, if necessary, to the individual chemicals in the CAG, in considering the relative toxic potency of each chemical member in the group. However, no uncertainty factors are carried over from the individual assessments. Chemical-specific adjustments are based on issues with the toxicity data for an individual chemical, for example, to account for use of a LOAEL rather than a NOAEL or use of sub-chronic data in the absence of chronic data. These adjustments allow each chemical's database to express a uniform effect level, allowing them to provide equivalent measures of toxicity to the extent possible. No chemical specific uncertainty factors were used in the preliminary OP cumulative risk assessment.

2. Group Uncertainty Factor

The group uncertainty factor for the CAG is applied after estimating the toxicity of the group. The group uncertainty factor covers areas of scientific uncertainty that pertain to the group as a whole rather than to an individual chemical's database. This includes, for example, differences between species (inter-species) and among individuals within a species (intra-species). In addition, EPA analyzes any overall database uncertainty. This includes any issues concerning the quality and completeness of the database as it relates to the common toxic effect for the group as a whole. The preliminary assessment does not specify a group uncertainty factor because that decision has not yet been made.

3. FQPA Safety Factor Determination

The Agency is preparing a science policy paper containing proposed guidance on the relationship between the FQPA Safety Factor and cumulative risk assessment. This document will further the policy development process to address questions surrounding how the FQPA Safety Factor relates to cumulative risk assessments. The Agency anticipates issuing this paper in mid-February 2002, shortly after the revised *generic* guidance document on the FQPA Safety Factor is released. Following this process, EPA will consider the specific case of the OP cumulative assessment. Therefore, the preliminary OP cumulative

risk assessment has not considered the FQPA safety factor.

C. Endpoint Selection & Relative Potency of Chemicals

1. Calculating Relative Potency Factors

Once an endpoint has been selected and before an exposure assessment can be done, the chemicals must be ranked according to their ability to produce the toxic effect of concern. In a cumulative risk assessment the toxic effect of concern is the effect which is common to all members of the group. The common endpoint for the OPs has been determined to be the inhibition of cholinesterase activity. The ability to produce this effect is quantified by a "potency" value. The method to estimate the relative potency of the OPs in producing the toxic effect of concern has been termed the "relative potency factor" method. This method includes the following elements:

- ❏ Determine the potency of each chemical.
- ❏ Select an index chemical.
- ❏ Express each chemical's potency in terms of the index chemical.
- ❏ Select the endpoints for the index chemical

The result of the method is the determination of a relative potency factor or RPF for each chemical. The table below shows the RPFs that have been developed. Only those chemicals with residential/non-occupational exposures have RPFs for the dermal and inhalation routes of exposure. The sections that follow describe how EPA is calculating RPFs for the dermal, inhalation, and oral routes of exposure. An example calculation is provided for each route.

Relative Potency Factors

Chemical	Oral	Dermal	Inhalation
Acephate	0.13	0.0025	0.208
Azinphos-methyl	0.092		
Bensulide	0.003	0.0015	
Chlorpyrifos	0.10		
Chlorpyrifos-methyl	0.012		
Diazinon	0.024		
Dichlorvos	0.037		0.677
Dicrotophos	1.95		

Chemical	Oral	Dermal	Inhalation
Dimethoate	0.33		
Disulfoton	1.23	0.47	6.596
Ethoprop	0.049		
Fenamiphos	0.039	1.5	0.315
Fenthion	0.35	0.015	
Fosthiazate	0.16		
Malathion	0.0003	0.015	0.003
Methidathion	0.37		
Methamidophos (Index Chemical)	1.00	1.00	1.00
Methyl Parathion	0.058		
Mevinphos	1.36		
Naled	0.083	0.075	0.820
Oxydemeton Methyl (ODM)	0.90		
Phorate	0.39		
Phosalone	0.024		
Phosmet	0.020		
Pirimiphos methyl	0.029		
Terbufos	0.84		
Tetrachlorvinphos	0.0008	0.00075	
Tribuphos	0.045		
Trichlorfon	0.014	0.0075	0.087

Note: Three pesticides included in the preliminary assessment, phostebupirim, profenofos, and chlorethoxyfos did not have quantified RPFs. These chemicals have no detectible residues in PDP monitoring data. They were included in a screening assessment for drinking water using RPFs of 25. This screening assessment demonstrated that their contribution to drinking water risk is very low. Chemical specific RPFs are being developed for these three chemicals.

The relative potency factor for each chemical is expressed in relationship to an index chemical. The relative potency of the index chemical is, by definition, one. The index chemical's measure of potency is divided by each chemical's measure of potency to produce its relative potency, as illustrated below.

$$\text{Index Chemical RPF} = \frac{\text{Index Chemical Measure of Potency}}{\text{Index Chemical Measure of Potency}} = 1$$

$$\text{Chemical A RPF} = \frac{\text{Index Chemical Measure of Potency}}{\text{Chemical A Measure of Potency}} = 0.5$$

$$\text{Chemical B RPF} = \frac{\text{Index Chemical Measure of Potency}}{\text{Chemical B Measure of Potency}} = 2.0$$

In this example chemical A is half as potent as the index chemical in producing the effect of concern, while chemical B is twice as potent as the index chemical in producing the effect.

Use of Relative Potency Factors to Express All Residues As Residues of the Index Chemical

After calculating the relative potencies of all of the chemicals in the CAG, for each exposure route that is being assessed (i.e., oral, dermal and inhalation), the residues of each chemical are multiplied by that chemical's relative potency factor for each exposure of interest (e.g., food residues). Where exposure to these residues can co-occur to the same population member, the resulting values are added together to get the total, cumulative exposure in terms of residues of the index chemical, as illustrated below.

$$\begin{array}{l} \text{Residue Index Chemical} \times 1.0 \\ \text{Residue Chemical A} \times 0.5 \\ +\ \text{Residue Chemical B} \times 2.0 \\ \hline \text{Total Residues (expressed as} \\ \text{residues of the index chemical)} \end{array}$$

2. Background on Different Types of Endpoints Used in Risk Assessment

The following provides some very basic background on different types of endpoints that can be used for risk assessment (and as measures of relative potency). The terms and definitions presented here will be used in the following discussion.

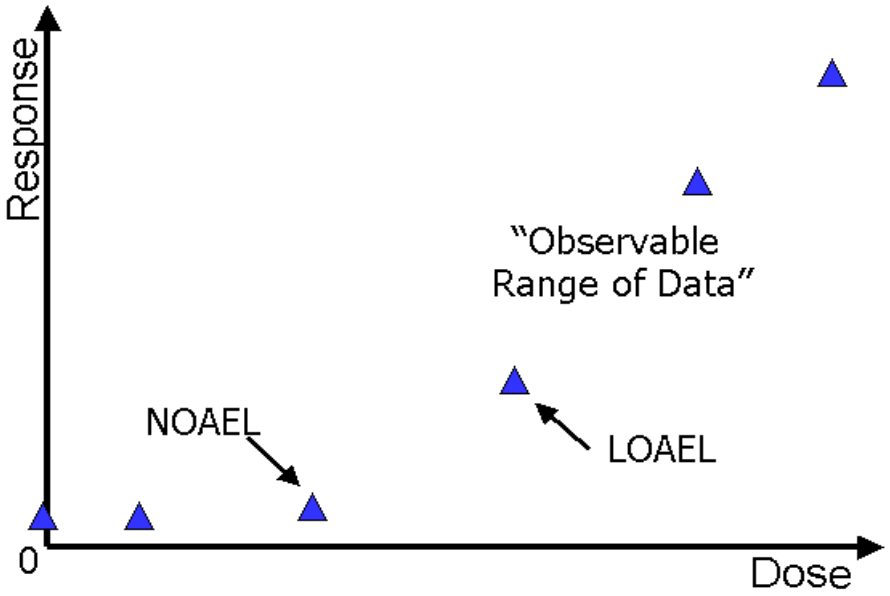
In individual chemical risk assessment OPP most often uses a No Observed Adverse Effect Level (NOAEL) as the endpoint. This is defined as the highest dose level that does not produce a significant increase in an adverse response. Significance usually refers to both statistical and biological considerations. Significance may depend on a number of factors including the number of dose levels tested, the number of animals per dose, and the background incidence of the adverse response in the control (non-exposed) group.

The NOAEL approach has several limitations, some of which are particularly important for cumulative risk assessment where one of the goals is to determine *relative* potency. These limitations include:

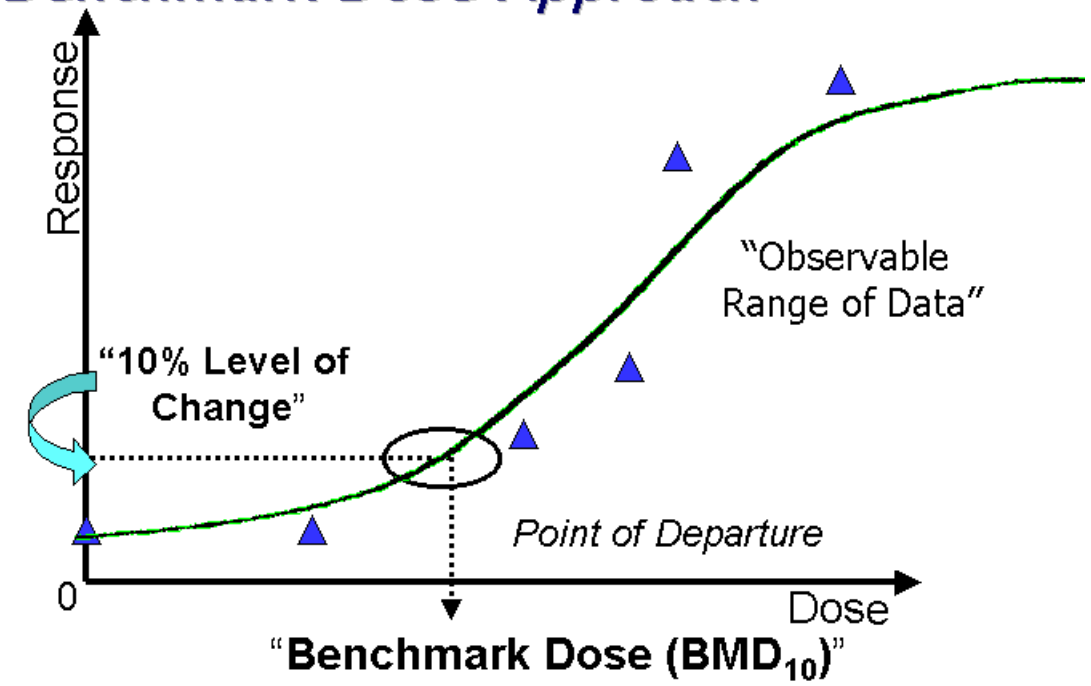
- ❏ the NOAEL by definition must be one of the experimental doses tested
- ❏ once the NOAEL is identified, information in the rest of the dose-response curve is ignored
- ❏ experiments that use fewer animals can result in NOAELs at higher dose levels thus rewarding testing procedures that produce less certain rather than more certain NOAELs
- ❏ the NOAEL approach does not identify actual (i.e., significant) responses and the NOAELs will vary based solely on the dose levels tested--resulting in NOAELs that may represent widely varying levels of risk; therefore, the NOAELs do not represent a common level or "common footing" on which to compare different chemical's potency

An alternative approach that addresses some of these limitations is the benchmark dose (BMD) method. Using this method all of the data points being considered are plotted to produce a dose response curve. Using various statistical techniques, this curve is then used to calculate a specified response level (the benchmark response). The benchmark response is usually specified as a 1 to 10% response (compared to the control). For example, the BMD_{10} is the benchmark dose associated with a 10% response compared to the untreated control. The Agency benchmark dose guidance recommends use of the lower bound confidence limit for a dose at the specified response level as an alternative endpoint to the NOAEL. Because of very narrow confidence limits, in the preliminary cumulative assessment the estimated benchmark dose itself is used, rather than the lower confidence interval. The following graphs illustrate these concepts.

NOAEL/LOAEL Approach



Benchmark Dose Approach



It should be noted that it is actually possible for the lower bound confidence limit (BMDL) on the BMD to be at a dose level below the NOAEL. This is because the confidence limits on the BMD take into account the quality of the data being used to estimate the response and reflect the variability in response. If there is a large amount of uncertainty and/or variability resulting in relatively large confidence intervals on the BMD, then the lower bound confidence interval may be below the NOAEL.

In the preliminary cumulative assessment of the OPs, it was not possible to use dose-response modeling to estimate relative potencies for the dermal and inhalation routes of exposure. For these routes a "Comparative Effect Level" (CEL) was used. A CEL is simply a defined response for the common mechanism which can be used for comparison. In the preliminary cumulative risk assessment the comparative effect level is defined as the dose causing no greater than15% cholinesterase inhibition compared to the control. CELs are dose levels from a study and in the preliminary cumulative risk assessment for the OPs the CEL was in many cases, in fact, the same dose identified as the NOAEL. The NOAEL chosen for a study reflects a weight-of-evidence decision from different types of toxic effects while the CEL is simply a defined response for the common mechanism effect used for comparison purposes.

Another term used in the cumulative assessment that is not used in the individual OP assessments is "Point of Departure". The Point of Departure (POD) is defined as the point in the dose-response curve at which a change in response can be reliably said to be due to dosing with the chemical, but is still within background variability. In the individual assessments it is equivalent to the "endpoint" used to calculate risk. In the cumulative assessment the POD is the level of response used to represent the toxicity of the index chemical, i.e., the "endpoint" for the index chemical. It is used to calculate the cumulative risk.

As will be discussed in detail below, for the oral route of exposure benchmark doses are used for the measures of relative potency and the point of departure of the index chemical. For the dermal and inhalation routes CELs are used for the measures of relative potency. The points of departure for the dermal and inhalation routes of exposure are the respective benchmark doses for the dermal and inhalation routes for the index chemical.

3. Implementing the Relative Potency Factor Method

The method itself, as illustrated above, is straightforward; however the details of its implementation in any given case are more complex. In order to implement the method, four critical pieces are necessary.

- ❑ Selection of a specific common endpoint and duration of exposure on which to compare potencies (e.g., for the OP's common mechanism the endpoint is cholinesterase inhibition--cholinesterase data are available for plasma, brain, or red blood cell (RBC) cholinesterase inhibition in male or female rats, rabbits, dogs, or mice and studies using many different time frames are available);

- ❑ Estimation of the measures of potency (e.g., BMD_{10}'s, CELs) and calculation of the relative potencies;

- ❑ Selection of an index chemical; and

- ❑ Selection of the specific level of response (e.g., $BMD_{10,}$ NOAEL) to represent the toxicity of the index chemical. This is the Point of Departure (POD).

The index chemical is selected based on which chemical in the CAG has the best data base for all routes of exposure (oral, dermal, inhalation) and has the best-characterized dose-response curve for the toxic effect. This allows a more reliable analysis of all the potential data available on the relative potencies of the other chemicals. The selection of the index chemical does not affect the individual chemical potency values used to calculate the *relative* potencies. The importance of the index chemical selection lies in the determination of the endpoint used in risk estimation (the Point of Departure mentioned above). It is desirable to have high confidence in the selected endpoints. Therefore, again, it is desirable that the index chemical have the best and most complete toxicity data base for the common endpoint.

In the OP preliminary assessment the selection of the index chemical has no effect on the estimated risks for the oral route of exposure, i.e., the estimated risks from the oral route of exposure would be the same regardless of which chemical was the index chemical. This is because the measures of potency and the Point of Departure use the same measure, the BMD_{10}. [This was not the case in the previous analysis where the measures of potency were the slope scaling factors (m) while the Point of Departure was the BMD_{10}.] For the dermal and inhalation routes, where CELs are the measures of potency while the Point of Departure is the BMD_{10} of the index chemical, the selection of the index chemical may affect the estimated risks.

Selection of a specific common endpoint, duration of exposure, and the method to compare potencies is based on a detailed analysis of the toxicity database. In presentations to the Scientific Advisory Panel (SAP), the Agency has discussed several approaches that could be used. The

Agency first proposed a method to the SAP in a pilot analysis in September 2000. In this analysis a single "representative" study was chosen for each chemical and route of exposure (oral, dermal, inhalation). Dose response was modeled with a linear equation using a probit model. In response to this analysis the SAP provided the following recommendations:

- ❏ There would be much greater confidence in the measure of relative potency if it were derived from several, relatively consistent studies as opposed to a single study, without benefit of confirmation by other studies.

- ❏ Reevaluate the selection of the probit model for determining the relative potencies. They specifically suggested considering Michaelis-Menton kinetics or an exponential model as the potential alternative methods.

The SAP comments were addressed in a second analysis completed in July 2001. In response to this second analysis, the panel recommended several refinements. A detailed discussion of those recommendations and how the Agency has addressed them in the preliminary risk assessment is provided below in Section 4–"Oral Relative Potency Factors". Another SAP meeting to review this work is scheduled for February 2002. The following table summarizes the key aspects of each analysis.

Summary of Three Hazard Analyses

Oral Route of Exposure			
	Pilot (September 2000)	**July 2001**	**Current (December 2001)**
Type of Model	Linear Equation (probit model)	Nonlinear Equation (exponential model)	Nonlinear Equation (exponential model expanded to include possibility of flat area in low dose region)
Studies Used	One Representative Study	All Studies	All Studies
Study Duration	> 21 Days	> 21 Days	> 21 Days
Proposed Compartment/Sex for RPFs	None Proposed	RBC/Male	Brain/Female
Potency Measure	BMD_{50}	Slope Scaling Factor (m)	BMD_{10}

Data Used in Model	CHEI Percent Inhibition	Mean CHEI, Standard Deviation, Sample Size	Mean CHEI, Standard Deviation, Sample Size
Analysis of Variability	No Measure	Weighting of Variance; Confidence Intervals Calculated	Weighting of Variance; Confidence Intervals Calculated
Analysis of Model Uncertainty	No Measure	Goodness-of-Fit Test	Statistical comparison of fit between basic and expanded model

Determination of the Relative Potency Factors for the Dermal and Inhalation Routes of Exposure

The Agency used two different methods to estimate potency, one for the oral, and another for the dermal and inhalation routes of exposure. This was necessary because there are different amounts of data available for the different routes. Determination of the relative potency for the dermal and inhalation routes of exposure will be discussed first, because these are the simplest cases. This will be followed by discussion of the oral route; the selection of the index chemical, which is the same chemical for all routes of exposure; and the Points of Departure for the index chemical.

The dermal and inhalation routes of exposure are only applicable to residential exposures. Therefore, RPFs were only determined for those chemicals which have residential uses.

4. Dermal Relative Potency Factors

Relative potencies for the dermal route of exposure were determined using Comparative Effect Levels (CELs) observed in dermal toxicity studies. The CEL is the dose causing up to15% cholinesterase inhibition. This is in contrast to the relative potency factors for the oral route, which, as will be discussed shortly, were determined through modeling. Even though the dermal data were not suitable for modeling, the dermal studies were used in the relative potency analysis and endpoint evaluation. They were chosen (as opposed to, for example, using oral data as a surrogate) because of the importance of using the same route of exposure, in this case dermal, for both the toxicity and exposure estimates. There are only a limited number of dermal studies for OPs with high quality dose-response data. Therefore, it was determined that the database of dermal toxicology studies, when considered across all of the chemicals, was not appropriate for dose-response modeling.

As noted above, determinations of relative potencies based on

tests using the same sex and species are preferred. As will be explained in detail in the section below on "Oral Relative Potency Factors," the Agency is using the data on inhibition of brain cholinesterase activity in female rats as the measure of relative potency for the preliminary OP cumulative risk assessment. Therefore, CELs for female brain cholinesterase inhibition from dermal toxicity studies were used to determine the dermal relative potency measures.

In the case of dermal exposure, tests on the same species were not always available. Four chemicals were tested by the dermal route in rats. Only rabbit studies were available for four OPs. Thus, both rat and rabbit data were used.

One chemical, dichlorvos, had no dermal exposure study of any kind. OPP waived the requirement for a dermal toxicity study due to the volatility of the chemical, which makes it very difficult to conduct such a study. Residential/non-occupational dermal exposure was not assessed for dichlorvos in the preliminary cumulative risk assessment of the OPs. This is because there is a limited potential for significant exposure via the dermal route. DDVP's high volatility limits its residence time on skin surfaces thus making the dermal (and subsequent oral) routes of exposure unlikely.

Based on the above considerations, the following CELs were chosen as the measures of potency for the dermal route of exposure.

Measures of Potency for the Dermal Route of Exposure: CELs for Female Brain Cholinesterase Activity from Dermal Toxicity Studies

Chemical	*Species*	*CEL(mg/kg/day)*
Acephate	rat	300*
Bensulide	rat	500*
Dichlorvos	Dermal exposure study waived due to volatility of compound.	
Disulfoton	rabbit	1.6
Fenamiphos	rabbit	0.5
Fenthion	rabbit	50
Malathion	rabbit	50
Methamidophos	rat	0.75
Naled	rat	10

Tetrachlorvinphos	rat	1000*
Trichlorfon	rabbit	100

* Highest dose tested.

The following examples illustrate how these CELs are used to calculate the relative potency factors. Using the measure of potency for the index chemical, 0.75 mg/kg/day, as explained above, the relative potency factors are calculated as:

$$\text{Index Chemical RPF} = \frac{\text{Index Chemical Measure of Potency}}{\text{Index Chemical Measure of Potency}} = \frac{0.75}{0.75} = 1$$

$$\text{Acephate RPF} = \frac{\text{Index Chemical Measure of Potency}}{\text{Acephate Measure of Potency}} = \frac{0.75}{300} = 0.0025$$

$$\text{Bensulide RPF} = \frac{\text{Index Chemical Measure of Potency}}{\text{Bensulide Measure of Potency}} = \frac{0.75}{500} = 0.0015$$

The remaining relative potencies can be calculated in a similar manner. All of the RPFs for the dermal route of exposure are listed in the table, "Relative Potency Factors," at the beginning of this section.

5. Inhalation Relative Potency Factors

Relative potencies for the inhalation route of exposure were determined using Comparative Effect Levels (CELs) from inhalation toxicity studies. The CELs are defined as the dose causing up to a 15% brain cholinesterase inhibition (compared to the control). This is in contrast to the relative potency factors for the oral route which, as will be discussed shortly, were determined through dose-response modeling. As described in the case of dermal exposure, the inhalation studies were chosen because of the importance of using the same route of exposure, in this case inhalation, for both the toxicity evaluation and the exposure estimate. As in the case of the dermal toxicity database, the number of available inhalation toxicity studies with quality dose-response data was limited. Therefore, it was determined that the database of inhalation toxicology studies, when considered across all of the chemicals, was not appropriate for dose-response modeling.

As noted above, determination of relative potencies based on tests using the same sex and species is preferred. As will be explained in detail in the section below on "Oral Relative Potency Factors", the Agency is

using the data on inhibition of brain cholinesterase activity in female rats as the measure of relative potency for cumulative risk assessment. Therefore, CELs for female brain cholinesterase inhibition from inhalation toxicity studies were used to determine the inhalation relative potency measures.

All of the inhalation studies were performed with the same species (rat); however four different strains of rats were used. The exposure conditions varied among the chemicals tested. Four used whole-body exposure while three used nose only exposures. The index chemical, methamidophos, used head/nose exposure. The studies were sub-chronic (21 to 90 days), with the exception of dichlorvos, which had only a chronic inhalation study.

No inhalation toxicity studies were available for three chemicals, tetrachlorvinphos, fenthion, and bensulide. No inhalation risk assessment was necessary for two of these chemicals, tetrachlorvinphos and fenthion, in the OP cumulative assessment. A quantitative risk assessment for tetrachlorvinphos was not included in the OP cumulative assessment due to lack of exposure data suitable for use in a probabilistic assessment. Tetrachlorvinphos's only remaining uses are pet uses. The individual chemical screening level assessment indicates risks of concern. Inhalation risks were not estimated for public health mosquitocide uses. This is the only remaining use of fenthion. Bensulide's inhalation RPF was estimated using the oral data for bensulide.

Based on the above considerations, the following CELs were chosen as the measures of potency for the inhalation route of exposure.

Measures of Potency for the Inhalation Route of Exposure: CELs for Female Brain Cholinesterase Activity from Inhalation Toxicity Studies

Chemical	*Method (species tested was the rat in all cases)*	*Female CEL (mg/kg/day)*
Acephate	nose only	1.492*
Bensulide	No inhalation toxicity study available.	
Dichlorvos	whole body	0.458
Disulfoton	nose only	0.047
Fenthion	No inhalation toxicity study available.	
Fenamiphos	nose only	0.984*

Malathion	whole body	121
Methamidophos	head/nose	0.310
Naled	whole body	0.378
Tetrachlorvinphos	No inhalation toxicity study available.	
Trichlorfon	whole body	3.574

* Highest dose tested.

These CELs are used to calculate the relative potency factors in exactly the same way as in the case of the dermal RPFs. Using the measure of relative potency for the index chemical, 0.310 mg/kg/day, as explained above, the relative potency factors are calculated as:

$$\text{Index Chemical RPF} = \frac{\text{Index Chemical Measure of Potency}}{\text{Index Chemical Measure of Potency}} = \frac{0.310}{0.310} = 1$$

$$\text{Acephate RPF} = \frac{\text{Index Chemical Measure of Potency}}{\text{Acephate Measure of Potency}} = \frac{0.310}{1.492} = 0.208$$

$$\text{Dichlorvos RPF} = \frac{\text{Index Chemical Measure of Potency}}{\text{Dichlorvos Measure of Potency}} = \frac{0.310}{0.458} = 0.677$$

The remaining relative potencies can be calculated in a similar manner. All of the RPFs for the inhalation route of exposure are listed in the table, "Relative Potency Factors," at the beginning of this section.

6. Oral Relative Potency Factors

a. Model Used to Estimate RPFs for the Oral Route of Exposure

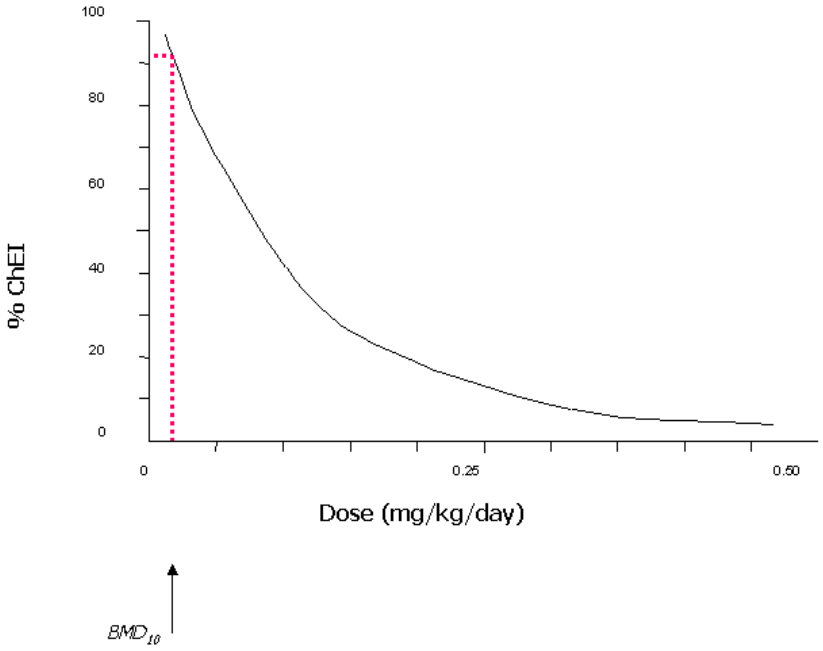
In the case of the oral route of exposure, numerous oral studies with comparable methodologies are available and suitable for dose-response analysis. Therefore, it was possible to determine relative potency factors for the oral route of exposure using a model developed in response to SAP comments. In response to the pilot analysis presented in September 2000, the Agency developed the following exponential equation to model the dose-response curves and estimate oral relative potencies.

$$y = B + (A - B) \times e^{-m*dose}$$

where:

y=cholinesterase activity
B=the y-asymptote (value of maximum cholinesterase inhibition)
A=background cholinesterase activity
m=slope scale factor (the measure of potency in the July assessment)
Dose=dose of the OP, in mg/kg/day

While the equation itself may appear rather daunting, the idea is fairly simple. All of the relevant data points are assembled and the equation employs a mathematical exercise that attempts to find a curve that comes the closest to the most data points (simultaneously) as possible. Statistical methods are then available to assess if this curve, and the measures derived from it (e.g. m, the BMD_{10}) are really good representations of these data points. A graph of this exponential function is provided below.



This model did provide a good representation of the data. Out of a total of 1312 data sets available for modeling, the above exponential function was a good representation of the dose-response for 1306 data sets. A data set in this case consisted of the cholinesterase measurements at a specific time point from a specific study for a specific compartment (plasma/RBC/brain) and sex combination (e.g., male/plasma).

The dose-response analysis was performed using a computer program developed for this purpose by the Agency's Office of Research and Development's National Health and Environmental Effects Laboratory (NHEERL). This program, OPCumulativeRisk (OPCumRisk), is publicly available on the internet at www.epa.gov/scipoly/sap/index.htm#september.

The SAP was very supportive of this approach when it was presented in September 2001. However, some additional analyses and revisions were recommended. The key recommendations that have been incorporated into the current analysis include:

1) reevaluation of the procedure for estimating the horizontal-asymptote, i.e., the "B" term in the above equation (the Panel suggested that the decision rules used to estimate "B" could be improved to result in more consistent values for the horizontal asymptote)

2) determination of the appropriate measure for relative potency (some members of the Panel suggested that a Benchmark Dose, e.g., BMD_{10}, was a more appropriate measure of potency than m, the slope scaling factor in the above equation)

3) a formal analysis of residuals (the residuals are the measures of how far each of the actual measured data points is from the estimated dose-response curve--the Panel suggested that the results of this analysis would help the Agency remove some bias in the potency estimates–see #4 below)

4) revision of the statistical procedures for weighting the various cholinesterase data points and calculating confidence intervals (the Panel was concerned that the residual plots presented at the September 2001 meeting appeared to indicate the residuals were larger in the low dose area of the curve than in the high dose area, the Panel suggested revising the weighting procedure would improve this bias--the weights determine the relative importance of different data points in the analysis; the Panel also suggested a particular statistical technique called "bootstrapping" for calculating the confidence intervals)

5) consideration of repeated measures of cholinesterase inhibition in the animal studies (in toxicity studies, measures of blood cholinesterase such as RBC and plasma can be obtained from a single laboratory animal multiple times, therefore, blood cholinesterase is often a “repeated measure”–in contrast, brain cholinesterase can only be measured from a laboratory animal one time and cannot be a “repeated measure”; statistical procedures need to incorporate information about the variability within a study–in the case of repeated measures, where animals are potentially measured more than once, it is necessary to track each individual animal in the statistical procedures--the Panel recommended the Agency consider how repeated measures impacted potency estimates)

Finally, there was considerable discussion at the technical briefing (August 2001) and the SAP meeting in September about the potential for a flat region in the low dose portion of the dose-response curve. (The concern was that the model only allowed for exponential decline. Some argued that initially–at low doses--the curve would not decline exponentially for some chemicals but would have a flat area where cholinesterase activity was not declining as quickly.)

The current analysis addresses these comments by incorporating the following changes. The analysis uses all of the data being considered all at once, together in a joint analysis rather than a tiered approach working up from single measures in individual studies. This joint analysis enabled the Agency to address two of the above recommendations. Recommendation (1) is addressed because there is only a single estimate of the horizontal asymptote for each sex and chemical, rather than multiple ones for each study. The joint analysis, because it considers all of the data at once, is based on more dose levels. As a result it was possible to look in more detail at the shape of the low-dose area of the dose-response curve.

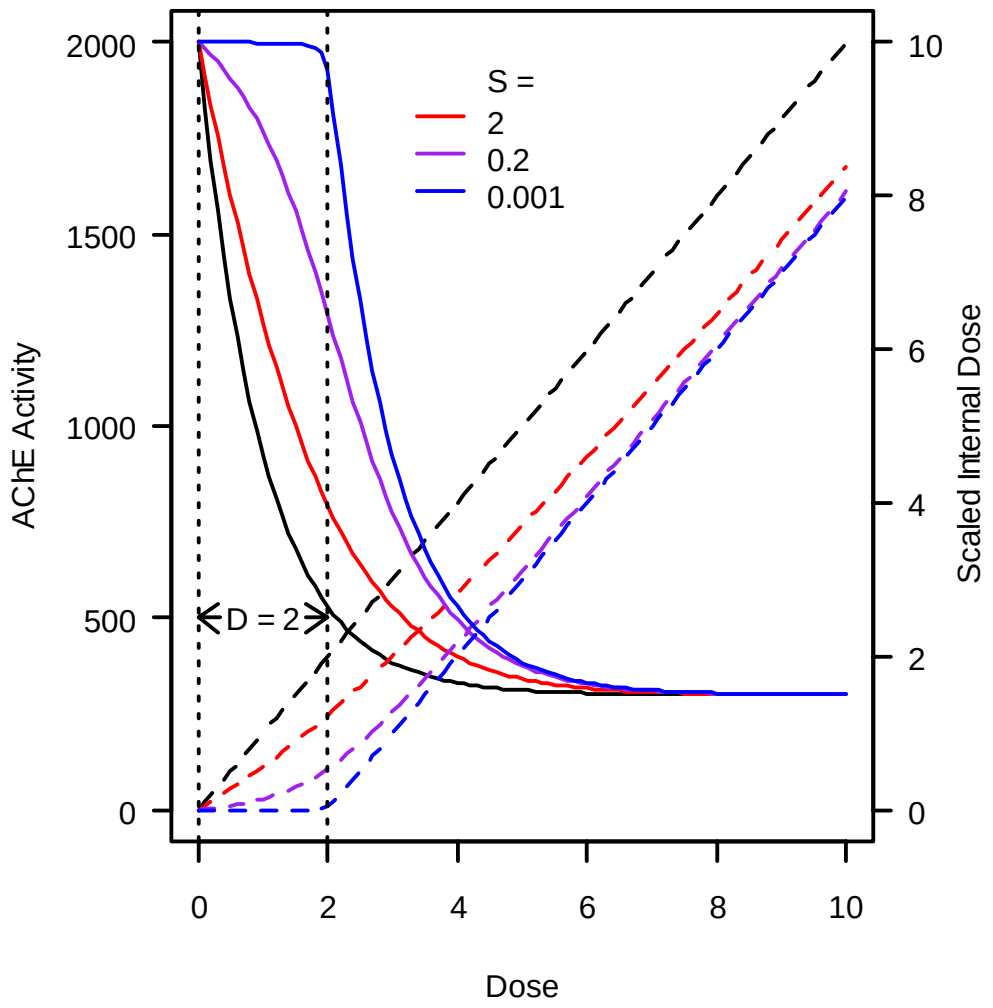
A new equation was developed to include the possibility of a flatter area in the lose-dose region of the dose-response curve. This new equation is shown below.

$$idose = 0.5[(Dose - S - D) + \sqrt{(Dose - S - D)^2 + 4 \times Dose \times S}]$$

where:

idose is the scaled internal dose
Dose is the administered dose level
S controls the shape of the curve in the low-dose region
D controls the horizontal width of the low dose part of the curve that is declining less rapidly than the rest of the curve

This equation can be added to the first equation, which we will now call the “basic” equation, by replacing Dose in the first equation with idose. When this is done the result is what we will refer to as the expanded equation. The expanded equation becomes equivalent to the basic equation as S gets larger and D approaches 0. A graph illustrating these relationships is shown on the following page.



The graph shows the effect of increasing values of S. On the left hand side of the graph are various exponential functions (the solid lines) with different values of S. Looking at these graphs from right to left, it can be seen that as S gets larger, the flat portion in the low dose area disappears, until when S is very large the curve is the same as the basic exponential equation. On the right hand side of the graph, the dashed lines represent the relationship between estimated internal dose and administered dose that is expressed in the expanded equation, with D=2 and increasing values of S going from right to left. This part of the graph demonstrates that as S gets larger Administered Dose and Internal Dose become equivalent.

The expanded equation estimated a dose-response curve that fit the data better than the basic curve for eight of the chemicals. These chemicals, whose dose-response curves were modeled using the expanded equation, are azinphos-methyl, bensulide, disulfoton, malathion,

methyl-parathion, phorate, phosmet, and terbufos. The remaining chemicals dose-response curves were estimated using the basic equation.

As noted above (recommendation 2) there was considerable discussion at the SAP about whether m, the slope scaling factor in the basic equation, or a Benchmark Dose (e.g., BMD_{10}) was the appropriate measure of potency. In the current analysis the BMD_{10} has been used as the measure of potency. This was necessary because the shapes of the dose-response curves for the basic and expanded models differ in the low dose region. Therefore, the slope-scaling factor (m) is no longer an appropriate measure of potency across all of the chemicals. In addition, the value of the slope-scaling factor is dependent on the value of the horizontal asymptote. The current analysis clearly shows that the values of the horizontal asymptotes for the different OP chemicals are not similar to each other. Thus, the slope scaling factor is not an appropriate measure for determining relative potency.

Another statistical concern noted above-- (recommendation 4) revision of the statistical procedures for weighting the cholinesterase data and calculating confidence intervals was partially addressed by use of a new estimation procedure in the joint analysis. This procedure, a nonlinear mixed effects model, was performed using the *nlme* package of *R* (an open source statistical programming language; http://cran.r-project.org). The R programs used in the current analysis are contained in Appendix B of the preliminary risk assessment.

In the July and in the current analysis data points were weighted to give those data points that were more reliable more influence on the estimated dose-response curve. In the July analysis the weights were based on the square of the estimated mean. In the current analysis the weights are proportional to the mean. The confidence intervals have not been recalculated using the method suggested by the SAP (bootstrapping), however; the calculation of the confidence intervals has been revised. Bootstrapping is a very time and resource-intensive procedure. Although it may be the preferred approach for calculating confidence intervals, the Agency has not conducted any bootstrapping procedures. The current method for calculating confidence intervals is adequate and satisfactory for this assessment. To address another statistical concern noted above--(recommendation 3), an analysis of residuals was done which indicates that the models generally capture the trend of the mean of the data, and the weighting function used in the current analysis is generally superior to that used in the July analysis.

b. Selection of Species/Compartment/Sex and Duration of Exposure for Comparison of Potencies

A central principle of the relative potency factor method is that relative potency should be determined using a uniform basis of comparison. This requires using to the extent possible a common response derived from a comparable measurement methodology, species, and sex for all the exposure routes of interest. Although many different methods are available for measuring cholinesterase activity, for this assessment they are all assumed to be comparable if the study was found to be acceptable. Studies are available for various species (e.g., dog, mouse, rat, and rabbit), however; toxicology studies in the rat provided, by far, the most extensive cholinesterase activity data for all routes (dermal, inhalation and oral) and in the three compartments (plasma, red blood cell, and brain) in both sexes. Therefore, only rat studies were used in determining relative potencies, except in the case of five chemicals for the dermal route, for which no rat study was available.

The Agency decided to use only those data that reflect steady-state conditions for cholinesterase inhibition to estimate relative potencies. Steady-state as used here is the point where continued dosing at the same level results in no further increase in cholinesterase inhibition. This was done because the steady state values produce relative potency factors that are reproducible and reflect less uncertainty due to the rapidly changing, time-sensitive differences in measures of cholinesterase that are observed prior to achieving a steady-state. Steady-state for each OP was determined qualitatively. The analysis showed that most chemicals appeared to reach steady-state by 21 to 28 days of exposure in both sexes and all three compartments (plasma, RBC, and brain). The available data sets for each chemical-sex-compartment included a range of exposure durations from 21 days to greater than 700 days.

In addition, monitoring data show that people generally have had some level of OP exposure, making it unlikely that any individual would encounter exposure to OP pesticides without having a previous exposure from other sources. Therefore, the Agency does not consider the use of toxic endpoints based on single-day exposures to be reflective of the actual human exposure situation. Furthermore, the effects of OP exposure can persist for several days to weeks depending on the magnitude of exposure, making the exposed individual potentially more vulnerable to subsequent exposures during that period. These considerations together with the very stable and reproducible levels of cholinesterase inhibition in studies of 21 days or longer resulted in the use of only those cholinesterase measures based on study duration of 21 days or longer in the development of the RPFs.

In its September 2000 review the SAP recommended against combining data (at least initially) across compartments, i.e., plasma, red blood cell (RBC), and brain, or for males and females. This led the Agency to analyze six separate compartment/sex combinations for each chemical, i.e., male/plasma; male/RBC; male/brain; female/plasma; female/RBC; and female/brain. These were analyzed in order to determine an appropriate compartment/sex on which to compare potencies of the chemicals. Overall there is a good agreement between potency values calculated for males and females. Therefore, the selection of either males or females would make little difference in the RPFs. Males were chosen for use in the comparison of potencies for the July analysis. For the current analysis which is based on brain cholinesterase inhibition, females were chosen instead of males. This was because, for the brain compartment, female rats were more sensitive than male rats for five OPs (diazinon, dichlorvos, pirimiphos-methyl, tetrachlorvinphos, and trichlorfon).

For most of the chemicals, the relative potencies were similar when calculated using plasma, RBC, and brain measurements. In the July analysis RBC cholinesterase inhibition was chosen for comparison of potencies. After considering the comments from the September 2001 SAP meeting in addition to the comments from the public, the Agency has decided to use brain cholinesterase data for quantifying cumulative risk for the OPs. This decision was based on:

- ❏ Compared to relative potency estimates using RBC, the estimates of relative potency based on brain cholinesterase inhibition have smaller confidence intervals and therefore, will result in less uncertainty in cumulative risk estimates. (Confidence intervals give the range of values within which the BMD_{10} is expected to actually fall. Thus, if the BMD_{10} is estimated to be 0.08 mg/kg/day and the confidence limits are from 0.0001 to 10.0 mg/kg/day, they are said to be wide, and this would not be a very good estimate. If the confidence limits are from 0.05 to 0.1, they are said to be narrow and the estimate is better.)

- ❏ Brain data represent a direct measure of the common mechanism of toxicity as opposed to RBC or plasma which are surrogate measures for the brain and peripheral nervous system. As noted above, the toxic potencies and points of departure estimated using brain cholinesterase inhibition are generally similar to the estimates using RBC data for the OPs.

- ❏ The SAP recommended that the Agency address the issue of repeated measures. This issue, which concerns repeated cholinesterase measures derived from a single animal, only pertains to the plasma and RBC data because blood data can be

collected several times from a single animal, while brain data can only be collected once. Therefore, using the brain data, repeated measures are not an issue.

Although the Agency has emphasized that the relative potencies and points of departure were similar when calculated using plasma, RBC, and brain measurements, extensive analysis was done to characterize the likely differences in the risk estimates resulting from using female brain data compared to male RBC data. Extensive analysis was also done to evaluate the effects of the changes in the statistical methods. These analyses showed:

- ❏ The revised statistical methods, while providing refined statistical estimates, had very little impact on the BMD_{10} values that were estimated, with the exception of those chemicals modeled with the expanded equation.

- ❏ 21 OPs have very similar oral RPFs based on female brain compared to male RBC data–the difference was less than 3X. These slight differences are likely due to experimental variability/errors rather than real differences in sensitivity between the RBC and brain measures.

- ❏ Oral RPFs are lower (i.e., less potent) using brain data for diazinon, malathion, fenamiphos, and tribufos. Malathion is the least potent of all the OPs and this difference is unlikely to impact the cumulative risk estimates. Diazinon's residential uses are being phased out as well as many of its agricultural uses. Tribufos does not have residential uses and is only used as a defoliant on cotton. The only residential exposure to fenamiphos is on golf courses. It has few detections in PDP. Because of limited exposure potential, using either RPFs based on RBC or brain for diazinon, tribufos, and fenamiphos would have little impact on the total cumulative risk estimates.

- ❏ Oral RPFs are higher (i.e, more potent) using brain data for mevinphos, methidathion, acephate, and naled. Dietary exposure to mevinphos is very low because it is only used on imported bananas. Methidathion does not have many detects in PDP. Because of limited exposure potential, using either RPFs based on RBC or brain for mevinphos and methidathion would have little impact on the total cumulative risk estimates. Dietary risks for acephate and naled could be underestimated using male RBC relative potency factors because both pesticides are used on numerous commodities.

In summary, the oral relative potency values are based on cholinesterase activity data derived from female rat brain data, taken from studies that lasted 21 days or longer. This choice was made after an extensive analysis of all available oral data and multiple reviews by the SAP. As we have seen, such extensive databases are not available for the dermal and inhalation routes of exposure. Therefore, because of the extensive oral database, which makes a detailed comparison between compartments for males and females possible, this same selection of female rat brain data was also used in the case of the dermal and inhalation routes. The only exception is that, when rat data were not available for the dermal route of exposure, rabbit data were used. In addition, as we will see shortly, the same selection was made for determining the points of departure for risk assessment.

After determining that female brain measures in the rat are the most appropriate for comparison of relative potencies and after selecting the BMD_{10} as the appropriate measure of potency, RPFs can be calculated. This is done using the BMD_{10} from the relevant (basic or expanded) exponential equation. These BMD_{10}'s for each chemical are listed in the table below.

ORAL $BMD_{10's}$

(chemicals marked with * were modeled using the expanded equation)

Chemical	BMD_{10} (mg/kg/day)
Acephate	0.63
Azinphos methyl*	0.90
Bensulide*	32.85
Chlorpyrifos	0.83
Chlorpyrifos-methyl	7.51
Diazinon	3.43
Dichlorvos	2.25
Dicrotophos	0.04
Dimethoate	0.25
Disulfoton*	0.07
Ethoprop	1.70
Fenamiphos	2.11
Fenthion	0.24
Fosthiazate	0.50

Chemical	BMD_{10} (mg/kg/day)
Malathion*	326.37
Methidathion	0.22
Methamidophos (Index Chemical)	0.08
Methyl Parathion*	1.41
Mevinphos	0.06
Naled	1.00
Oxydemeton Methyl (ODM)	0.09
Phorate*	0.21
Phosalone	3.38
Phosmet*	4.13
Pirimiphos methyl	2.88
Terbufos*	0.10
Tetrachlorvinphos	101.92
Tribuphos	1.81
Trichlorfon	6.03

The following illustrates how these BMD_{10}'s are used to calculate the relative potency factors. Using the measure of potency for the index chemical, 0.08 mg/kg/day, the relative potency factors are calculated as:

$$\text{Index Chemical RPF} = \frac{\text{Index Chemical Measure of Potency}}{\text{Index Chemical Measure of Potency}} = \frac{0.08}{0.08} = 1$$

$$\text{Acephate RPF} = \frac{\text{Index Chemical Measure of Potency}}{\text{Acephate Measure of Potency}} = \frac{0.08}{0.63} = 0.13$$

$$\text{Bensulide RPF} = \frac{\text{Index Chemical Measure of Potency}}{\text{Bensulide Measure of Potency}} = \frac{0.08}{32.85} = 0.003$$

Where the Measures of Potency for all of the chemicals are the BMD_{10}'s estimated using the relevant exponential equation calculated using that chemical's female brain data, from studies 21 days or longer.

The oral relative potencies for the remaining chemicals can be calculated

in a similar manner. All of the RPFs, for the oral route of exposure are listed in the table, "Relative Potency Factors," at the beginning of this section.

7. Selection of the Index Chemical and the Points of Departure for Risk Assessment

The index chemical is selected based on which chemical in the cumulative assessment group has the best data base for all routes of exposure (oral, dermal, inhalation) and the best-characterized dose-response curve for the toxic effect. It is important that it acts toxicologically as purely as possible by the common mechanism defining the group, that is, it has no other mechanisms of appreciable toxicity; and that quantitative data for assessing potency be available for as many routes of exposure, genders, species, and strains of animals as possible. This allows a more reliable analysis of all the potential data available on the relative potencies of the other chemicals.

Methamidophos was chosen to be the index chemical for the preliminary OP cumulative assessment. The oral database contains studies that characterize the entire dose-response range from very low doses to high doses. Within the oral route of exposure, potency values for methamidophos were consistent between adult male and female rats and among the three compartments (plasma, RBC, and brain). Quality dose-response data were also available for the dermal and inhalation routes of exposure. Available data from the literature support the conclusion that methamidophos acts "toxicologically as purely as possible." It is a direct-acting anti-cholinesterase OP that appears to selectively inhibit cholinesterase, the target enzyme.

The selection of the index chemical does not affect the potency values used to calculate the relative potencies for the individual chemicals, since these are based solely on the individual chemical's data, nor does it affect the relative potencies of the chemicals, which is simply an indexing exercise. The importance of the index chemical selection lies in the determination of the dose level that will be used in risk estimation. This dose level is called the Point of Departure or POD. It can be an observed NOAEL from a single study, as was the case in the individual OP risk assessments or it can be a Benchmark Dose based on a modeled estimate.

In the OP preliminary assessment the selection of the index chemical has no effect on the estimated risks for the oral route of exposure, i.e., the estimated risks from the oral route of exposure would be the same regardless of which chemical was the index chemical. This is because the measures of potency and the Point of Departure use the same measure, the BMD_{10}. [This was not the case in the previous

analysis where the measures of potency were the slope scaling factors (m) while the Point of Departure was the BMD_{10}.] For the dermal and inhalation routes, where CELs are the measures of potency while the Point of Departure is the BMD_{10} of the index chemical, the selection of the index chemical may affect the estimated risks.

The oral, dermal, and inhalation PODs for the cumulative assessment are based on benchmark dose modeling of the rat female brain data for studies of 21 days or longer for methamidophos. The benchmark dose where cholinesterase activity is reduced by 10% compared to background activity (BMD_{10}) is the effect level selected. OPP has traditionally used 10% cholinesterase inhibition for plasma and RBC as the decision-point for selecting an effect level when cholinesterase inhibition is the effect of interest. These PODs are listed in the following chart. They are the endpoints the Agency used in the preliminary OP cumulative risk assessment. The lower bound confidence limit (BMDL) on these PODs is also listed. The narrow confidence intervals demonstrate the high quality data available for methamidophos.

Points of Departure (from the Index Chemical Methamidophos): Female Rat Brain Cholinesterase Activity from Toxicity Studies 21-Days or Longer

Route of Exposure	BMD_{10} (mg/kg/day)	BMDL (mg/kg/day)
Oral	0.08	0.07
Dermal	2.12	1.77
Inhalation	0.39	0.21

8. Summary and Example Risk Calculation

Three elements are required for endpoint selection in the case of cumulative assessments:

- ❏ Selection of an index chemical,
- ❏ Calculation of relative potency factors, and
- ❏ Selection of points of departure.

These elements perform exactly the same function as the elements in an individual chemical assessment. The following summary relates the elements used in the cumulative assessment back to the basic risk assessment equation that is used in all risk assessments:

Risk = Hazard x Exposure

The exposure part of the equation is obtained by summing all of the relevant residues to which a person is exposed, for the relevant time period. In individual chemical assessments these residues can simply be added together, because they are all residues of the same chemical. In a cumulative assessment these residues must first be put on a common scale before they can be added. This is done by multiplying each of the potentially multiple residues of each chemical by a number that represents that chemicals relative potency, as shown below.

Residues		Relative Potency Factor		Residues Expressed as Residues of the Index Chemical
1 mg Chemical A	X	0.5	=	0.5 mg
2 mg Chemical A	X	0.5	=	1.0 mg
0 mg Chemical B	X	2.0	=	0.0 mg
3 mg Chemical B	X	2.0	=	6.0 mg
2 mg Chemical Index	X	1.0	=	2.0 mg
4 mg Chemical Index	X	1.0	=	4.0 mg
				13.5 mg/day of the index chemical

Once all of the residues have been converted by this process, the "Exposure" side of the equation is exactly the way it is for an individual chemical–it is as if all of the residues are residues of the index chemical.

Just as in the case of an individual chemical assessment the "Hazard" part of the equation is obtained by selecting the endpoints that will be used for risk assessment. Since all of the residues are now expressed in terms of the index chemical, the endpoints for use in risk assessment are selected for the index chemical and compared to the residues, to obtain the estimate of risk.

For example, to perform a dermal risk assessment using a margin of exposure (MOE) approach, the methamidophos point of departure for dermal risk assessment, 2.12 mg/kg/day, and the above exposure estimate,13.5 mg/day of methamidophos (converted to mg/kg/day by dividing by body weight = 13.5÷ 62 kg = 0.22 mg/kg/day), would be used to calculate the following MOE.

$$\text{MOE} = \frac{\text{Hazard}}{\text{Exposure}} \quad \textbf{\textit{or}} \quad \text{MOE} = \frac{\text{Point of Departure}}{\text{Exposure}} = \frac{2.12 \text{ mg/kg/day}}{0.22 \text{ mg/kg/day}} = 9.6$$

The "new and complicated" part of the OP cumulative risk assessment is determining (and keeping track of) what measures are being used for relative potency, and what points of departure for the index chemical are being used in risk assessment. The measures of potency were selected to provide the best measures of *relative* potency. The

points of departure were selected to provide the best measures of the index chemical's toxicity for use in risk assessment. All of the measures of potency for each route (dermal, inhalation, and oral) are listed in the tables above, as are the points of departure for methamidophos. The following table provides a summary of what measures were used in each case.

Route of Exposure	Measure of Potency	Point of Departure
Dermal	CELs (from a dermal study for each chemical using female rat brain data and a study 21 days or longer)	BMD_{10} (modeled from Methamidophos Dose-Response Curve based on female rat brain data from one methamidophos dermal study)
Inhalation	CELs (from an inhalation study for each chemical using female rat brain data and a study 21 days or longer)	BMD_{10} (modeled from Methamidophos Dose-Response Curve based on female rat brain data from one methamidophos inhalation study)
Oral	BMD_{10} (modeled using all acceptable oral studies for each chemical using female rat brain data from studies 21 days or longer)	BMD_{10} (modeled from Methamidophos Dose-Response Curve based on female rat brain data from three methamidophos oral studies 21 days or longer)

V. Cumulative Exposure Model And Interpretation Of Model Outputs

A. Background

Developing a modeling tool that permits the assessment of co-occurrence is a necessary aspect of the development of cumulative methods. The model must be able to integrate exposure through food, water, and residential/non-occupational pathways in a manner that reflects both the probability of exposure by any given pathway and the timing of exposures through different pathways. This means the model should reflect the exposure of discrete individuals/population members in which routes of exposure are linked.

The estimated exposures should reflect the individual's location and other demographic characteristics of the individual such as age and weight; the time of year; the individual's anticipated patterns of pesticide use (for residential exposure); and the individual's history of exposure. For example, if an individual's house was treated for termites today, that exposure could continue for a period of time for that individual, but would not be randomly spread through a population. Similarly, for drinking water, the source of an individual's/population member's drinking water today is likely to be the same source tomorrow, and the spatial and temporal linkage must be preserved. As a result, the building blocks for the cumulative risk assessment are specifically defined individuals/population members for whom the spatial, temporal, and demographic aspects of their exposures are linked. The outputs included in the preliminary OP risk assessment are:

- ❑ Cumulative risk from OPs in food
- ❑ Cumulative risk from OPs in drinking water
- ❑ Cumulative risk from OPs in residential/non-occupational settings
- ❑ Cumulative risk from OPs across multiple pathways (food, water, and residential/ non-occupational)
- ❑ All of the above assessments contain some elements that are dealt with qualitatively

The following section describes the attributes of the software model, Calendex™, in some detail. This is the model that was used in the preliminary OP cumulative risk assessment. In addition, the attributes and current status of other models that allow assessment of cumulative risks will be briefly reviewed. Calendex™ is a proprietary software package licensed from Novigen Sciences, Inc. The Calendex™ model and its dietary component, DEEM™, have been the

subject of review at two SAP meetings. [The following papers were presented at those meetings: "Dietary Exposure Evaluation Model (DEEM™) and DEEM™ and Max LIP (Maximum Likelihood Imputation Procedure) Pesticide Residue Decompositing Procedure and Software," dated February 29, 2000 and "Calendex™; Calendar-Based Dietary & Non-Dietary Aggregate and Cumulative Exposure Software System", dated September 27, 2000].

B. Calendex™

Calendex™ contains demographic and food consumption data for a sample of individuals/population members that is representative of the U.S. population. This is the CSFII (USDA's Continuing Survey of Food Intakes by Individuals) for 1994-1996 together with the 1998 Supplemental Children's Survey. The demographic variables (e.g., age, sex, weight) for each individual/population member in the survey can be used as part of the basis for selecting potential non-food exposures for the individuals as well as to link these non-food exposures to the food exposure for these individuals. For each scenario that is developed, routes (e.g., oral and dermal) can be linked if exposures are dependent on each other. If the exposures are linked, then the model assumes that the exposures occur at the same time. For example, the inhalation and dermal exposures that may result from application of a lawn pesticide should occur on the same day. Calendex™ uses the calendar day as the unit of time for calculating exposure. If exposure estimates for more than one day are required, these are built by adding together sequential daily exposures for an individual and averaging them over the number of days to provide an average daily exposure over the desired time frame. If single-day exposures are considered, the output of the analysis is a distribution of daily exposures.

Calendex™ calculates daily food exposure using the DEEM™ dietary exposure model. This is the same model OPP currently uses for individual chemicals. In the cumulative analysis, however, time is an important consideration and it is necessary to estimate food exposure for every single day of the year so that the daily food exposures can be combined with daily drinking water and residential exposures. It is assumed in this analysis, that the consumption data in the CSFII is reflective of food choices across the year and around the country. No attempt has been made to estimate seasonal or regional differences in food exposures. Drinking water concentrations are, however, related in space and time. The pesticide concentration in drinking water at a particular site on any given day is correlated with the concentration on a subsequent day. The model must preserve this time-series relationship. A similar relationship exists for residential exposures in which concentrations present on Day 1 are related to concentrations on Day 2.

Calendex™ uses the following steps to estimate food and water exposures in the case of single day exposures. Starting with January 1st,

- ❑ It calculates exposure from food for individual #1 using one of his two diets in the CSFII and randomly assigns a residue value from PDP for each

food included; after multiplying each amount of food consumed by its selected residue value the total exposure for food for this individual is calculated by summing the exposure through each food

- ❏ For water, it selects a random year from the multiple years of daily concentrations that are available, and calculates the water exposure on January 1. These daily concentrations were estimated with PRZM/EXAMS-IR, which provides a distribution of daily concentrations over a wide range of years. Calendex™ calculates the exposure from water for individual #1 by multiplying the concentration in water by the water consumption reported in the CSFII by individual #1
- ❏ It then sums the total exposure for food and water for individual #1 on that day.
- ❏ This process is repeated multiple, e.g., ten times, for each consumption record (for the relevant age group) in the CSFII to develop a distribution of exposures for January 1.
- ❏ This process is then repeated for each calendar day of the year. In this way a distribution of single-day exposures is generated for the entire year.

Finally, the whole process is repeated for each region. The output is a distribution of exposures for the population subgroups of concern for each region.

Calendex™ uses the following analogous steps to calculate residential/non-occupational exposures. Starting with January 1st,

- ❏ It uses the probability that the individual would be using a pesticide for a particular purpose to determine if the individual might have a chance of being exposed to various pesticides that might be used that day.
- ❏ If the answer to that question is “yes” it determines the specific dates that are possible for those exposures to make a probability decision on whether the individual is actually exposed on that day, i.e., a probability-based decision is made to determine whether or not that scenario will actually be encountered by the individual on that date.
- ❏ If a scenario is assigned a “yes” answer, then the appropriate values defining the exposure are selected from the many distributions of input parameters for residential exposure scenarios.
- ❏ The exposures for the appropriate dermal, oral and inhalation exposures are calculated for all selected residential scenarios. In doing these calculations the model is able to use information on the frequency and amount of chemical used and the degradation of the chemical over time. The estimates of the amount of residues available to be contacted, how easily they dislodge (i.e., come off) when contacted, and how often contact is made are provided as inputs into the model. The model also evaluates for each day whether an individual applied a pesticide on a previous day–and, if so, estimates exposure as a result of that previous application (appropriately considering any degradation that may have subsequently occurred).
- ❏ All the exposures are converted to route-specific MOEs, i.e., separate MOEs for oral, dermal, and inhalation, and added together with the food

and water exposure for that individual for that day to estimate the total exposure for that individual on January 1.

- ❏ As noted above, this process is repeated multiple, e. g., ten times, for each consumption record (for the relevant age group) in the CSFII to develop a distribution of exposures for January 1.
- ❏ This process is then repeated for each calendar day of the year. In this way a distribution of single-day exposures is generated for the entire year.

Finally, the whole process is then repeated for each region. The output is a distribution of exposures for the population subgroups of concern for each region.

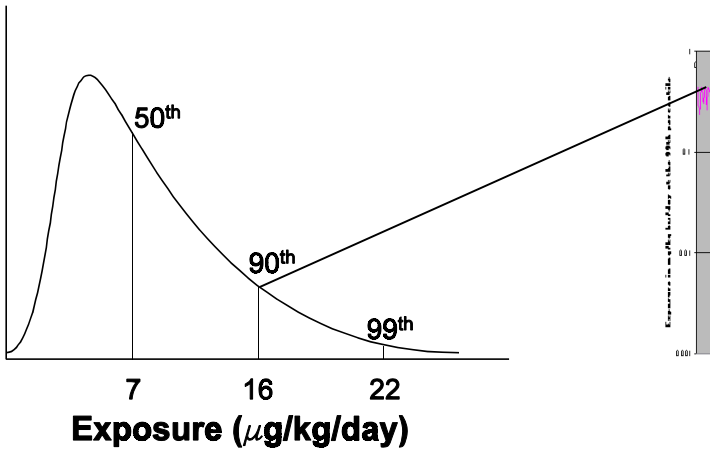
A more detailed description of how Calendex™ operates, including numerous examples, can be found in the Appendices to this document.

The Agency has worked extensively with the components of Calendex™ and has developed the capability to track the exposure input data that correspond to individual daily risk estimates. This allows analysis of specific pesticide residue inputs, including the specific pesticide and commodity for food and water exposure or specific use of the pesticide for residential exposure. As such, Calendex™ will permit the Agency to identify and analyze sources of exposure in order to identify further refinements or mitigation strategies.

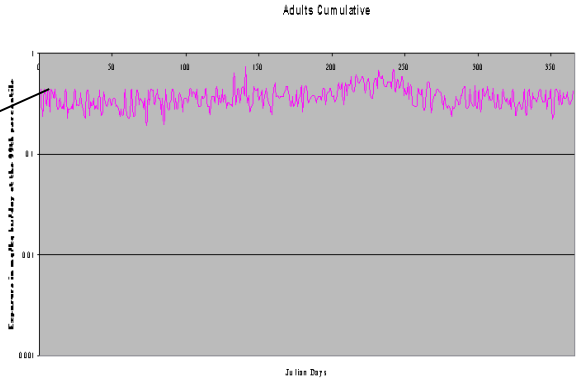
C. Interpretation of Model Outputs

As discussed above, the model outputs are a series of daily exposure distributions, one for each day of the year. Each daily distribution represents the result of repeatedly estimating the possible exposures for each individual in the relevant population for that day of the year. For any given percentile of exposure of interest, e.g., the 90th, these daily distributions can be shown as a time series of MOEs across the entire year. Taking January 1st as an example, this is done by selecting from the January 1st daily distribution the exposure level that corresponds to the 90th percentile of exposure and calculating the corresponding MOE. This MOE is placed on January 1st of the yearly graph for the 90th percentile. This is illustrated for January 1st in the following graphs.

January 1st Distribution



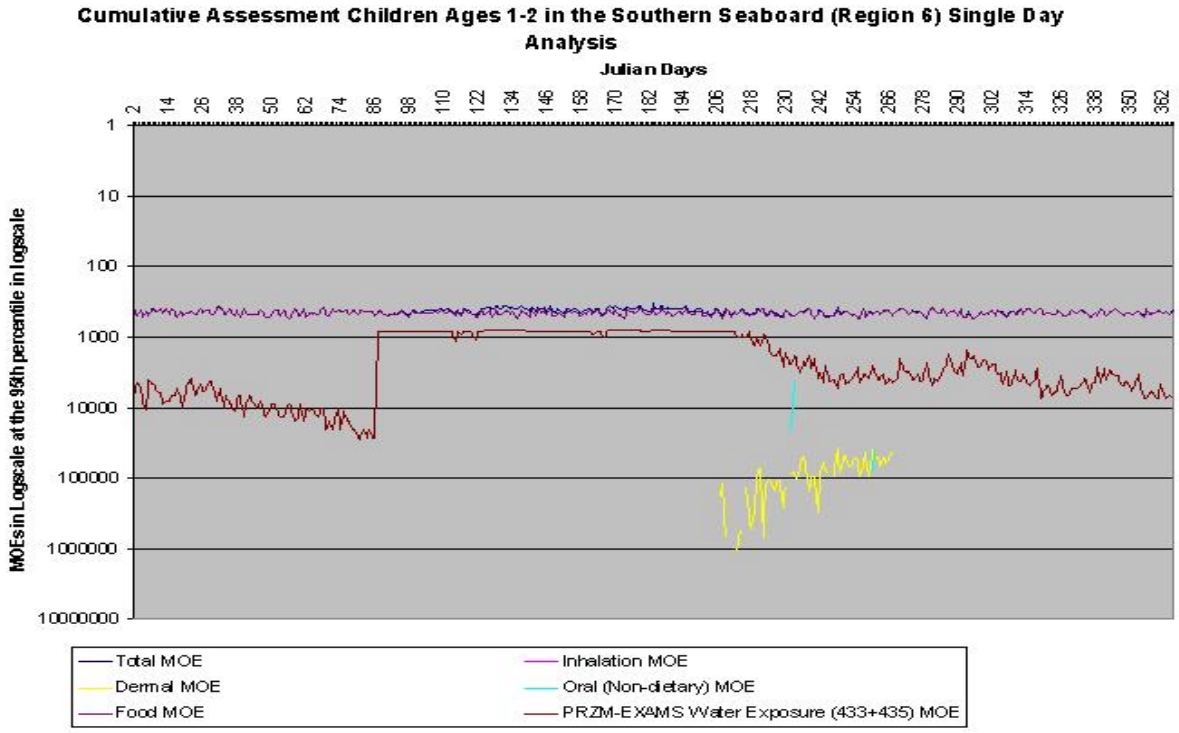
Graph of Daily
MOEs at 90th Percentile for One Year



In a similar manner, time series could be developed for any other percentile of exposure by selecting the exposure for that percentile from each daily distribution. These 365 MOEs would be placed on another graph for the year that would represent the new percentile of exposure.

In the case of the food assessment, interpretation of the output distribution is the same as for the individual chemical assessments. Because of the wide distribution of both fresh and processed foods, food is assumed to be a "national" commodity with little seasonal or regional variation. Any differences resulting from time of the year or region of the country are reflected in the PDP sampling of food residues and the sampling scheme used in the CSFII to reflect consumption. Therefore, the results for food alone really represent single Margins of Exposure (MOE) corresponding to a given percentile of exposure which are considered representative of any day of the year in any region of the country. Nevertheless, the food output distributions were calculated and arrayed for each day across the year as described above, so that they can be incorporated with the water and residential output for each region. However, as can be seen in the calculated food output distributions, there is very little variability in the results from day to day and the same distribution is used for every region.

In the case of the water and residential assessments, there is both a spatial and temporal component that can be seen very clearly in the output distributions. The spatial component is reflected in the 12 separate regional assessments that were done. The temporal component is reflected in the significant variation that can be seen in the water and residential output distributions over the course of a year. A typical graph showing the food, water, and residential output distributions in a specific region is shown below. It should



be noted that the residential output distributions are really three separate distributions representing dermal, inhalation, and non-dietary oral MOEs.

The analysis and interpretation of the temporal component of the risk assessment involves two related aspects: first the exposure duration used to calculate the MOEs and second the length of the exposure period that is relevant when viewing the above output distributions across the year. The nature of the toxic response, i.e., brain cholinesterase inhibition is also relevant to determine an appropriate time frame over which to consider exposure to OPs. Cholinesterase inhibition is not immediately reversible, with effects persisting for days to weeks depending on the magnitude of exposure. Because of this and because there is a continued background exposure to OPs from food, a period of multiple days might be considered an appropriate window over which to evaluate the pattern of exposures and resulting MOEs for the OP cumulative assessment.

In the preliminary OP cumulative assessment, single day exposures have been used to calculate the MOEs. In this case, analysis and interpretation of the output distributions relies heavily on examination of these distributions to discern changing *patterns* of exposure. When viewed in this way, there are periods of higher exposure (i.e., periods with low MOEs) and periods with lower exposure (i.e., periods with higher MOEs). Changes in the pattern of exposure can be interpreted by examining different pathways of exposure (food, water, residential) and different routes of exposure (oral, dermal, and inhalation) separately to determine the factors causing any increased exposure estimates. Given the

hazard framework defined for the OPs, elevated exposures that continue over multiple days would likely be of more concern using this method of analysis (i.e., MOE's calculated using a single day exposure), than if the elevated exposure was for only a very short period, such as a few days. Using this mode of analysis raises issues concerning the appropriate interpretation of examining the elevated exposure of different individuals over multiple days. This population based approach to risk estimation is discussed in more detail below.

As noted above Calendex™ can also calculate exposure over multiple sequential days (e.g., 7, 14, 21) for each individual. In this mode of analysis Calendex™ calculates single consecutive daily exposures for each individual as described above, for the selected number of days, and then averages these together. The resulting exposure distributions can be arrayed across the year in the same way as the single day distributions. However, their interpretation would likely be different. In this case elevated exposures over short time periods would likely be of more concern than in the case of the single day analyses. Using this mode of analysis raises issues concerning how appropriate the available data are for conducting such a longitudinal (multiple consecutive day) analysis for an individual.

It should be noted that the single day analysis does not depend on any knowledge of the day-to-day exposure patterns of any particular individual, since each day is modeled separately for each individual. This type of assessment, therefore, highlights between-individual patterns of exposure (population risk) rather than within- individual patterns of exposure (individual risk). Using this approach the focus is on a snapshot of potential *population* risk from a variety of sources. The likelihood of a sustained elevation in an individual's exposure is anticipated to be lower than an elevated population exposure at any given percentile. The rationale behind this conclusion is provided in the following example. Few individuals are likely to repeat residential applications for every day of the pest season. However, on a population basis, the upper percentiles of exposure will reflect the phenomenon of a large number of individuals encountering an increase in exposure due to performing these tasks. It is this increase in population risk that may be a concern. As a result, this approach to calculating the exposure to the population is considered to be health protective.

OPP will continue to pursue a series of further analyses to evaluate alternative strategies for combining the data and selecting appropriate time frames to consider. This will also be the subject of several questions presented to the SAP in February 2002.

D. Other Models

The Agency is aware of three other models that have been developed or are under development to conduct multi-pathway assessments and that can be adapted to incorporate inputs for data from multiple chemicals. Two of these have been presented to the SAP as aggregate risk assessment models:

LifeLine™, a model developed by Hampshire Research Institute, currently licensed by the LifeLine Group; and Rex™, a product of Infosciences. Neither of these packages appeared to provide the scope with regard to the number of pathways, routes, or sources of pesticides required in the current OP cumulative assessment. CARES, a product of ACPA, is still under development. It is expected to be presented to the SAP in April/May 2002.

LifeLine™ is a multi-pathway model that can be adapted to evaluate multiple chemicals. It focuses on identifying the periods during an individual's life where pesticide exposures are likely to occur, and identifying the source of those exposures. LifeLine™ produces a longitudinal estimate of possible exposures, focusing on looking across many years of a person's life. It draws upon a subset of natality records from the U.S. Census to develop the demographic characteristics of the population under evaluation. Consumption data from the CSFII are matched to the other information available using the demographic, regional, and seasonal information from the two surveys. Residential exposure is estimated by linking data from a group of surveys to develop scenario characteristics that are anticipated to occur due to the use patterns of the group of chemicals under evaluation.

CARES is intended to perform cumulative and aggregate assessments, focusing on a population-based, cross-sectional analysis of a hypothetical year of exposure. CARES is anticipated to generate a series of exposure estimates moving across the calendar year, similar to that described for Calendex™. The demographic characteristics of the population being assessed will be drawn from a subset of the U.S. Census. CARES is intended to provide the user with a flexible, easily used tool to develop total and pathway-specific estimates of exposure, and to facilitate identification of the sources of exposure.

VI. Dietary Risk Assessment

A. Dietary Risk From Food

1. Residue and Consumption Data Used in the Food Assessment

Dietary exposure from food is calculated considering what is eaten by individuals in one day and residue values for each food. The food exposure assessment is extensively refined using probabilistic Monte Carlo analyses. Information on the amount of residues that may be on foods was obtained mainly from the USDA's Pesticide Data Program (PDP) supplemented with information from the Food and Drug Administration (FDA) Surveillance Monitoring Program and Total Diet Study. PDP data were used for the commodities that have been directly monitored as part of the program and were also used to estimate residues on commodities where this data can be reliably used as a surrogate (e.g., measured data for broccoli was used to estimate cauliflower residues). Commodities directly monitored by PDP accounted for approximately 86% of the diet of children 3-5 years old. Commodities for which surrogate PDP data were used accounted for an additional 1.3 % of the diet of children 3-5 years old.

Consumption data were taken from the USDA Continuing Survey of Food Intake by Individuals (CSFII 1994-96), and the 1998 Supplemental Children's Survey. The CSFII records one-day food and nutrient intake data and is considered to be representative of the U.S. population. The CSFII 1994-1996 contains survey data on 20,607 participants interviewed over two discontinuous days. The supplemental children's survey includes an additional 5,459 children, birth through 9 years old.

The Agency limited the food assessment to use of mainly PDP monitoring data for several reasons. The PDP program is designed to provide the best available data for risk assessments. PDP collects samples of selected food commodities throughout the year on a nationwide basis. It focuses on foods consumed by children and on foods typically available throughout the year. Foods are washed and inedible portions removed before analysis. These samples are analyzed for numerous pesticide residues and, therefore, capture co-occurrence of different pesticide residues on a particular sample. The distribution of residues that results from this program reflects a range of pesticide use patterns. It also takes into account the percentage of the crop nationwide to which each pesticide is typically applied (known as percent crop treated). Data collected between 1994 and 2000 were used in the assessment. The PDP data were adjusted to remove chemicals or uses that have been cancelled or are being phased out.

Other available monitoring data are collected for different purposes than

those of the PDP program and are not necessarily designed to reflect the overall consumption by the U.S. population. However, some FDA monitoring data were used to supplement the PDP data. The FDA surveillance data measure residues on commodities generally sampled closer to the point of production than for PDP. The program has extensive data on eggs and fish, two commodities not sampled in PDP. These data were used in the current assessment to support the judgement that OP residues are negligible on eggs and fish. The FDA total diet study is excellent for assessing the occurrence of pesticides in foods that have actually been prepared for consumption; however, the number of samples analyzed is very small. These data have been used in the current assessment to estimate residues in meats other than poultry. The data show that only limited residues of OP pesticides have been found on a few meats at low levels. This information was used to develop a conservative residue estimate for meat commodities. The maximum residue found for each type of meat in the 26 market baskets collected between 1991 and 1999 was used in the assessment. Commodities for which FDA data were used in the assessment accounted for 6.3 % of the diet of children 3-5 years old.

The last case in which supplemental information was used in the assessment is highly refined sugars and syrups. PDP includes high fructose corn syrup and has found no pesticide residues. However, no other sugar or syrup sources are included in PDP. The FDA total diet survey has analyzed refined sugar and maple sugar and found no OPs in 26 market baskets. This limited residue data together with the knowledge of the highly refined nature of sugars and syrups is the basis for assuming negligible residues of OPs on sugars and syrups. In the current assessment residues were assumed to be zero for these foods derived from sugarcane, sugar beet, and maple. These foods account for about 3% of the consumption of children 3-5 years old.

The following table summarizes the above discussion on the sources of residue information used in the assessment and the percentage of children's diets covered by each source.

PROPORTION OF THE DIET OF CHILDREN (3-5 years old) COVERED IN THE CUMULATIVE FOOD ASSESSMENT

Source of Residue Estimate	Percent of Per Capita Consumption
PDP	85.7
Translation of PDP (PDP data used as surrogate for other commodities)	1.3
FDA Data (eggs, fish, meat other than poultry)	6.3
Assumed Negligible (sugars and syrup sources)	3.1
Not Covered in Current Assessment	3.6

OP Market Basket Data

A task force of pesticide producers has provide the Agency with an OP pesticide market basket survey. The results of this survey, conducted in 1998, were submitted to the Agency in 2001. The final report is still under review but the data are being examined to determine what they show concerning cumulative exposure for OPs on food. Samples were taken from grocery stores and single-serving size samples were analyzed by methods with very low limits of detection. The foods collected, all of which are also covered by PDP, were apples, broccoli, cherries, cucumbers, green beans, grapes, peaches, sweet corn, lettuce, oranges, potatoes, strawberries, and tomatoes. Preliminary examination of the data indicate that cumulative exposure estimates using these data are in general agreement with a similar assessment using PDP data. These data will continue to be examined.

2. Processing Factors Used

Residues of organophosphates may be either concentrated or reduced by the activities of drying (e.g., prunes), processing (e.g., juice), washing, peeling and cooking. The Agency uses processing factors to account for these situations in the risk assessment. EPA has utilized, to the extent possible, the processing studies that have been submitted to the Agency in support of the registration and reregistration activities for the individual OP pesticides. In cases where no acceptable data were available, the assessment relies on assumptions regarding processing factors. The preliminary assessment lists the processing factors that were used for each chemical/commodity (see Section 6 “Data” below).

3. Pesticides Included in the Food Assessment

After exclusion of data on pesticides that have been cancelled or do not have food uses, there are residues for 22 OPs in the PDP data. The following 22 OPs have, therefore, been included in the food assessment.

acephate	ethoprop	oxydemeton-methyl
azinphos methyl	fenamiphos	phorate
chlorpyrifos	malathion	phosalone
chlorpyrifos-methyl	methidathion	phosmet
disulfoton	methamidophos	pirimiphos-methyl
diazinon	mevinphos	terbufos
dichlorvos	methyl-parathion	tribufos
dimethoate		

The following chemicals, which have not been sampled in PDP, are not expected to contribute to food risk for the reasons described below.

- Naled degrades rapidly to dichlorvos and is analyzed and included in PDP

as dichlorvos

- Bensulide is expected to have negligible residues based on field trial data
- Cadusafos is used only on imported bananas and field trial data indicate residues will not occur in the edible portion of the banana
- Chlorethoxyfos and phostebupirim are used only in soil applications to corn, therefore, significant residues in edible portions of the corn would not be expected
- Dicrotophos and profenofos are only used on cotton; cottonseed oil is the only food commodity derived from cotton and any residues are expected to be low due to the extent of refining and blending of the oil
- The only food related use of trichlorfon and tetrachlorvinphos are livestock uses--as a pour-on treatment of beef cattle and for livestock and livestock premises respectively; any potential residues are expected to be covered by the conservative residue estimate for meat commodities that is being used in the assessment

4. Elements of the Cumulative Analysis Which May Differ From Individual Chemical Assessments

a. Use of Composite Samples/Estimating Residues on a Sample-by-Sample Basis

Only the residue data from composite samples were used in the preliminary OP cumulative assessment. A single composite sample may contain several individual servings of some foods (e.g., five pounds of apples). For this assessment, it was assumed that residues found on the composite samples adequately reflected the residues that would be on any given single-serving contained in the sample.

In addition, all of the different chemical residues found on a sample were summed to generate a single cumulative residue for each sample. By summing on a sample-by-sample basis, the potential for capturing any co-occurrence on the same commodity is enhanced. A majority of PDP samples contained no detectable residues of any OP. For those that contained detectable residues, a single OP was most common, but many multi-residue samples were found. The maximum number of OPs on a single PDP sample was five (this occurred on only 5 samples during the period 1994-1999). For food forms (e.g., grains) that are highly blended before consumption, the residue value used was the average of all the cumulative residues for that food form.

b. Use of Zero as the Residue Estimate When No Detectable Residues are Found

It has been the usual practice in Agency assessments on individual pesticides to assume, for samples which showed non-detectable residues,

that residues are present at ½ the limit of detection (LOD) of the analytical method for that part of the crop that is treated. For the untreated part of the crop, residues are assumed to be 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 multiple residues on the same crop. In the current assessment *all* OP residues reported as non-detectable are assumed to be zero.

In a complex analysis such as this assessment, in which there are abundant samples with detectable residues, the assumption of zero for non-detects would not be expected to greatly impact the exposure estimates at the highest percentiles of exposure. This assumption was tested and found to be the case in an earlier stage of the assessment as reported in the case study presented to the SAP in December 2000. Cumulative food exposure assessments were conducted using two extreme default assumptions: all non-detects = 0 and all non-detects = ½ LOD for the chemical with the highest percent crop treated for a given food.

c. Use of Measured PDP Data on Related Commodities that Were Not Measured in PDP (Translation of Data)

In chemical specific dietary exposure assessments the Agency routinely translates residue data from one food commodity to related ones if the pesticide use patterns are similar on those commodities. For example, data on cantaloupes is often used as surrogate data for watermelons and other melons. For a cumulative assessment, in which a grower has a choice of several chemicals from the cumulative assessment group, these translations become more difficult to make. In the current assessment, translations of the residue data were made exactly as they are in the individual assessments except that a residue was not included if the chemical was not registered on the crop that the data were being translated to. This allowed maximum use of the PDP data. The uncertainty introduced by this method is not expected to have a major impact on the assessment because the foods for which translated data were used comprise a relatively small portion of the per capita consumption of children. An analysis of critical commodities contributing to the higher percentiles of exposure in this assessment is currently under way. If any translated foods appear in this analysis then the sources of data for those specific contributors will be examined even more closely for their validity as surrogate residue estimates.

d. Over-Tolerance and Other "Violative" Residues

Residue values that exceed the tolerance on the commodity and residue values for commodities with no registered use for the associated

pesticide have been excluded. These “violative” residues are rare in both PDP and FDA monitoring.

5. Risk Estimates for Food Alone

Separate assessments were conducted for children 1-2 years old, children 3-5, adults 20-49 , and adults 50+. The most highly exposed subgroup, that is the group with highest estimated risks, are children 1-2 years old. The risk estimates for this sub-group are presented below.

Estimated Percentile of per capita Days Falling Below Calculated Exposure (mg/kg/day) with Margin Of Exposure for Children 1-2

Percentile	Exposure	Margin of Exposure (MOE)
90.00	0.000100	800
95.00	0.000176	454
97.50	0.000285	280
99.0	0.000499	160
99.50	0.000735	108
99.75	0.001045	76
99.90	0.001541	51

It is assumed in this assessment that food distribution and storage systems in the U.S. result in essentially a national distribution of the major foods in the U.S. diet that is constant throughout the year. Thus, there is no regional or temporal component for the food only assessment. For some of the seasonal changes in availability of certain foods, PDP has designed its sampling program to concentrate on these time frames so that the residue data reflect the foods, including imports, available to the consumer. This same national food estimate is, therefore, combined with the specific regional water and residential assessments to calculate each regional assessment.

6. Data

All of the data used in the preliminary OP cumulative risk assessment are available in the public docket and on the internet at www.epa.gov/pesticides/cumulative. The following summarizes the major data tables related to the food assessment that are included in the preliminary risk assessment and where they may be found.

❑ Table III.C.1 in Section III (Appendices), beginning on page III.C.1 Page 1,

contains the source of the residue values used for every food in the assessment (e.g., PDP, FDA total diet, etc.)

- ❑ Table III.C.5 in Section III (Appendices), beginning on page III.C.5 Page 1, contains all of the Processing Factors used in the assessment
- ❑ Other Tables in Section C of the Appendices summarize the residues found in PDP and FDA monitoring; show the co-occurrence of OPs in PDP samples; provide the translation scheme used to apply PDP data to other crops; and include a series of tables showing how the data were input into the DEEM™ dietary software

B. Dietary Risk From Water

1. Introduction

Drinking water exposure to pesticides can occur through surface water and ground water contamination. Potential for exposure to pesticides in drinking water varies for different parts of the country and in different times of the year. Contributing factors to these differences include time of pesticide application and weather conditions shortly after application. These differences are also influenced by the inherent local and regional differences in soils, crops, and site vulnerabilities.

To make the water assessments reflect geographic variations as realistically as possible, OPP used USDA Economic Research Service maps to divide the continental United States into12 regions. These regions are grouped according to similarity in crops. They take into account the geographic and climatic differences that lead to different agronomic practices, pest pressures, pesticide application methods and rates, and factors that affect pesticide transport to water. Water was assessed for watersheds that are potentially vulnerable to OP contamination within each of these regions. This regional approach allows the assessments to account for effects on drinking water that are driven by the different characteristics of these regions.

Scenarios for developing estimates of pesticides in drinking water within each region were chosen based on organophosphate use, watershed vulnerability (which accounts for such factors as rainfall frequency and intensity, slope of the land, and soil type which affect pesticide runoff), and source of drinking water (surface water or ground water). Information on the use of different pesticides within the same region, the timing of use, and the fate and transport properties of the pesticides was used to identify pesticides that are likely to co-occur.

Factoring drinking water exposure into the framework for food exposures means developing a person-by-person approach to estimating drinking water exposure over time, which preserves the individual's demographic characteristics and associates only those exposures that are appropriate for such an individual, as described above in Section V. "Cumulative Exposure Models and

Interpretation of Model Outputs." The probabilistic cumulative risk assessment for the organophosphates necessitates that drinking water exposures be based on daily concentrations of pesticides in the drinking water sources. When longer term exposure estimates are used, multiple sequential daily exposures would be averaged to obtain the relevant exposure estimate. To estimate risk the assessment used modeled distributions of daily concentrations of pesticides in a probabilistic analysis.

The differences in the individual chemical and cumulative approaches for the determination of pesticide concentrations in drinking water are summarized in the following table.

Aggregate Screening vs Cumulative Assessments

Aggregate Screening Assessment for A Single Pesticide	Cumulative Assessment for Multiple Pesticides
point estimate (single value), 99.9th percentile concentration	**distribution** of all daily concentrations (13,000+ days)
national estimate (single site represents entire US)	regional estimate (**multiple sites**, regional differences)
national Percent Crop Area (PCA)	regional Cumulative Adjustment Factor (CAF), reflecting variation in crop intensity
maximum label rates & frequency, minimum interval between applications	**typical rates**, frequencies, intervals
comparison of point estimate to DWLOC value	**probabilistic** assessment of water exposures
one compound at a time	**multiple compounds** considering co-occurrence

2. Available Monitoring Data

EPA's three main sources of monitoring data for organophosphates in water are:

(1) USGS ambient water samples, which include 9 currently registered OPs,

(2) USGS-EPA reservoir monitoring project, which includes 27 OP parent compounds and 19 OP transformation products, and

(3) ground and surface water monitoring information collected by states or submitted by registrants.

The Agency is committed to using all available monitoring data as extensively as possible. Monitoring data were used extensively in the individual assessments, and the Agency has relied on these assessments in developing its approach to the cumulative assessment. In addition to guiding the Agency in focusing its regional assessments, monitoring data were used for comparison to the modeling distributions for the cumulative assessment.

However, two main considerations made it difficult to base the cumulative assessment solely on monitoring data. First, the monitoring databases are not robust enough to assess even a single chemical over time in various regions of the country. Sampling is too infrequent to assess daily concentrations. The lack of monitoring data for some compounds makes it difficult to use the available data to assess the co-occurrence of multiple chemicals over time across the country. The available monitoring data was, however, used where possible to help assess co-occurrence. Secondly, mitigation developed as the result of the risk management for individual OP chemicals has resulted in use deletions, lower application rates, and reduced numbers of applications. The available monitoring data do not reflect these changes.

In summary, although the quantitative assessment was based on modeled distributions used in a probabilistic assessment, water monitoring data were used throughout the assessment in three main ways.

- ❏ Groundwater monitoring data were used to assess the vulnerability of groundwater to organophosphates.

- ❏ Any available monitoring was used as background information for scenario selection. The primary criterion for scenario selection was actual use information, but available monitoring data were also considered.

- ❏ Monitoring data were used to evaluate modeling results at every level of the assessment process.

Monitoring data confirm that OPs do occur in surface water drinking water sources. The frequency of detections is generally low, except for chlorpyrifos, diazinon, and, in some instances, malathion. While the residential uses of chlorpyrifos and diazinon, which contributed to many of those detections, have been cancelled, the individual chemical risk mitigation for malathion is in progress. The magnitude of detections generally ranges from sub-parts per billion to a few parts per billion. Significantly greater frequencies of detection occur in the limited number of targeted monitoring studies. In general, surface water sources are

more likely to be vulnerable to OP contamination than are ground water sources.

The USGS-EPA Reservoir Monitoring Project although only in the pilot stage, included more OPs than any previous study. Therefore, it is particularly useful for considering the possibility of exposure to multiple OPs. Of 314 intake samples, 137 (44%) had one or more detectable OPs. Of the 137 with detectable OPs, 16 (12%) had more than one OP detected. Of 67 outfall samples, 17 (25%) had one or more OPs detected. Of these 17, 2 (12%) had more than one OP detected. Of the 12 reservoirs included in the study, no more than 3 or 4 were located in areas with substantial OP use. A comparison of weather data during the sampling period with long-term trends indicates that the first year of this 1.5 year study had drier than normal rainfall. Thus, results of this study are not reflective of particularly vulnerable sites or weather conditions for this OP assessment.

Of 218 finished water samples collected in the study, 24 (11%) had one detectable OP. None of the finished samples had more than one OP detected. It is important to note that available evidence suggests that water treatment may convert the parent OP compounds into compounds that are also of toxicological concern. Not all of these transformation products were included in the monitoring study. Thus, EPA cannot draw definitive conclusions regarding the co-occurrence of parent OP and toxic transformation products based solely on the results of this study.

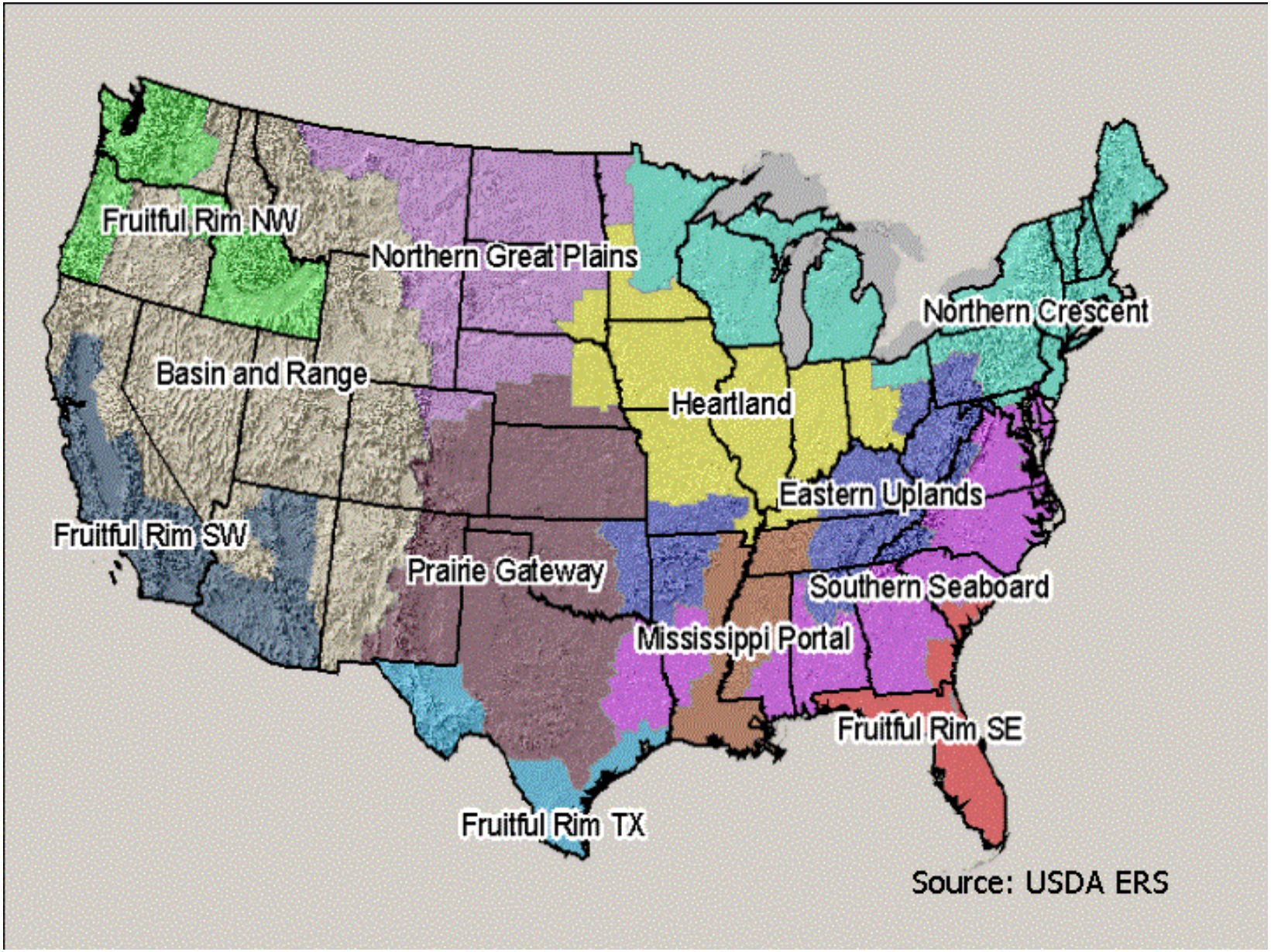
Model estimates were compared to available monitoring data. This comparison indicates that the assessment is by no means worst case or unrealistic. In each region, levels of one or more OP pesticides detected in monitoring studies are greater than that estimated by the cumulative water assessment. In some cases, the model estimates are lower by an order of magnitude or more. However, in that same region, estimates of other OP pesticides are similar to or greater than detections found in monitoring studies. Because the cumulative assessment focuses on the cumulative impact from multiple OP pesticides, it does not necessarily focus on the conditions that lead to the highest concentration of one particular OP.

Although monitoring for OPs in treated drinking water is very limited, the weight of evidence from available studies is that chlorination may transform the OPs to oxons, sulfoxides, and sulfones which are of toxicological concern. A few studies indicate that the oxon transformation product will be stable in chlorinated water for at least 24 to 48 hours after treatment.

3. Regional Approach

As shown on the map on the following page, the 48 contiguous

states were divided into 12 regions. These twelve regions were recently developed by the USDA Economic Research Service to depict geographic specialization in the production of U.S. farm commodities. The regions represent areas with similar types of farms and similar physiographic, soil, and climatic traits. By design, there are many similarities within each region such as crops grown, application timing (use season), and application rates. There are also many similarities in key environmental factors affecting runoff, such as precipitation, irrigation practices, soil types, and average slopes of the land. These regions provide a framework for identifying one or more locations that represents an area of the greatest concern for drinking water exposure within each region. Considered together, this set of locations represents drinking water exposure throughout the U.S. for the cumulative OP assessment.


Fruitful Rim NW
Northern Great Plains
Northern Crescent
Basin and Range
Heartland
Eastern Uplands
Fruitful Rim SW
Prairie Gateway
Southern Seaboard
Mississippi Portal
Fruitful Rim SE
Fruitful Rim TX
Source: USDA ERS

Each region in the assessment is represented by a geographic area within the region that has the highest apparent potential for cumulative exposure to OPs in drinking water. Each of these locations has a relatively high usage of multiple OPs (in relation to other parts of the region) which coincides with surface and/or ground water sources of drinking water which are vulnerable to potential contamination by these OPs. Since the purpose of the assessment is to identify the impact from multiple OPs occurring in water in the same area, the area(s) selected for the assessment do not necessarily represent the highest exposure of a single chemical, but rather the highest multiple OP exposure within the region. Locations within each region were selected using the following steps:

- ❏ Identify the high OP usage areas and high agricultural intensities with each region
- ❏ In each high usage area within the region determine the types and locations of drinking water sources
- ❏ Assess the vulnerability of drinking water sources within the high usage area within the region; OPP adapted vulnerability schemes proposed by Kellog and others at USDA for this purpose
- ❏ Compare locations of surface drinking water intakes overlain on runoff vulnerability maps to determine where potentially vulnerable surface water sources of drinking water coincided with high use areas; for groundwater, compare OP use areas with a leaching vulnerability map

Details of this process of selecting a location to represent each region are provided in each regional assessment. One region, Region 7–the Fruitful Rim, Ca--which covers the central and coastal valleys of California, southern California, and south-central Arizona had two different locations selected. The remaining 11 regions were represented by a single location. Region 8–the Basin and Range–which covers Nevada, Utah, most of Oregon, and part of California, Washington, Idaho, Wyoming, Colorado, New Mexico, Arizona and Montana was represented by the same scenario developed for Region 3, the Northern Great Plains. Region 11–the Fruitful Rim, Texas–which covers much of the eastern coast of Texas, was represented by the same scenario developed for Region 4, the Prairie Gateway.

The Northwest fruitful Rim provides an illustration of the location selection process within a region. Three high OP-use areas occur in the Northwest Fruitful Rim: Yakima County and eastern Washington are the highest OP use area (predominantly on orchards) and have the highest percent crop area. The Snake River Valley in southeast Idaho is the second highest use area (predominantly on potatoes and sugar beets). The Willamette Valley, Oregon, is the third high-use area with a mix of OP uses. There are predominantly ground-water sources of drinking water in Idaho and eastern Washington, with vulnerability to leaching potentially

higher in eastern Washington. A few surface-water intakes occur in the Yakima County area. The Willamette Valley has more surface water intakes and is more vulnerable to runoff. Available monitoring from NAWQA study units in Willamette Valley, Snake River Basin, and Pugett Sound suggest that the Willamette Valley will be more vulnerable to OP contamination with a higher potential for co-occurrence of multiple pesticides.

The surface water assessment for the Northwest Fruitful Rim was therefore based on the Willamette Valley in Oregon. Potential impacts of OP pesticides on ground water resources in eastern Washington and southeast Idaho were qualitatively analyzed, relying largely on ground-water monitoring available through the USGS NAWQA program and state monitoring programs.

The following table shows, for each region, the location selected for the surface water assessment and the crops and pesticides used in the estimates.

Locations, Crops, and Pesticides Included in the Regional Water Assessments

REGION	LOCATION	CROPS	PESTICIDES
1) Heartland	Central Illinois	Corn	Terbufos Chlorethoxyphos Chorpyrifos Phostebupirim
2) Northern Crescent	South Central Pennsylvania	Apple Pear Peach Corn Alfalfa Pumpkin Cantaloupe Corn	Chlorpyrifos Dimethoate Azinphos-methyl Diazinon Terbufos Methyl parathion Phosmet Methidathion Phostebupirim
3) Northern Great Plains	Red River Valley (Minnesota, North Dakota)	Corn Wheat Sugar Beet Potato	Chlorpyrifos Dimethoate Azinphos-methyl Phorate Terbufos
4) Prairie Gateway	Central Hills, Texas	Cotton Corn Alfalfa Wheat Potato Sorghum	Acephate Azinphos-methyl Chlorpyrifos Dicrotophos Malathion Methyl parathion Phorate Phostebupirim Terbufos Tribufos Dimethoate

5) Eastern Uplands	Western North Carolina	Apple Alfalfa Corn		Azinphos-methyl Chlorpyrifos Dimethoate Methyl Parathion Phosmet Terbufos	
6) Southern Seaboard	East Coastal Plain, North Carolina	Cotton Tobacco Corn Peanuts		Acephate Chlorpyrifos Dimethoate Disulfoton Ethoprop Fenamiphos Phorate Terbufos Tribufos	
7a) Fruitful Rim, CA	North Central Valley, California	Corn Alfalfa Almond (Walnut) Pear Peach Apricot Grape Plum Apples (Pear) Broccoli	Nectarine Asparagus Melons Cucumber Pumpkin Squash Tomato Dry Beans Sugar Beet Cantaloupe	Acephate Azinphos-methyl Chlorpyrifos Diazinon Dimethoate Disulfoton Fenamiphos Fonofos Malathion Methamidophos	Methidathion Methyl-parathion Naled ODM Phorate Phosmet
7b)Fruitful Rim, CA	South Central Valley, California	Cotton Citrus Alfalfa Almond (Walnut) Apple (Pear) Orange Melon Peach	Cantaloupe Apricot Nectarine Plum Grape Sugar Beet Lettuce Prune Broccoli	Acephate Azinphos-methyl Bensulide Chlorpyrifos DDVP Diazinon Dimethoate Disulfoton Fenamiphos Methamidophos Methidathion	Malathion Methyl-parathion Naled ODM Phorate Phosmet Profenofos Tribufos
8) Basin and Range	Region 3 location used.				
9) Mississippi Portal	Southern Louisiana	Cotton Corn Soybean		Acephate Chlorpyrifos Dicrotophs Dimethoate Disulfoton Malathion Methamidophos Phostebupirim	Methyl-parathion Phorate ProfenofosteTerbufos Tribufos
10) Fruitful Rim, NW	Willamette Valley, Oregon	Apple Pear Cherry Pea Broccoli Cabbage Nursery (Trees & Shrubs) Squash Onion Snap Beans	Cauliflower Blackberries Blueberries Raspberries Cucumber Sweet Corn Mint Hazelnut Sweet and Tart Cherries Christmas Trees	Acephate Azinphos-methyl Bensulide Chlorpyrifos Diazinon Dimethoate Siculfoton Ethoprop Malathion Methidathion Methyl-parathion Naled ODM Phosmet	

11) Fruitful Rim, TX	Region 4 location used.		
12) Fruitful Rim, FL	South Central, Florida	Tomato Pepper Cucumber Watermelon Sweet Corn Lettuce Citrus Corn Sugarcane	Acephate Chlorpyrifos Diazinon Ethoprop Methamidophos Phorate

4. Assessment Tools

The limitations of the available monitoring data for estimating daily concentrations of OP pesticides in multiple regions, together with recommendations from the SAP, resulted in the evaluation of modeling tools that would allow production of time-linked regional assessments which are as realistic as possible.

Surface Water

After consideration of available predictive tools, EPA used the PRZM/EXAMS-IR model which has been modified by using scenarios and inputs that are specifically designed for performing drinking water assessments. The model simulates runoff into an index drinking water reservoir (IR), which is based on Shipman City Lake in Shipman, Illinois.

The PRZM component of the model is designed to predict the pesticide concentration dissolved in runoff waters and carried on sediments from the field where it was applied to an adjoining edge-of-field surface water body. The model can simulate specific site, pesticide, and management properties including soil properties (organic matter, water holding capacity, bulk density), site characteristics (slope and surface roughness of the land, field geometry), pesticide application parameters (application rate, frequency, spray drift, application depth, application efficiency, application methods), agricultural management practices (tillage practices, irrigation), and pesticide environmental fate and transport properties (soil half-life, soil:water partitioning coefficients, foliar degradation and dissipation, and volatilization). OPP selected a combination of these different properties to represent a location-specific scenario for each particular pesticide-crop regime in each region.

The EXAMS component of the model is used to simulate environmental fate and transport processes of pesticides in surface water (after they have reached the edge-of-field water body). The model simulates abiotic and biotic degradation, sediment:water partitioning, and volatilization. The actual inputs used in the model for each region/location/crop/pesticide combination are provided in the Appendices of the risk assessment (see Section 6 “Data” below).

Changes have been made to model input parameters to produce outputs that focus on co-occurrence of pesticides, the central concern of the cumulative risk assessment. For example, a regional as opposed to a national Percent Crop Area (PCA) is being used in the model to account for the amount of land on which crops are grown in the different localities where the drinking water is being assessed. In addition, all available crop-pesticide use information was utilized. Instead of using the maximum label rates, maximum numbers of applications, and minimal time intervals between applications, EPA used typical rates, frequencies and intervals, which again makes the model outputs more realistic and likely closer to the actual agronomic practices of the growers. The use of the model output has also been changed. Instead of generating one conservative high end exposure number, the Agency used all 13,000-plus daily concentration values to produce distributions that were used in a probabilistic risk assessment for the different regions.

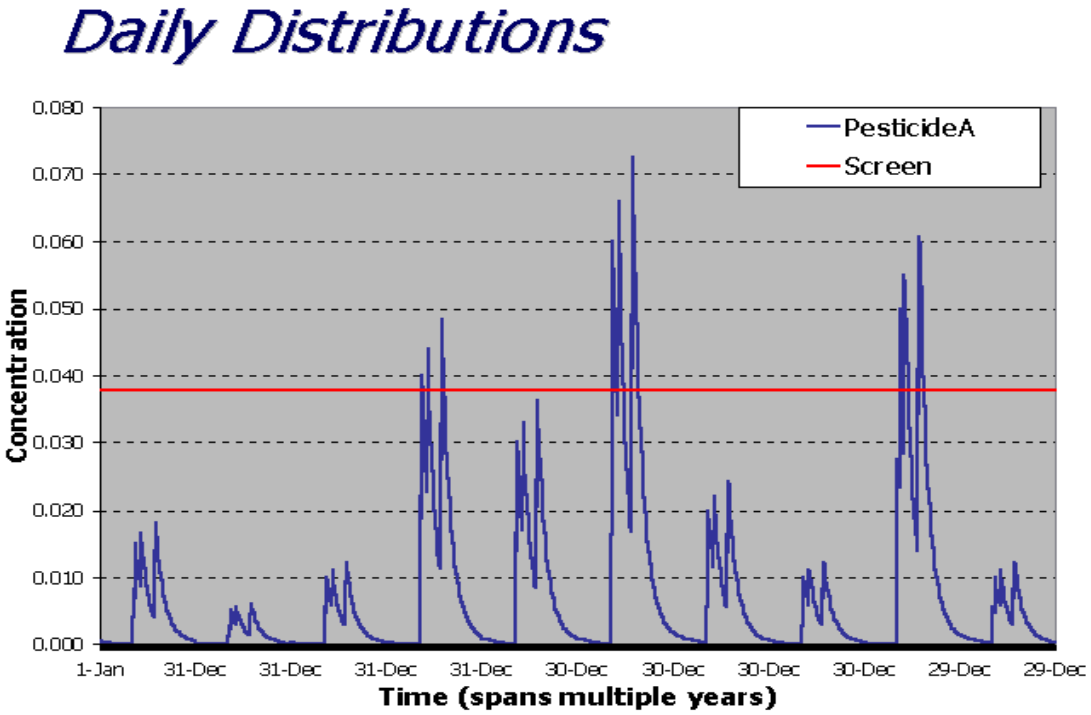
The Agency believes that this approach is the best method currently available to estimate daily residue concentrations in drinking water:

- ❏ it allows for the assessment of multiple chemicals
- ❏ the data generated span a time frame of over 30 years, which captures the variability due to changing weather conditions
- ❏ distributions can be generated in different locations across the entire country thus capturing regional variability
- ❏ since daily distributions are generated, it is possible to maintain the time dependency that is needed for this type of risk assessment
- ❏ because the entire distribution was used in the Calendex™ model the differences in exposures on different days are taken into account.

Each of these aspects of the assessment is discussed in more detail below.

Use of the Full Distribution of PRZM/EXAMS-IR Output

The following graph illustrates the full output of the PRZM/EXAMS-IR model for a given region when 36 years of weather data are available. It also shows the concentration point estimate that would be selected when the screening level assessment is used.



Drinking water residues are estimated from this output for a specific day in this specific region, by selecting one of the 36 estimates available for that day. This is in contrast to the individual chemical assessments where a single point estimate corresponding to approximately the 99.9th percentile concentration is used in the initial assessment. Use of the full distribution in the cumulative assessment allows the probabilistic risk assessment to take account of the day-to-day variations in expected pesticide concentrations across the year in a specific location.

Because the application rates, frequencies, and timing of applications are held constant, the PRZM/EXAMS-IR estimates over multiple years evaluate the impact of the variability in precipitation on the amount of pesticide that reaches surface water. Because weather data spanning 24 to 36 years is available for many locations across the country, PRZM/EXAMS-IR can account for OP runoff from a wide range of weather patterns not otherwise possible with monitoring studies that span relatively few years.

Cumulative Adjustment Factors for Cropped Area and OP Crop Use

The estimation of separate regional risk assessments allows use of a Cumulative Adjustment Factor (CAF) based on the total reported number of acres which receive OP applications in a particular region. In the individual chemical assessments, the adjustment factor most often used was the Percent Cropped Area (PCA) of 87% which represents the highest percentage of agriculture (cropped area) in any large watershed in

the U.S. Using a regional approach, regions with less intense cropping will have lower estimated concentrations based on a regional CAF compared to the national PCA.

The following example illustrates how CAFs are calculated and used in the cumulative assessment. The CAF is calculated as:

$$CAF_{OP/Crop} = (\text{Acres Planted}_{\text{All OP Crops}}/\text{Total Acres}_{\text{In Watershed}}) \times (\text{Acres Treated}_{\text{OP-Crop}}/\text{Acres Planted}_{\text{All OP Crops}})$$

The CAF for each OP chemical/crop combination is used to adjust the initial output of PRZM/EXAMS-IR for that chemical/crop combination. This adjustment allows the PRZM/EXAMS-IR output to reflect only the contribution of the number of acres estimated to be treated with that pesticide.

EXAMPLE:

- ❏ The total area for a location (watershed) is 800,000 acres.
- ❏ Agricultural crops treated with OPs account for 320,000 acres.
- ❏ Two crops, corn and alfalfa, are treated with OP Pesticides.
- ❏ 60,000 acres of corn are treated with Pesticide A and 40, 000 with Pesticide B.
- ❏ 16, 000 acres of alfalfa are treated with pesticide A and 10,000 with Pesticide B.

The four CAFs for this region are calculated below.

$CAF_{\text{Corn-OP(A)}} = (320{,}000/800{,}000) \times (60{,}000/320{,}000) = 0.075$

$CAF_{\text{Corn-OP(B)}} = (320{,}000/800{,}000) \times (40{,}000/320{,}000) = 0.05$

$CAF_{\text{Alfalfa-OP(A)}} = (320{,}000/800{,}000) \times (16{,}000/320{,}000) = 0.02$

$CAF_{\text{Alfalfa-OP(B)}} = (320{,}000/800{,}000) \times (10{,}000/320{,}000) = 0.0125$

Each daily residue estimate from PRZM/EXAMS-IR for pesticide A application to corn in the region would be multiplied by 0.075. Similarly each daily residue estimate from pesticide B application to corn would be multiplied by 0.05. And the corresponding adjustments would be made for the alfalfa estimates. In this manner, since the use statistics come from actual reported data in the region, competing and compatible uses of the various OPs applied in that region are taken into account.

It should be noted that the percent cropped area part of the regional CAFs ($\text{Acres Planted}_{\text{All OP Crops}}/\text{Total Acres}_{\text{In Watershed}}$) is based on data from

a large area. The size of the hydrologic units used (average > 1000 square miles) generally span multiple counties and may contain several watersheds that supply drinking water intakes. These regional PCAs represent the aggregation of crop areas from county-level NASS data and assume that the cropping area is uniformly distributed. (For the source of these data see Section 6 "Data" below.) However, in reality, cropping intensity is variable and smaller watersheds, including those capable of supporting drinking water supplies, may have a much higher percentage of crop land than the rest of the large basin.

An example is Zollner Creek in the Willamette River Valley. This watershed had the highest concentrations and frequencies of detection of OPs among all of the NAWQA monitoring sites in the Willamette Valley. This stream drained a watershed that was 99% agriculture, much greater than the regional PCA of 60% used in this assessment. The regional assessment areas generally coincided with the area with the highest PCA. However, in some regions, such as the Northwest Fruitful Rim and the Eastern Uplands, the regional assessment focused in a lower-intensity agricultural area which was other wise more vulnerable because of OP usage and/or the nature of the drinking water source.

The percent acres treated part of the CAF (Acres Treated $_{\text{OP-Crop}}$/Acres Planted $_{\text{All OP Crops}}$) is derived from state-level data (or NASS reporting districts) and assumes uniform use practices across the state. In reality an uneven distribution of percent acres treated would be expected in response to differing pest pressures. Thus, this assumption will underestimate areas where pest pressures may dictate a higher percentage of acres treated in a given year; similarly, it will overestimate areas where low pest pressures will require fewer acre treatments.

Pesticide Application Information Used in the Assessment

Typical usage was estimated by dividing the pounds reported as applied in a given area by the acres treated in that area. Estimates for these statistics were generally taken from the most recent USDA pesticide use surveys to reflect current practices. This derivation of the "typical" number assumes that all applications were made at this typical or average rate and that frequencies of applications were constant year to year. The assessment considered only yearly variations in weather, and not variations in application rates. This contrasts with the individual chemical assessments where the range of rates considered always includes the maximum label rates.

With the exception of Region 7 (California), application dates were determined based on pesticide application windows established for each of the OP pesticide/crop combinations in each region. This window represents an approximate beginning and ending date for the use of the pesticide on a particular crop. In many cases USDA handbooks also

provide “most active” periods during the planting and/or harvesting windows. The mid-point of the most-active period was selected as the application date for a pesticide applied at the “planting” stage of crop production and, for example, for the defoliant tribufos used as a harvest aid for corn. When “most active” periods were not available, the single application date for a pesticide is the beginning of the crop stage window. Multiple applications, such as OP cover sprays for tree fruits, were placed at the beginning and equidistant within the application window. A most likely, or predominant, application method was designated for each pesticide–either air or ground application.

Sensitivity analyses may be conducted on each of these use parameters: the percent of crop treated, the typical application rate, and number and corresponding dates of applications. A preliminary evaluation of selecting the midpoint date of the most active application period as the application date of the pesticide on a particular crop has been done for the Heartland region. This evaluation found that variations based on date selection may result in differences of approximately two to three times in cumulative concentration estimates. In the case of the Heartland, the highest concentrations were estimated when applications were assumed to be made at the end of the most active application period rather than at the midpoint, which was used in the probabilistic exposure assessment.

Section 6 “Data” describes the source of the data used to make these decisions and where the complete information can be found in the risk assessment.

Ground Water

Ground water estimated concentrations were not included quantitatively in the risk estimates. However, in areas of the United States that receive their drinking water from ground water, monitoring data from vulnerable ground water sources were examined. In each region, it was determined that the surface water estimates would be protective of groundwater, i.e., the surface water estimates would be expected to be higher than any groundwater estimates. In those cases the surface water estimates were considered to cover groundwater.

The concentrations of OPs in ground water were not significant in most regions due to the fate parameters (chemical properties) of the organophosphate class of compounds. This class is not very persistent or mobile in the environment. Persistence and mobility are necessary for pesticides to move through soils and contaminate ground water. The available data generally do not provide evidence that parent OP pesticides will co-occur in groundwater**.** Few data are available to determine if OP transformation products might co-occur in groundwater.

An example of an exception to these general conclusions is

Fenamiphos. Fenamiphos and its degradates, fenamiphos sulfoxide and fenamiphos sulfone, have been detected at high levels in ground-water studies conducted in Florida, and to a lesser extent in California. Such detections led to the phase-out of fenamiphos use on citrus in the Central Ridge area of Florida. The individual chemical risk mitigation for fenamiphos has not been completed. As noted above, each regional assessment discusses the available information on OPs in groundwater.

5. Results

The preliminary OP cumulative risk assessment indicates that drinking water is not a major contributor to the total cumulative risk. For all regions the results of the assessment indicate that the contribution to the OP cumulative risk from drinking water is generally at least one order of magnitude lower than the contribution from OPs in food at percentiles of exposure above the 95th, for all population subgroups evaluated. As the percentile of exposure increases, the difference between the food and water contributions increase.

6. Data

All of the data used in the preliminary OP cumulative risk assessment are available in the public docket and on the internet at www.epa.gov/pesticides/cumulative. The following summarizes the major data sources used, the tables related to the water assessment that are included in the preliminary risk assessment, and where they may be found.

<u>Water Monitoring Data</u>

- ❏ Section III.E.1 (Appendices), beginning on page III.E.1 Page 1, contains the USGS NAWQA program data on the occurrence of OPs in ambient water
- ❏ Section III.E.2 (Appendices), beginning on page III.E.2 Page 1, contains data from state monitoring programs
- ❏ Section III.E.3 (Appendices), beginning on page III.E.3 Page 1, contains data from the USGS-EPA Pilot reservoir monitoring program

<u>Inputs to PRZM/EXAMS-IR</u>

- ❏ Section III.E.5 (Appendices), beginning on page III.E.5 Page 1, contains, for each OP in the water assessment, the chemical specific inputs that were used and their source
- ❏ Section III.E.6 (Appendices), beginning on page III.E.6 Page 1, contains, for each OP/Crop combination in each region the scenario specific inputs: application method, incorporation depth,

application rate, application efficiency, spray drift, application dates, and application frequencies and intervals.

- ❏ Section III.E.7 (Appendices), beginning on Page III.E.7 Page 1, contains background information on the remaining inputs to PRZM which are used for each crop scenario

Water Treatment Data

- ❏ Section II.E.4 (Appendices), beginning on page III.E.4 Page 1, contains the available information of the effects of drinking water treatment on OPs

Other Information

- ❏ Each regional assessment contains other use information including the sources of that information as well as information on locations of surface water intakes of drinking water in the region.

VII. Residential (& Other Non-occupational) Risk Assessment

The residential component of the preliminary OP cumulative risk assessment is the most sophisticated analysis of its type that OPP has ever conducted. It is the first application of distributional analysis to residential exposure assessments. It also factors in the seasonal and regional aspects of pesticide use.

Potential for exposure to pesticides from residential and other non-occupational uses differs in different parts of the country and at different times of the year. Contributing factors to these differences include amount and time of pesticide application. OPP has used the calendar based model Calendex™ to address the temporal aspects of the residential use of pesticides in 12 distinct geographic regions throughout the U.S. These regions are the same regions used in the water assessment. Although based on major crop growing areas, these regions also present an opportunity to consider the unique climate patterns and pest patterns that influence residential pesticide use and expected exposure. Calendex™ allows delineation of the critical timing aspects of seasonal use of OPs that result in exposure to pesticides and enables the identification of potential co-occurrences from multiple sources.

Exposures to pesticides can occur through dermal, inhalation, and non-dietary ingestion routes as a result of homeowner (i.e., “do-it-yourself”) and commercial applications in residential and public areas. Exposure can result from mixing, loading, and applying the pesticide, and/or reentering a treated site. Residential exposure to organophosphates in outdoor settings may result from applications to lawns, ornamentals, and "backyard" orchards and vegetable gardens. Indoor organophosphate exposures may result from crack and crevice treatments, use of pest strips, and from pet products (e.g., impregnated collars, dips, powders). EPA also considered post-application exposures in indoor/outdoor public areas such as parks, recreational areas, golf courses, schools or office buildings. Furthermore, the risk assessment includes residential bystander exposures from public health uses of organophosphates (e.g., mosquito and blackfly abatement). Certain residential uses that are assumed to result in negligible exposure (e.g., ant/roach bait stations in child resistant packaging or post-application exposure to treated fire ant mounds) were not included in the assessment. That was the case in the individual chemical assessments as well. The following chart delineates the current residential use picture for the organophosphates:

Residential Uses for the Organophosphates

Chemical	*Indoor Residential Uses*	*Outdoor Residential Uses*	*Golf Course and Public Area Uses*	*Pet Uses*	*Public Health Uses*
acephate	N/A	Ornamentals, residential turf, sod farms	Golf course turf	N/A	N/A
bensulide	N/A	Residential turf	Golf course turf	N/A	N/A
chlorpyrifos	N/A	N/A	Golf course and sod farm turf	N/A	Mosquito adulticide
dichlorvos (DDVP)	Resin pest strips, crack and crevice (professional applicators only)	Residential turf and ornamental plants (professional applicators only)	N/A	Flea collars, sponge, spray and dip (applied by veterinarians only)	N/A
disulfoton	Potted plant treatments	Flower gardens, roses, ornamentals, shrubs, small trees.	N/A	N/A	N/A
fenamiphos	N/A	N/A	Golf course turf	N/A	N/A
fenthion	N/A	N/A	N/A	N/A	Mosquito adulticide
malathion	N/A	Residential turf, ornamentals, garden, fruit trees.	Golf course turf, pick-your-own strawberries/orchards, turf in public areas	N/A	Mosquito adulticide
naled	N/A	N/A	N/A	N/A	Mosquito adulticide, black fly control
tetrachlorvinphos	N/A	N/A	N/A	Dips, powders, sprays, and flea collars.	N/A
trichlorfon	N/A	Residential turf and ornamentals	Golf course turf, turf in public areas	N/A	N/A

Seventeen OPs had registered uses when the Food Quality Protection Act (FQPA) was passed in 1996. Seven of these have been excluded from the cumulative residential assessment since all residential uses with any significant exposure or risk have been eliminated. These pesticides are: chlorpyrifos, diazinon, dimethoate, ethoprop, fenitrothion, phosmet, and protetamphos. Six of the remaining 10 OPs have completed individual risk mitigation and the cumulative assessment reflects the most up-to-date residential use picture for these chemicals: acephate, bensulide, disulfoton, fenthion, naled, and

trichlorfon. Four OPs are still in the risk mitigation process, and any future risk mitigation actions will be incorporated into the revised cumulative assessment: dichlorvos (DDVP), fenamiphos, malathion, and tetrachlorvinphos.

Two OPs, tetrachlorvinphos and DDVP are currently registered for use on pets. EPA did not have sufficient data on exposure for these uses to include them in a calendar-based probabilistic assessment. The screening level assessments for these uses indicate risks of concern. As noted above, the individual chemical risk mitigation for these chemicals is in progress.

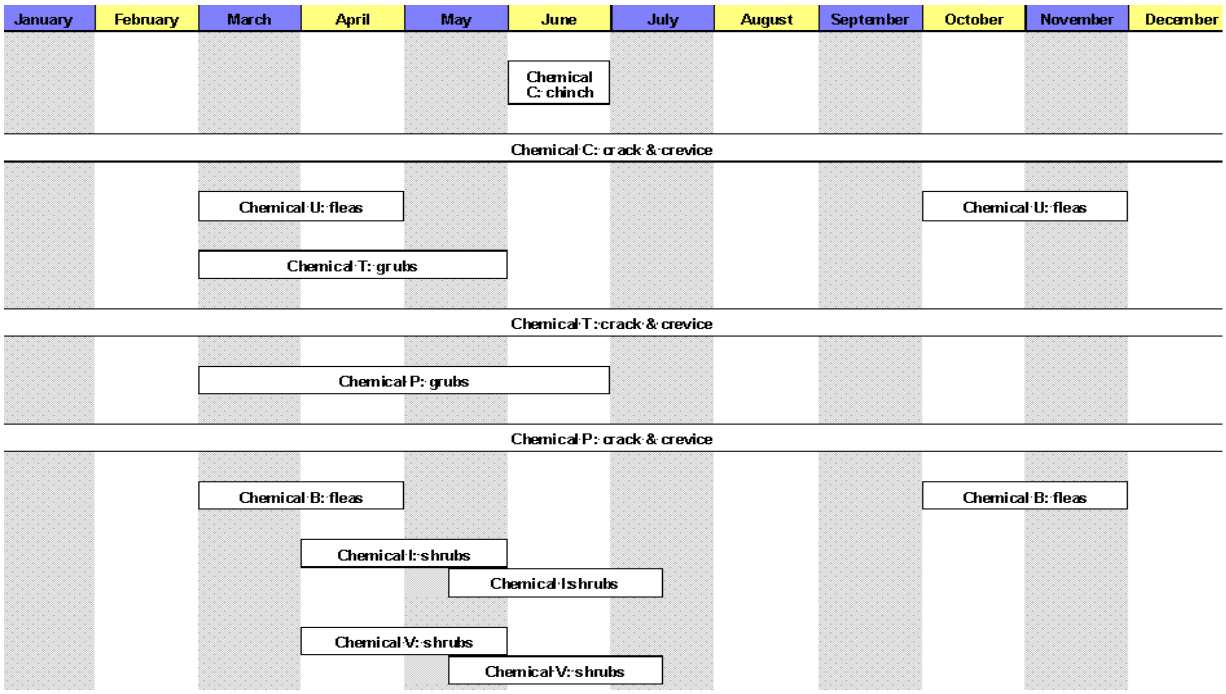
Other OP uses were not included because they resulted in negligible exposures or because their single chemical assessments showed very low risk. These low exposure uses include ant and roach baits, paint additives, post-application residential exposure from sod farm applications, and applications to fire ant mounds. Chlorpyrifos use for mosquitoes was not included because very low exposures and risk were estimated in the single chemical, screening level assessment.

A. Spatial and Temporal Aspects of the Residential Assessment

Information relating to both the temporal and spatial aspects of exposure is reflected in the residential portion of the cumulative risk assessment. The assessment matches exposure scenarios with uses representative of a particular region. The residential risk assessment scenarios are based on application timing, duration of use, and frequency of application for each chemical in each region. For example, if you live in Buffalo, New York, and it's January, you will not be exposed to pesticides by mowing your lawn.

Chemical use patterns greatly affect potential exposure scenarios. By evaluating a pesticide’s geographic and temporal pattern of use, a profile for each chemical can be developed to establish the potential routes, durations, and frequencies 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. These possible exposures will then be associated to individuals in the assessment, again preserving linkages to demographic characteristics of the individuals as well as appropriate linkages in uses. In some cases, products may serve essentially the same purpose, such that the use of one will almost certainly preclude the use of the other, that is, they are competitors.

The chart on the following page provides a visual example of the results of the likelihood and frequency assumptions for the assessment within one example region. It displays the various residential applications and their timing (including repeated applications) over the course of a year, for one region/site. Each regional assessment contains a chart like this for that region’s uses.



These likelihood and frequency assumptions for residential scenarios were used to superimpose a pattern of relevant residential exposures that could reasonably be expected to occur throughout the year for a given individual/population member in the region. Any individual's exposure is based on probabilistic methods that account for the percentage of the population likely to be using the product in the first place, as well as preserve relevant time, space, and demographic characteristics associated with the individual and his probability of exposure. A detailed discussion of these methods is contained in Appendix II of this document.

Five residential scenarios were used in the assessment. They represent the critical OP uses that have the potential for significant exposure or risk when considered in a cumulative assessment. These are:

- ❏ Lawn care
- ❏ Home vegetable gardens/ornamentals/orchards
- ❏ Golf courses
- ❏ Wide area public health sprays
- ❏ Indoor (crack and crevice sprays and impregnated pest strips)

The following table shows, for each region, the residential scenarios that were assessed and the pesticides used in the estimates.

Residential Scenarios and Pesticides Included in the Regional Residential Assessments

REGION	SCENARIO	PESTICIDES
1) Heartland	Lawn	DDVP, Malathion, Trichlorfon
	Golf Course	Bensulide, Trichlorfon
	Gardens	Malathion, Acephate, Disulfoton
	Indoor	DDVP
2) Northern Crescent	Lawn	Malathion, Trichlorfon
	Golf Course	Bensulide, Trichlorfon
	Gardens	Acephate, Disulfoton, Malathion
	Indoor	DDVP
	Public Health	Malathion, Naled
3) Northern Great Plains	Lawn	DDVP, Trichlorfon
	Golf Course	Bensulide, Malathion
	Gardens	Acephate, Disulfoton, Malathion
	Indoor	DDVP
4) Prairie Gateway	Lawn	Bensulide, DDVP, Malathion, Trichlorfon
	Golf Course	Acephate, Bensulide, Fenamiphos, Malathion, Trichlorfon
	Gardens	Acephate, Disulfoton, Malathion
	Indoor	DDVP
	Public Health	Malathion
5) Eastern Uplands	Lawn	DDVP, Malathion, Trichlorfon
	Golf Course	Acephate, Bensulide, Fenamiphos, Malathion, Trichlorfon
	Gardens	Acephate, Disulfoton, Malathion
	Indoor	DDVP
6) Southern Seaboard	Lawn	Malathion, Trichlorfon
	Golf Course	Acephate, Bensulide, Fenamiphos, Trichlorfon
	Gardens	Acephate, Disulfoton, Malathion
	Indoor	DDVP
	Public Health	Malathion
7a) Fruitful Rim, CA	Lawn	Malathion, Trichlorfon
	Golf Course	Bensulide, Fenamiphos, Trichlorfon
	Gardens	Acephate, Disulfoton, Malathion
	Indoor	DDVP

7b)Fruitful Rim, CA	Lawn	Malathion, Trichlorfon
	Golf Course	Bensulide, fenamiphos, Trichlorfon
	Gardens	Acephate, Disulfoton, Malathion
	Indoor	DDVP
8) Basin and Range	Lawn	Malathion, trichlorfon
	Golf Course	Bensulide, Trichlorfon
	Gardens	Acephate, Disulfoton, Malathion
	Indoor	DDVP
9) Mississippi Portal	Lawn	Malathion, Trichlorfon
	Golf Course	Acephate, Trichlorfon, Malathion
	Gardens	Acephate, Disulfoton, Malathion
	Indoor	DDVP
	Public Health	Malathion, Fenthion
10) Fruitful Rim, NW	Lawn	Malathion, Trichlorfon
	Gardens	Acephate, Disulfoton, Malathion
	Indoor	DDVP
11) Fruitful Rim, TX	Lawn	Malathion, Trichlorfon
	Golf Course	Acephate, Bensulide, Fenamiphos, Malathion, Trichlorfon
	Gardens	Acephate, Disulfoton, Malathion
	Indoor	DDVP
	Public Health	Malathion
12) Fruitful Rim, FL	Lawn	Malathion, Trichlorfon
	Golf Course	Acephate, Bensulide, Fenamiphos
	Gardens	Acephate, Disulfoton, Malathion
	Indoor	DDVP
	Public Health	Malathion, Naled

B. Hazard

The estimated exposures to each pesticide will be converted to index chemical equivalents using route-specific relative potency factors for oral, dermal, and inhalation exposures, as described above in Section IV. “Endpoint Selection.” Exposures will be compared to route-specific BMD_{10} values of the index chemical to develop route specific MOEs. Oral, dermal, and inhalation MOEs were combined by taking the inverse of the MOE for each route, adding these together, and then taking the inverse of that sum to get the total MOE for the oral, dermal, and inhalation routes of exposure.

C. Types of Data Used in the Assessment

Three types of data are used in the residential assessment: pesticide use; pesticide residue dissipation; and exposure contact and exposure factors. Pesticide use data are utilized to determine the percent of households using a pesticide, whether the applicator is a professional or not, the timing of the pesticide treatments, and frequency and duration of exposure. Use data are also important in identifying geographic regions where the pesticide may be applied. This type of information is needed together with chemical residue fate, residue contact data and exposure factors to predict the potential for co-occurrence of exposure events in cumulative assessments.

In this assessment, use data are specific to the region under evaluation. Pesticide residue dissipation data address the fate of the pesticides once applied and much of this data is region specific also. Exposure contact data describes how often humans are expected to come into contact with the chemical or its residues. Human exposure factors, such as breathing rates, body weight and surface areas used in this assessment come from the Agency Exposure Factors Handbook. Other exposure factors such as the size of the area being assessed (e.g., the lawn) and time spent in the area are also important in assessing risk. The data used in the assessment are discussed below.

1. Use Data

The majority of use-related information in the cumulative risk assessment was obtained from the sources described below:

- ❏ National Garden Survey (1996 -1997) tracks the percent of households employing lawn care applicators and was used to estimate the number of households that may use a given pesticide; it also contains information on variables such as vegetable garden size
- ❏ National Home and Garden Pesticide Use Survey (1989-1990) delineates percent of households using pesticides based on a large national survey. These values consider users and non-users as well as homes having lawns and those that do not.
- ❏ National Home and Garden Pesticide Use Survey (1991) provided information on indoor use of DDVP
- ❏ Survey data were also used to estimate frequency of applications, the type of application equipment used, and the type of clothing worn while making applications
- ❏ Doanes GolfTrak (1998-1999) was used to identify the percent of golf courses treated with OP pesticides; a 1992 survey conducted by the Center for Golf Course Management was used to establish the percent of individuals playing golf
- ❏ The Occupational and Residential Exposure Task Force (ORETF) provided estimates of time spent in the garden performing post-application activities as well as information on the frequency of applications

- ❑ Regional Cooperative Extension Services recommendations were used to determine the timing of pesticide application windows, especially for turf uses, but also for timing aspects of various gardening activities.
- ❑ For Public Health Uses estimates of use and timing of use are based on information provided by representatives of Florida Mosquito Abatement Districts, Florida A&M; and Health Canada (black fly). Where specific timing information was not available for regions having public health spray uses, a spray schedule of once every two weeks was assumed for the summer season.
- ❑ Non-Occupational Pesticide Exposure Survey (NOPES)–provided information on pest strips

2. Exposure Data

The major generic exposure factors used for each exposure scenario included in the assessment are shown below. In addition to this information, each regional assessment contains a chart showing, for each specific use scenario considered in that region, the specific input data that were used for: application method, amount applied, number and frequency of applications, the period of time over which it may be used, % applied by a professional, % applied by the homeowner, % of households in the region using the chemical, and the active exposure period (how long residues are available for contact after application). In addition, each regional assessment contains information on the region specific residue dissipation data sources that were used.

The reasoning behind the selection of the following exposure factors and the specific data source for each of them is contained in the risk assessment in section I.D. pages 1-19. It should be noted that all of the data were obtained from actual measured data of some kind–e.g., registrant submitted chemical specific data, ORETF data, literature studies, etc.–and do not rely on default assumptions.

Two types of input distributions were used in the residential assessment. A uniform distribution is one in which each value within the range specified has an equal probability of being selected. Therefore, it does not reflect what the actual shape of the distribution may be. A log-normal distribution approximates the expected shape of the data distribution, with low values having a higher probability of selection because there are more low values in a log-normal distribution.

a. Lawn Scenario (DDVP, Bensulide, Malathion, Trichlorfon)

Application:
Unit Exposure for Granular Applications:
Dermal: 0.02-7.6 mg/lb ai handled (uniform distribution)
Inhalation: 0.00019-0.0096 mg/lb ai handled (uniform distribution)
Unit Exposure for Hose-end Sprayer Applications:

Dermal: 0.017-49 mg/lb ai handled (uniform distribution)
Inhalation: 0.007-0.089 mg/lb ai handled (uniform distribution)

Each of these distributions reflects a range of clothing from short-pants and short sleeved shirts to long pants and long sleeved shirts. ORETF data showed that 55% of those who treat their lawns wear short sleeved shirts and 38% wear short pants when applying liquid formulations while70% wore short sleeved shirts and 32% wore short pants while applying granulars. The distributions for the hose-end sprayers also reflect the range derived from study data that included a ready to use hose-end sprayer and a sprayer that required pouring pesticide into the hose-end device.

Lawn Size:
500-15,000 ft^2 (Uniform Distribution)

Post-Application
Dermal:
Adult transfer coefficient: 1,930-13,200 cm^2/hr (uniform distribution)
Child transfer coefficient: 700-16,000 cm^2/hr (uniform distribution)

Oral (for hand-to-mouth activity if children):
# of mouthing events: 0-26 (uniform distribution)
Surface area of hand associated with each mouthing event: 0-20 cm^2/event (uniform distribution)
Adjustment for greater residue transfer on wet hands: 1.5-3X (uniform distribution)
Removal efficiency of residues on hands by saliva: 10-50% (uniform distribution)

The last two adjustments are applied to the residue data to account for the expected greater residues that are picked up on wet hands and the expected greater efficiency of removal of those residues in the mouth by saliva.

Time Spent on Lawn:
Adult: 0-2 hours (cumulative distribution)
Child: 0-3.5 hours (cumulative distribution)

b. Vegetable Gardens/Orchards/Ornamentals (acephate, disultofon, malathion)

Application:
Unit Exposure for Hand Pump Sprayer:
Dermal: 7.99-354.4 mg/lb ai handled (uniform distribution)
Inhalation: 0.002-0.0142 mg/lb ai handled (uniform distribution)
Unit Exposure for Hand Garden Duster:
Dermal: 7.99-1375.4 mg/lb ai handled (uniform distribution)
Inhalation: 0.0044-8.29 mg/lb ai handled (uniform distribution)
Unit Exposure for Ornamental Granular Incorporated Treatment:

Dermal: 0.0034-0.356 mg/lb ai handled (uniform distribution)
Inhalation: 0.00001 mg/lb ai handled (point value)

All of the above distributions reflect a range of clothing from short-pants and short sleeved shirts to long pants and long sleeved shirts, with the exception of the granular treatment which is a point estimate based on the Limit of Quantitation from the study.

Ornamental Bed Size:
500-2,000 ft^2 (Uniform Distribution)
Vegetable Garden/Orchard Size:
135-8,000 ft^2 (Log-normal Distribution)

Post-Application
Dermal:
Transfer coefficient: 100-5,000 cm^2/hr (uniform distribution)

Time Spent in Garden:
0.083-1 hour (Uniform Distribution)

c. Golf Course (acephate, bensulide, fenamiphos, malathion, trichlorfon)

Post-Application
Dermal:
Transfer coefficient: 200-760 cm^2/hr (uniform distribution)

Time Spent Golfing:
4 hours (point estimate for all chemicals except bensulide)
2-4 hours (uniform distribution–used for bensulide because its use is restricted to tees and greens)

d. Public Health (malathion, naled, fenthion)

Post-Application
% of Application Deposited on Lawns:
3.8 - 30% (uniform distribution)
This distribution combines ground and aerial applications for which data show a deposition range for ground from 3.8 to approximately 5% and for air values that range from approximately 15-30%.

Estimates of lawn residues were based on the chemical specific transfer efficiency of malathion (up to 2.2%) and naled (up to 1.5%). The Malathion estimate was used for fenthion since the two chemicals have very similar formulations, vapor pressures and molecular weights.

Exposures to residues on lawns were estimated using the same dermal transfer coefficients, hand to mouth variables, and duration of time spent on the lawn as shown above for lawn uses.

e. Indoor
The only indoor use chemical is DDVP. The only relevant route of exposure for DDVP is inhalation due to its volatility. Exposure while handling the impregnated pest strips is considered minimal and was not included.

Application:
Unit Exposure for Crack and Crevice Applications:
Inhalation: 0.72-2.499 mg/lb ai handled (uniform distribution)

Post-Application
Inhalation:
Post-application airborne concentration from crack and crevice treatments: 0.0754-0.548 mg/m^3 (uniform distribution)
Post-application airborne concentration from pest strips: 0.11-0.005 mg/m^3 (samples taken at 1, 7, 14, 28, 56,and 91 day intervals-uniform distribution for each sample period)
Breathing Rate Multiplier:
1 for at rest; 2 for moderate activity (uniform distribution)

Breathing rates were taken from the exposure factors handbook and the multipliers reflect the fact that people were assumed to be at rest half of the time and engaged in moderate activity the other half of the time.

Time Spent in Home:
0-24 hours (Cumulative Distribution)

E. Individual Versus Cumulative Assessment

In general, the individual chemical assessments are designed to reflect reasonable high-end risks to an individual/population member represented in each exposure scenario (e.g., adults applying pesticides to a lawn with push-type spreader, children playing on treated lawns). The cumulative risk analysis focuses not on risk to the individual, but population risk (see discussion in section V. “Cumulative Exposure Model and Interpretation of Model Outputs”). To estimate these risks, It combines many data sets into a single assessment. As a result it is important to reduce the likelihood of compounding conservative assumptions and over-estimation bias. Therefore, the assessment is not based on high-end risk estimates but on estimates of potential exposure that appropriately bound the risks while realistically capturing possible multiple exposures.

F. Results

The results of the residential portion of the cumulative risk assessment are relatively straight-forward to interpret. Inhalation exposures to DDVP from No-Pest strips and crack and crevice treatments are the major contributors to indoor residential exposures. This determination is simple to make because these are

the only remaining indoor uses for OPs. Some of the regional assessments from the southern regions also indicate hand-to-mouth activities by children in conjunction with lawn scenarios are a contributor to exposure. In examining these potential risks after the release of the preliminary assessment the Agency found an error in the computer input. Correction of this error resulted in estimated risks that do not appear to be significant for hand-to-mouth activities by children in conjunction with lawn scenarios.

VIII. Cumulative Risk and Risk Characterization

Risk characterization is the interpretation phase of the assessment process. Appropriate interpretation of results is especially important for an assessment as complex as the OP cumulative assessment. EPA has combined many types of data, derived from a variety of sources, to produce detailed estimates of risk from multiple OPs in food, drinking water, or use in residential areas. The outputs of the assessment should be evaluated in a variety of ways. The risk characterization identifies potential biases in input parameters, the direction of the bias, and the uncertainly surrounding the inputs and the exposure model with regard to their potential impact on the results of the assessment. An entire section of the preliminary OP cumulative risk assessment is devoted to risk characterization. It can be found in Section I part G.

In summary, the results of the OP cumulative assessment indicate that the contribution to OP cumulative risk from drinking water is generally at least 10 times lower (one order of magnitude) than the contribution from OPs in food at percentiles of exposure above the 95th for all population subgroups evaluated. As the percentile of exposure increases, the difference between the food and water contributions increases. This pattern is consistent for all regions. Those regions with the lowest total MOEs (highest risk estimates) at the upper percentiles in the exposure distribution generally reflect the contribution of the inhalation route of exposure from residential indoor uses of DDVP. The exposures occur from the No Pest Strips and crack and crevice treatments. This observation is consistent for all regions evaluated. The same pattern of risk from each pathway is observed for all regions. At these higher percentiles of population exposure, residential uses are a major source of risk–specifically, inhalation exposure by all age groups. These patterns occur in all sub-groups, although estimated risks appear to be higher for children than for adults regardless of the population percentile considered. EPA believes that the results of the assessment provide a highly refined, health protective estimate of the cumulative risk to the U.S. public from the use of OPs.

IX. Occupational and Ecological Risk Assessment

Cumulative occupational and ecological risk assessments are not required by FQPA and have not been conducted. Occupational and ecological risks were addressed in the individual risk assessments for the OPs.

X. Summary of Future Work

The preliminary OP cumulative risk assessment provides a detailed picture of possible exposure to oprganophosphorus pesticides. Details in the assessment provide the basis to evaluate the effects of the methods and assumptions on the results of the assessment. This evaluation process is particularly important for a cumulative OP assessment because it reflects additional data compared to previous, single-chemical assessments. It uses distributions of data in place of point estimates to the extent possible, and introduces new data sources, particularly in the residential portion of the assessment. EPA has used the OP cumulative risk assessment as a vehicle to introduce a number of advances in its risk assessment methodology. These changes are most evident in the hazard, drinking water and residential components, as well as in the methods used to combine pathways to develop a total risk profile for all of the OPs together. Therefore, EPA plans to conduct additional analyses of the data before reaching final conclusions. At this point in the planning process, EPA in cooperation with USDA has developed a set of follow-up analyses that will be conducted to assist in interpreting the results of the preliminary analysis, and to prepare an OP cumulative risk assessment for making regulatory decisions. Some examples of planned analyses are:

- ❏ Conduct a series of sensitivity analyses for input parameters to determine those most likely to impact the outcome of the assessment
- ❏ Conduct detailed analysis of food exposure to identify major contributors to risk, identifying specific food-pesticide combinations
- ❏ Evaluate the tails of the food distribution to determine whether isolated data points reflecting unusual consumption patterns or residue levels are inappropriately affecting the results of the assessment
- ❏ Evaluate the effect of assumptions about residue concentrations in baby foods in the assessment.
- ❏ Verify residential use patterns for OPs
- ❏ Define the data that are needed to better characterize the toxicity of OP degradates and treatment by-products in water systems. Evaluate and summarize existing data

List of Abbreviations

a.i.	Active Ingredient
AGDCI	Agricultural Data Call-In
BMD	Benchmark Dose
BMR	Benchmark Response
CAF	Cumulative Adjustment Factor
CAG	Cumulative Assessment Group (of chemicals)
CEL	Comparative Effect Level
CL	Confidence Limit
CMG	Common Mechanism Group (of chemicals)
CNS	Central Nervous System
CWS	Community Water Systems
CSF	Confidential Statement of Formula
CFR	Code of Federal Regulations
CSFII	Continuing Surveys for Food Intake by Individuals (from USDA)
DCI	Data Call-In
DEEM	Dietary Exposure Evaluation Model
DFR	Dislodgeable Foliar Residue
DWLOC	Drinking Water Level of Comparison.
EC	Emulsifiable Concentrate Formulation
ED_{10}	Effective Dose: central estimate on a dose associated with a 10% response adjusted for background.
EEC	Estimated Environmental Concentration–The estimated pesticide concentration in an environment, such as a terrestrial ecosystem.
EP	End-Use Product
EPA	U.S. Environmental Protection Agency
FDA	Food and Drug Administration
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FFDCA	Federal Food, Drug, and Cosmetic Act
FQPA	Food Quality Protection Act
G	Granular Formulation
GIS	Geographical Information System
GLC	Gas Liquid Chromatography
GLN	Guideline Number
GM	Geometric Mean
GOF	Model Goodness-of-Fit
GRAS	Generally Recognized as Safe as Designated by FDA
HDT	Highest Dose Tested
HED	Health Effects Division
ILSI	International Life Sciences Institute
idose	Scaled internal dose
IR	Index Reservoir

LCO	Lawn Care Operator
LED_{10}	Lower Limit on an Effective Dose (95% lower confidence limit on a dose associated with 10% response adjusted for background)
LEL	Lowest Effect Level
LOC	Level of Concern
LOD	Limit of Detection
LOAEL	Lowest Observed Adverse Effect Level
MCLG	Maximum Contaminant Level Goal–used by the Agency to regulate contaminants in drinking water under the Safe Drinking Water Act
mg/kg/day	Milligram Per Kilogram Per Day
mg/L	Milligrams Per Liter
MOE	Margin of Exposure
MP	Manufacturing-Use Product
MPI	Maximum Permissible Intake
MRID	Master Record Identification (number)–EPA's system of recording and tracking studies submitted.
N/A	Not Applicable
NAS	National Academy of Sciences
NAWQA	USGS National Water Quality Assessment
NHEERL	National Health and Environmental Effects Laboratory
nlme	Non-linear mixed effects model
NOEC	No Observable Effect Concentration
NOAEL	No Observed Adverse Effect Level
NPDES	National Pollutant Discharge Elimination System
NR	Not Required
NRC	National Research Council
OP	Organophosphate
OPCumRisk	Organophosphate Cumulative Risk (computer program)
OPP	Office of Pesticide Programs
OPPTS	Office of Prevention, Pesticides and Toxic Substances
ORETF	Occupational and Residential Exposure Task Force
PADI	Provisional Acceptable Daily Intake
PAG	Pesticide Assessment Guideline
PBPK	Physiologically Based Pharmacokinetics
PAM	Pesticide Analytical Method
PCA	Percent Crop Area
PCO	Pest Control Operator
PDP	Pesticide Data Program (USDA)
PHED	Pesticide Handler's Exposure Database
POD	Point of Departure
ppb	Parts Per Billion
ppm	Parts Per Million
PRN	Pesticide Registration Notice
PRZM/ EXAMS	Pesticide Root Zone Model/EXposure Analysis Model System–Coupled models used to estimate pesticide concentrations in surface water.
RAC	Raw Agriculture Commodity
RBC	Red Blood Cell
RED	Reregistration Eligibility Decision

RfD	Reference Dose
RPF	Relative Potency Factor
RUP	Restricted Use Pesticide
SAP	FIFRA Scientific Advisory Panel
SCI-GROW	Tier I Ground Water Computer Model
SF	Safety Factor
SLN	Special Local Need (Registrations Under Section 24© of FIFRA)
SOP	Standard Operating Procedures
TC	Toxic Concentration–The concentration at which a substance produces a toxic effect.
TD	Toxic Dose–The dose at which a substance produces a toxic effect.
TEP	Typical End-Use Product
TGAI	Technical Grade Active Ingredient
TLC	Thin Layer Chromatography
UF	Uncertainty Factor
μg/g	Micrograms Per Gram
μg/L	Micrograms Per Liter
USDA	United States Department of Agriculture
USGS	United States Geological Survey
UV	Ultraviolet
WARP	Water Analysis Regression Program
WHO	World Health Organization
WP	Wettable Powder

Glossary of Terms

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

Additivity: When the "effect" of a combination of chemicals is estimated by the sum of the exposure levels or the effects of the individual chemicals.

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

Aggregate Exposure: The amount of a chemical available at the biological exchange boundaries (e.g., respiratory tract, gastrointestinal tract, skin) for all routes of exposure.

Aggregate Exposure Assessment: A process for developing an estimate of the extent of a defined population to a given chemical by all relevant routes and from all relevant sources.

Aggregate Risk: The risk associated with all pathways & routes of exposure to a single chemical.

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

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

Benchmark Dose (BMD_L): A statistical lower confidence limit on the dose producing a predetermined level of change in adverse response compared with background response. The BMD is derived by fitting a mathematical model to the dose-response data. A BMD_{10} is a benchmark dose with 10% change in adverse response compared with background response.

Benchmark Response(BMR): A designated level or percent of response relative to the control level of response used in calculating a BMD.

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

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

Common Mechanism Group (CMG): A group of pesticides determined to cause adverse effects by a common mechanism of toxicity. The CMG is defined using the previously released "Guidance for Identifying Pesticide Chemicals and Other Substances that Have a Common Mechanism of Toxicity" (February 5, 1999). Not all members of a CMG will necessarily be incorporated in the cumulative risk assessment.

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

Comparative Effect Level (CEL): A dose by which potency of chemicals may be compared; e.g. the dose causing a maximum of 15% cholinesterase inhibition.

Concurrent Exposure: The potential human exposure by all relevant pathways & routes that allows one chemical to add to the exposure of another chemical such that the total risk of a group of common mechanism chemicals is an estimate of the sum of the exposures to the individual chemicals. The accumulation of the common toxic effect may or may not depend on simultaneous or overlapping exposures depending on the duration and recovery time for the toxic effect.

Cumulative Adjustment Factor (CAF): Accounts for the percent of land in a given location that is planted to crops and treated with a given OP.

Cumulative Assessment Group (CAG): A subset of the CMG. The CAG is that group of pesticides selected for inclusion in the cumulative risk assessment. The chemicals in the CAG are judged to have a hazard and exposure potential that could result in the expression of a cumulative risk.

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

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

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

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

Dependent (events): The probability of one event occurring is affected by whether or not another event has or has not occurred.

Deterministic: This approach to risk assessment uses point estimates, for example, single maximum values or average values, to represent input variables in an exposure model. This can be compared to a probabilistic approach which considers the full range of potential exposures incurred by members of a population.

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

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

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

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

Effective Dose (ED): The effective dose is a measured or estimated dose level associated with some designated level or percent of response relative to the control or baseline level of response. For example, the ED_{10} is a dose associated with a 10% response. The effective does is essentially the same as a benchmark dose (BMD). It is determined by using a curve-fitting procedure that is applied to the dose-response data for a chemical.

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

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

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

Independent (events): The probability of one event occurring is not affected by whether or not another event has or has not occurred.

Index Chemical: The chemical selected as the basis for standardization of toxicity of components in a CAG (or a mixture). The index chemical should have a clearly defined dose-response relationship.

LED_{10} : The lower confidence limit on an effective dose, that is, in this case the 95% lower confidence limit on a dose associated with 10% response adjusted for background.

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

Lowest Observed Adverse Effect Level (LOAEL): The lowest dose in a toxicity study resulting in adverse health effects.

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

Mechanism of Toxicity: Mechanism of toxicity is defined as the major steps leading to an adverse health effect following interaction of a substance with biological sites. All steps leading to an effect do not need to be specifically understood. Rather, it is the identification of the crucial events following chemical interaction that are required in being able to describe a mechanism of toxicity.

Monte Carlo Analysis: One of several mathematical techniques for performing probabilistic assessments. The method relies on the computational powers of modern computers to simulate the range and frequency of all possible outcomes of a process based on repeatedly sampling from the inputs provided by the user. These inputs are combined according to the model that is specified by the user.

No Observed Adverse Effect Level (NOAEL): The highest dose in a toxicity study which does not result in adverse health effects.

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

Point of Departure (POD): Point on the dose-response curve where each chemical's response is close to or within the background level of response, in other words, the dose at which effects from a pesticide are first distinguishable. Depending on the kind of data available and the purpose of the analysis, there are differing procedures for estimating the point of departure.

Reference Dose (RfD): NOAEL/UF.

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

Relative Potency Factor (RPF) Method: The RPF approach expresses the potency of each chemical in a CAG in relation to the potency of another member in the group which has been selected as the index chemical. A relative potency factor is calculated for each chemical for each route of exposure (e.g., oral, dermal, inhalation). For example, if compound A is determined to be one-tenth as toxic as the index compound the RPF for compound A is 0.1. Using this approach, for each route of exposure for each chemical, exposure is expressed as exposure equivalents of the index chemical. The exposure equivalents are calculated by multiplying the residues and the RPF for each route. These exposure equivalents are summed to obtain an estimate of total exposure by route in terms of the index chemical.

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

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

Steady State Inhibition: The time point at which continued dosing at the same level results in no further increase in cholinesterase inhibition.

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

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

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

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

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

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

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

Uncertainty: Lack of knowledge about specific factors, parameters, or models.

Uncertainty Factor: Uncertainty factors applied to account inter- and intra-species differences in relation to toxic effects, and uncertainties associated with the data.

Unit Exposure: The amount of a pesticide residue's to which individuals are exposed, normalized by the amount of active ingredient used.

Variability: Differences attributed to true heterogeneity or diversity in a population or exposure parameter.

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