U.S. Environmental Protection Agency

Revised OP (Organophosphate) Cumulative Risk Assessment

June 10, 2002

This document was only published electronically.
Accessed 1/14/04 from:
http://www.epa.gov/pesticides/cumulative

Executive Summary

A. Introduction

In 1996 Congress enacted the Food Quality Protection Act (FQPA), which among other things, requires EPA to take into account when setting pesticide tolerances (maximum residue legally allowed on a food) "available evidence concerning the cumulative effects on infants and children of such residues and other substances that have a common mechanism of toxicity." Also, FQPA mandates that by 2006, EPA must review the safety of all existing tolerances that were in effect as of August 1996. The law requires EPA to place the highest priority for tolerance reassessment on pesticides that appear to pose the greatest risk, such as the organophosphorus (OP) pesticides.

To implement the cumulative provision of FQPA, EPA has been working to develop methodologies for conducting cumulative risk assessments and then conduct its first such risk assessment on the OP pesticides. This has been a challenging task given that historically, the potential health risks associated with exposure to pesticides has focused on *single pathways of exposure* (e.g., exposure from food, or water, or pesticide use in and around the home) for individual chemicals and not on the potential for individuals to be exposed to *multiple (common mechanism) pesticides by all pathways concurrently*, as is required under FQPA.

This scientific assessment of OP pesticide food safety contains good news for American consumers. After years of rigorous scientific work, it strongly supports our confidence that the United States has one of the safest food supplies in the world. Specifically, with this groundbreaking work, EPA has evaluated over 1,000 OP pesticide tolerances and virtually all of them are now consistent with the highest levels of safety. Please note that EPA is still evaluating the tolerances for a few of the OP pesticides.

This finding comes after years of scientific work, countless scientific and public meetings, and an existing regulatory process to ensure these pesticide tolerances meet the tough food safety standard in the Food Quality Protection Act. In the last several years, EPA has taken a variety of regulatory actions on the OP pesticides, ranging from lowering application rates to complete cancellations of specific uses. These actions have substantially reduced the risks and have contributed to the high level of safety found in the cumulative risk assessment.

On December 3, 2001 EPA issued for public comment its "Preliminary OP Cumulative Risk Assessment." That assessment was a preliminary review of the results of a new way of analyzing data regarding potential exposure to pesticides. The focus of the assessment was on the methods used to assess the risk. In contrast this revised risk assessment describes the potential risks of OP's by presenting a range of estimates that reflect the variability inherent in an assessment of this scope. Table 1 provides a side-by-side comparison of the major changes between the December 2001 and current documents. The changes were made due to comments submitted during the public comment period, suggestions from the FIFRA Scientific Advisory Panel (SAP), and issues that EPA was aware of at the time the preliminary cumulative risk assessment was issued but had not yet addressed. These major changes are discussed under "Hazard Assessment" and "Exposure Assessment," below.

With the release of this document the Agency has met its deadline obligation under a Consent Decree with the Natural Resources Defense Council to issue a revised risk assessment of the OP pesticides by August 3, 2002. As existing analyses are revised or new information is obtained, EPA will review this assessment and will make further changes as appropriate.

Not all of the changes result in quantitative impacts on the risk assessment. For example, in February 2002 the FIFRA SAP suggested that the Agency conduct more "sensitivity analyses" to assure the quality and robustness of the model being used (see text box). While these analyses provide valuable information on the reliability of the models, they do not change the quantifications of risk (e.g., MOEs). On the other hand, other changes do impact the risk quantification. During the public comment period food processing factors were submitted; EPA has updated its food exposure estimates using this information.

Sensitivity Analysis is the study of how the variation in the output of a model can be apportioned to different sources of variation–it aims to ascertain how the model depends upon the information fed into it, upon its structure, and upon the assumptions made to build it. Overall, sensitivity analysis is used to increase the confidence in the model and its predictions by providing an understanding of how the model response variables respond to changes in the inputs.
http://sensitivity-analysis.jrc.cec.eu.int/default.htm

It has become evident that addressing issues such as the FQPA Safety Factor and the threshold of concern are both dependent on the available data. The decisions made regarding these two issues involve risk management considerations and will be made on a case-by-case basis. EPA intends to use a systematic approach in making these decisions to reflect such factors as the quality of the available data and the characteristics of the modeling analysis.

Table ES-1. Major Differences Between the Preliminary OP Cumulative Risk Assessment and the Revised OP Cumulative Risk Assessment

	December 2001	June 2002
Toxicity		
Relative Potency Factors (RPF's)	Used best available data	Additional RPF's were calculated: chlorethoxyphos, phostebupirim, profenofos and omethoate (a metabolite of dimethoate)
FQPA Factor	Not addressed	FQPA Safety Factors were assigned based on available information; 1X for three OP's and one metabolite; 3X used for the others
Treatment of Animal Data	Used means and standard deviations	To see how the results would be affected, single animal data were used in a sensitivity analysis
Exposure		
Food: Processing Factors	Used best available data	Revised based on data provided during the public comment period
Consumption Data	Used the CSFII data "as is"	Conducted a sensitivity analysis to look for 'extreme' outliers
Residue Data	Did not use any over-tolerance residues	Included over-tolerance residue values
Impact of High-End Exposure	Not considered	Conducted an analysis to determine whether specific high-end consumption and/or residue values are significantly responsible for the exposure estimates at the higher percentiles of the exposure distribution
Duration of Exposure	One-day	One - and seven-day rolling average. Also, a sensitivity analysis was conducted using 14- and 21-day rolling averages
Populations Considered	The standard populations	Conducted a sensitivity analysis by looking at additional subpopulations
Drinking Water: Number of Regions*	13	7; EPA found that a number of the Regions could be combined due to similarities among geography, climate, and soil type
Sensitivity Analysis	Some performed	Extensive analyses conducted, as suggested by the SAP
Residential: Populations Considered	The standard populations	Conducted a sensitivity analysis by looking at additional subpopulations
Type of Distribution	Uniform	log normal, as recommended by the SAP
Number of Regions[1]	13	7; EPA found that a number of the Regions could be combined due to similarities among geography, climate, and soil type
Pet Uses	Not included	New data on tetrachlorvinphos
Risk		
Risk Quantification	Summary results; MOE's for single-day exposures at various percentiles of exposure	Identified pestide/crop combinations that have significant roles in the estimates. Risk presented as ranges of MOEs at various percentiles reflecting one- and seven-day exposures, and 14 and 21-day rolling averages

[1]A Note on "Regions." Because the United States is so climatologically and geographically diverse, EPA has divided the country into different risk assessment "Regions" so that this diversity could be factored in to the assessments.

B. Hazard Assessment

1. RPF's

The RPF's were revised and relative potency factors for four additional chemicals have been calculated (chlorethoxyphos, phostebupirim, profenofos, and a metabolite of dimethoate).

2. FQPA Safety Factor

In the December 2001 preliminary cumulative risk assessment, EPA discussed and characterized the potential multiple sources of exposure to children but did not address the FQPA Safety Factor. The decision regarding the Safety Factor is determined based on the available data for the specific chemicals in this assessment. The Revised OP Cumulative Risk Assessment provides an analysis on the sensitivity and susceptibility of infants and children to cholinesterase (ChE) inhibition (the common mechanism of toxicity) caused by OP pesticides.

In summary, based on available information, the FQPA Safety Factor is 1X for three OP's and one metabolite (dimethoate; omethoate, a metabolite of dimethoate; chlorpyrifos; and methamidophos) and 3X for the remaining OP's. A summary of the rationale is provided below; please note that these Safety Factors are appropriate for this risk assessment only.

- In making an FQPA Safety Factor decision, EPA considers both the potential for pre- and postnatal toxicity and the completeness of the toxicology and exposure databases (USEPA, 2002a). Looking at the exposure side of the equation–there is a high degree of confidence in the exposure data and methodologies used–EPA believes that it is not necessary to retain the default 10X FQPA Safety Factor based on the exposure database.

- The toxicity endpoints for this assessment were developed in consideration of a 10X uncertainty factor to account for interspecies variability and a 10X uncertainty factor to account for intraspecies variability. Because some OP pesticides show age-dependent sensitivity and there are missing comparative ChE inhibition data in young animals for many of the OP's, EPA chose an FQPA Safety Factor of 3X for most of the OP pesticides. There were a few whose data supported a 1X FQPA Safety Factor:

  - Age-dependent susceptibility data are available for seven of the OP's. The data for dimethoate, omethoate (a metabolite of dimethoate), chlorpyrifos, and methamidophos support an FQPA Safety Factor of 1X.

On June 25 to 27, 2002 EPA is consulting with the FIFRA Scientific Advisory Panel on this sensitivity and susceptibility analysis for children. For more information see: http://www.epa.gov/fedrgstr/EPA-MEETINGS/2002/May/Day-31/.

For future cumulative risk assessments the FQPA Safety Factor may be retained, reduced, or removed, based on the available data which are specific to the chemicals examined.

C. Exposure Assessment

1. Regions

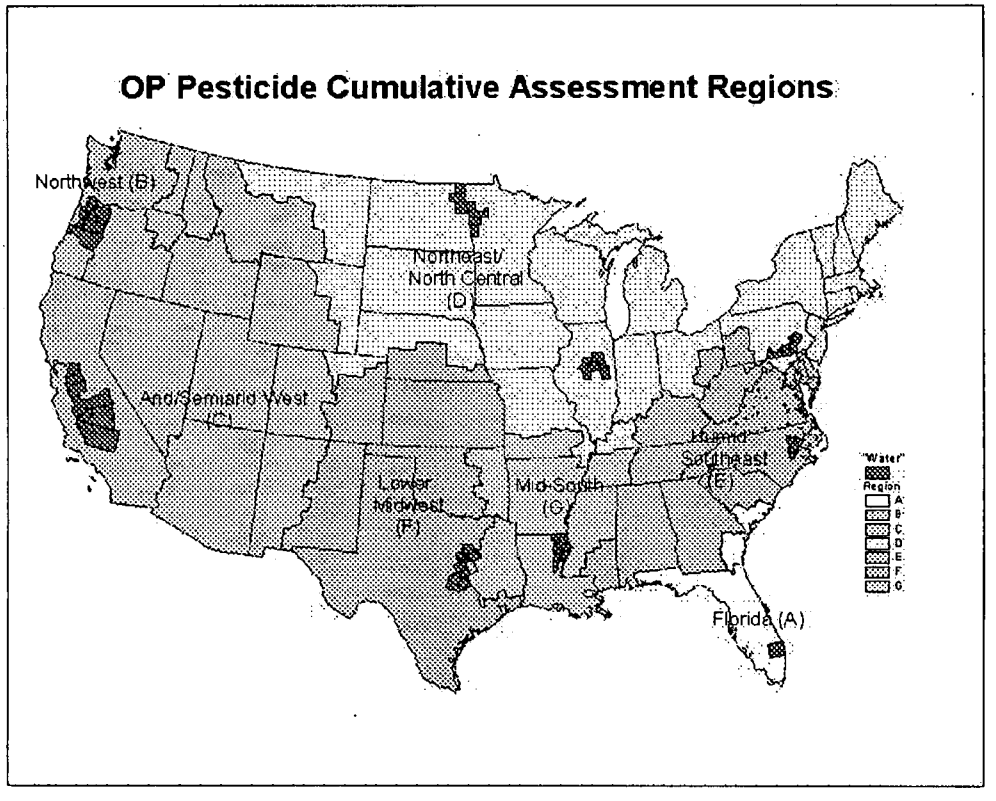
Because the United States is climatologically- and geographically-diverse, EPA divided the country into Regions so that it could account for factors such as weather and soil type (these affect the amounts and types of pesticides used). In the December 2001 analysis 13 Regions were used; the current analysis has seven. The reason for this reduction is that EPA realized that some of the Regions were not truly distinct so they were combined. Provided in Figure ES-1 is a map of the United States that shows the seven Regions.

As mentioned in the "Introduction" sensitivity analyses were conducted for a number of variables. The exposure data used for these analyses were from Region A. EPA chose Region A because it has the highest estimated exposure.

2. Food

The amount of pesticide to which an individual is exposed (i.e., exposure) is determined by combining the amount of pesticide that is in or on the food (i.e.,

ES-1. Regions Used for Exposure Assessment



residue levels) and the amount and type of foods that people eat (i.e., food consumption). In the Revised OP Cumulative Risk Assessment EPA conducted a number of sensitivity analyses on the data and models supporting the food risk assessment.

Consumption Data. EPA uses USDA's Continuing Survey of Food Intake by Individuals (CSFII) for its food consumption data. One of the criticisms that has been raised regarding the food consumption data is that it may include individuals who have "extreme" diets. EPA scientists, including a nutritionist, have conducted a sensitivity analysis on the food consumption database; no outliers were identified. Consumption data that appeared unusually high and were associated with high exposures in the cumulative risk assessment were fully investigated.

Although they did not identify any outliers, it is important that appropriate sensitivity analysis be conducted so that any outliers are evaluated. Please note that several individual OPs are still undergoing individual assessments and for these pesticides future analysis on food consumption will continue.

Residue Data. All of the residue data in this assessment came from USDA's Pesticide Data Program (PDP) and FDA's Center for Food Safety and Applied Nutrition (CFSAN) monitoring data. In the Revised OP Cumulative Risk Assessment EPA incorporated over-tolerance residue values from the PDP data.

Impact of High-End Exposure. The December 2001 document pointed out that:

> The data inputs and assumptions need to be verified, and the results at the tail end of the distribution at the higher percentiles of exposure for children's age groups need to be evaluated to ensure they reflect reasonable consumption patterns. Additionally, OPP is in the process of conducting sensitivity analyses that will permit a fuller characterization of the contributors or sources of potential risks associated with the food pathway.

The Revised OP Cumulative Risk Assessment includes an analysis of the upper tail of the exposure distribution to determine whether specific high-end consumption and/or residue values are significantly or mainly responsible for the exposure estimates at the higher percentiles of the exposure distribution. In addition, a range of percentiles of exposure as well as the percentiles at which the MOEs approach 100 (100 because the toxicity endpoints for this assessment were developed in consideration of a 10X uncertainty factor to account for interspecies variability and a 10X uncertainty factor to account for intraspecies variability) are presented in the body of the risk assessment. This information provides the basis for bounding and characterizing exposures.

Duration of Exposure. In the December 2001 risk assessment EPA used one-day as the duration over which an individual would be exposed to a pesticide residue in food. However, this analysis overestimates risk because the toxicity data and consumption reflect different time frames. For the current analysis EPA added a second exposure duration, that of the seven-day rolling average in an attempt to better match the time frames for the toxicity data with the consumption data which are not directly comparable. EPA also believes using these time intervals will bound the risk (i.e., the potential risk is best represented by a range of values for different exposure durations). In addition the Agency evaluated 14- and 21-day averages for one Region (Region A). EPA conducted these additional analyses to determine whether estimates of average daily exposure changed significantly over longer durations.

The chart provided below (Table ES-2) provides a discussion of how the one- and seven-day durations are affected by four key factors.

Table ES-2. How the One- and Seven-Day Durations Are Affected

Factor	Impact on Durations
The degree to which the exposure and toxicity time frames correspond to each other.	The use of a steady state hazard endpoint–based on toxicity studies that are 21-days or longer–tends to overstate the risk for the one-day analysis. Use of the steady state value is more appropriate with the 7-, 14-, and 21-day analyses.
The degree to which the Agency has captured the previous day's cholinesterase inhibition.	For the one-day analysis, the consideration of only a single day's exposure may underestimate risk, to the extent an individual's previous days' exposures continue to cause ChE inhibition. For the same reason, multiday exposures may also underestimate risk.
Day-to-day variation in individuals' diets.	Day-to-day variability in an individual's diet does not affect the one-day estimate. Limited data about such variability requires EPA to make assumptions that tend to underestimate the potential exposures for the seven-day analysis.
Possible correlation among residues on different days.	EPA's multiday analyses do not account for the possibility that a person may be more likely to encounter high residues in food because some portion of their consumption comes from the same source. This limitation means that multiday analyses may underestimate food exposure somewhat. This limitation does not affect the one-day analysis.
Interpretation of Model Outputs	The one-day analysis assumes that an individual is exposed to OP residues from the tail of the distribution every day. This assumptions overestimates risk. The seven-day analysis incorporates day-to-day variability in exposure and is more representative of anticipated exposures.

The Agency believes the timeframe considerations, as they relate to both hazard and exposure, to be among the most important for the OP cumulative assessment. This is not surprising since the essence of the cumulative assessment is to estimate likely co-occurrence in exposure to multiple chemicals and the likely combined effect of those exposures.

Populations Considered. Standard population subgroups that EPA considers in dietary risk assessment include: children one- to two-years-old; children three- to five; adults 20 to 49; and adults 50 and older. Upon SAP's recommendation, EPA looked at other subpopulations such as infants less than one year and teenagers. This was done to demonstrate that indeed children one- to two-years-old are the most highly exposed, due to their high consumption-to-body weight ratio.

3. Drinking Water

EPA evaluated the contribution to overall exposure resulting from OP pesticide residues in drinking water across different Regions and found that drinking water is not a significant source of exposure. EPA looked at the impacts that periods of high-volume runoff (e.g., during the spring and storm events) have on the level of pesticide residue estimated in drinking water. It was found that there are higher concentrations of pesticides in the drinking water during such periods. The analysis shows that, even considering such events, drinking water is not a significant contributor to overall risk.

4. Residential

Populations Considered. The population subgroups that EPA considers for residential exposure are the same as those considered for the food exposure. Similar to the food assessment, EPA conducted sensitivity analyses by looking at additional subgroups such as infants. This was done to see how including more population subgroups would change the risk estimates. The Agency is still working to evaluate individual residential uses (as part of the cumulative assessment) where additional risk mitigation will likely be necessary. In the next several weeks, EPA will continue the scientific and regulatory work to evaluate and address these potential risks.

Type of Distribution. EPA reassessed residential exposure using log-normal distributions of the available data (instead of a uniform distribution), wherever possible. This change was made because, according to the SAP, a log-normal distribution better represents the data set. Some of the resulting residential exposure estimates, and in turn risk, are lower than the December 2001 estimates.

Pet Uses. New data on exposure from the pet uses of tetrachlorvinphos have been used to quantitatively include tetrachlorvinphos in the residential assessment.

D. Risk Characterization

The risk characterization summarizes and integrates all of the information from the various components of the assessment. Risk characterization looks at the strengths and weaknesses of the data used, including any potential biases in input parameters and the direction of that bias, reliability and availability of the data, as well as the characteristics of the exposure models, and attempts to bound that uncertainty. The revised assessment discusses in great detail what data have been used; how the data have been used; and the strengths and weaknesses of the resulting analysis.

The risk estimates presented in this Revised OP Cumulative Risk Assessment are the culmination of several years of Agency analyses, outside input, and risk mitigation efforts on the part of the regulated community. Beginning in the summer of 1998 EPA started to seek public input on its individual OP risk assessments by issuing *Federal Register* notices asking for comment. In addition, EPA actively sought the advice of the regulated community, environmental groups, and others through two Federal advisory committees, the Tolerance Reassessment Advisory Committee (TRAC) and the EPA-USDA Committee to Advise on Reassessment and Transition (CARAT).

Throughout this period of public review and scrutiny, a good deal of risk reduction has been achieved through the risk mitigation measures taken on the individual OP's. In 1996 49 OP pesticides were registered for use in agriculture and residential settings. Today, 14 of those pesticides have been canceled completely and for another 28, considerable risk mitigation actions have been taken. For example:

- Methyl Parathion. Methyl parathion had been one of the most widely used OP's. In 1999 the registrants voluntarily canceled many methyl parathion uses that contribute most to the children's diet. These included: apples, peaches, pears, grapes, nectarines, cherries, and plums, carrots, succulent peas, succulent beans, and tomatoes.

- Ethyl Parathion. Before 2000, ethyl parathion had been one of the most highly restricted pesticides registered for use in the United States. A 2000 agreement canceled all remaining uses of the OP pesticide ethyl parathion, which included use on nine agricultural crops. Use of parathion on corn grown for seed was to stop immediately, with the use on other crops to be phased out over the next few years.

- Chlorpyrifos. Before the risk mitigation measures were taken, chlorpyrifos had been one of the most widely-used pesticides in and around the home. It is also one of the most widely used OP pesticides in agriculture. In 2000 the registrants agreed to cancel nearly all indoor and outdoor residential uses, as well as use on several food crops that contributed most to children's dietary exposure.

- Diazinon. Diazinon is one of the most widely used agricultural insecticides and until 2000, one of the most widely used insecticides for household lawn and garden pest control. In 2000 all indoor residential uses were terminated; outdoor residential uses will be phased-out over the next several years. Additionally, many agricultural uses of diazinon also are being canceled.

Without these measures, pesticide exposure through food and in and around the home would have been more significant. December's preliminary analysis and now the revised analysis reflect all these important risk mitigation measures.

1. Risk Quantification

This version of the cumulative risk assessment presents results showing a range of estimated risks depending on the exposure period considered (one-day or seven-day average) and the percentile of exposure. Ranges of estimated risk at various percentiles of exposure are also presented for 14- and 21-day averages for Region A. The selection of the range for the percentile of exposure must take into account the data from the particular group of chemicals in the assessment. For most portions of the ranges presented from the different exposure periods, the estimated Margins of Exposure (MOEs) do not represent levels of potential concern. After careful analysis, the Agency believes that the potential exposures are bounded by the estimates for the one- and seven-day exposure durations, and generally the margins of exposure in this assessment do not represent major concerns.

In considering the possible need for risk mitigation actions, EPA believes that it is important to consider the range of risk assessment values, which in turn take into account different exposure periods, for different age groups, living in different Regions, with risks shown at different percentiles of estimated exposures. It is also important to consider risk characterization, including the factors that may tend to overestimate or underestimate risk, and the identification of major sources contributing to potential exposure.

It appears that one of the major factors influencing the results at the highest portion of the range derives from the fact that, for a few individual OP's, risk assessments and mitigation actions have not been finalized. This is particularly true for DDVP and dimethoate. The Agency expects to complete these risk assessments and possible mitigation actions very soon.

Finally, it is important to remember that portions of this document are currently under review by the FIFRA SAP. For instance, EPA intends to present preliminary results of cumulative risk using two additional models–CARES and Lifeline™–to the SAP during the June 2002 meeting. EPA will evaluate SAP's comments, as well as other comments or data that it receives, and will modify this assessment, as appropriate. In addition, as existing analyses are revised or new information is obtained, EPA will review this assessment and will make further changes as appropriate.

E. Conclusion

This scientific assessment of OP pesticide food safety contains good news for American consumers. Regulatory actions taken over the last six years have considerably reduced the risks posed to Americans from OP residues that may be found in food, drinking water, and in and around the home. After years of rigorous scientific work, the Revised OP Cumulative Risk Assessment strongly supports our confidence that the United States has one of the safest food supplies in the world.

F. Road Map

The Revised OP Cumulative Risk Assessment is divided into three parts: (1) the actual risk assessment which draws on the regional risk assessments and the supporting toxicology analyses (I. Revised OP Cumulative Risk Assessment); (2) the seven regional risk assessments (II. Revised Regional Assessments); and (3) the detailed toxicology analyses such as the derivation of the RPF's and how the FQPA Safety Factors were determined (III/ Appendices).

Glossary

BMD_{10} is a Benchmark Dose associated with a 10% response adjusted for background.

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

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).

Comparative effect level (CEL) is a dose by which potency of chemicals may be compared; *e.g.* the dose causing a maximum of 15% cholinesterase inhibition.

Cumulative Assessment Group (CAG) is a subset of chemicals selected from a common mechanism group for inclusion in a refined quantitative estimate of risk.

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

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

Index chemical is a chemical used as the point of reference for standardizing the common toxicity of the chemical members of the CAG.

Lowest-Observed-Adverse-Effect Level (LOAEL) is the lowest dose in a toxicity study resulting in adverse health effects

No-Observed-Adverse-Effect Level (NOAEL) is the highest dose in a toxicity study which does not result in adverse health effects

OPCumRisk is a computer program developed at ORD's NHEERL to determine relative potency estimates and PoDs for the index chemical.

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

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

Relative Potency Factor (RPF) is 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.

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

Steady state inhibition is the time point at which continued dosing at the same level results in no further increase in cholinesterase inhibition.

Acronyms

A	Estimate of A (background cholinesterase activity)
AChE	Acetylcholinesterase
B	Estimate of B (horizontal-asympote from July 2001 analysis)
B/A	Ratio of estimate of B/estimate of A
BMD_{10}	A Benchmark Dose associated with a 10% response adjusted for background
BMDL	Lower 95% confidence limit on the BMD_{10}
BMR	Benchmark Response -a designated level or percent of response relative to the control level of response used in calculating a BMD
CEL	Comparative effect level - Dose level used to compare potencies
ChEI	Cholinesterase inhibition
CL	Confidence limit
CNS	Central nervous system
D	Displacement parameter in expanded model
DER	Data evaluation record, a review of a toxicity study
F	Female
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FQPA	Food Quality Protection Act
GOF	Model goodness-of-fit
HED	Health Effects Division
idose	Scaled internal dose
m	Estimate of absolute potency for a single cholinesterase measurement in the July 2001 analysis
*l*A	Log of background cholinesterase activity
*l*m	Log slope-scale factor
M	Male
MOE	Margin of exposure
MRID #	Study identification number
NA	Not available
NERL	National Exposure Research Laboratory
NHEERL	National Health and Environmental Effects Laboratory
nlme	Non-linear mixed effects model
NOAEL	No-Observed-Adverse-Effect Level - the highest dose in a toxicity study which does not result in adverse health effects
OP	Organophosphorous pesticide
OPCumRisk	Computer program developed at ORD's NHEERL to determine relative potency estimates and PoDs for the index chemical.
OPP	Office of Pesticide Programs
OPPTS	Office of Prevention, Pesticides, and Toxic Substances
ORD	Office of Research and Development
P_B	Limiting value of minimum cholinesterase activity (horizontal asymptote)
P_{BF}	Female specific value of P_B
P_{BM}	Male specific value of P_B
PBPK	Physiologically Based Pharmacokinetics
POD	Point of Departure

PNS	Peripheral nervous system
RBC	Red blood cells
RfD	Reference Dose - A dose not expected to cause adverse health effects in humans
RPF	Relative Potency Factor
S	Shape
SAP	Scientific Advisory Panel
*t*B	Transformed horizontal asymptote

Part I.

Revised OP Cumulative Risk Assessment

I. Revised OP Cumulative Risk Assessment

A. Introduction

The Food Quality Protection Act of 1996 significantly amended the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) and the Federal Food, Drug, and Cosmetic Act (FFDCA). One of the major changes is the requirement that EPA consider risk posed by pesticides acting by common mechanism of toxicity.[1] For such groups of pesticides, EPA's Office of Pesticide Programs has treated cumulative risk, under FQPA, as the risk of a common toxic effect associated with concurrent exposure by all relevant pathways and routes.

Since the enactment of FQPA, EPA's Office of Pesticides Programs (OPP) has been working to develop new methodologies in a number of risk assessment areas. The steps necessary to complete the Revised OP Cumulative Risk Assessment were:

- Development of approaches for grouping chemicals by a common mechanism of toxicity (USEPA, 1999a) and
- Conducting aggregate (USEPA 1999c and 2001d) and cumulative risk assessments (USEPA 2000a and 2001a)

At each major step in development OPP consulted with the FIFRA Science Advisory Panel (SAP) to seek expert review, advice, and recommendations. We held several external peer review meetings with the SAP and asked for comment on our approaches to grouping chemicals based on common mechanism of toxicity, grouping chemicals for the purpose of cumulative assessment, improved methods for exposure assessment, approaches to aggregating food, drinking water and residential exposure and proposed models for combining these exposures. We also held several meetings with the FQPA Federal Advisory Committee Act (FACA) Groups of stakeholders (public interest groups, state agricultural agencies, pesticide industry representatives, growers, USDA and others) to present our methodologies as they were developed, and to seek comments and recommendations. All of the new science policies which are a foundation of this assessment were proposed for public comment. The work to develop the methodology was completed with the publication of the Revised Guidance Document for Cumulative Risk Assessment USEPA 2001a). The document was proposed for public comment on June 30, 2000 (65 FR 127:40644-40650). The SAP and public comments were reconsidered and the Guidance was revised in December, 2001. All of these documents played roles in preparation at the Preliminary OP Cumulative Risk Assessment which was issued

[1] For details see The Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), 7U.S.C. §§ 136 et seq., and Federal Food, Drug, and Cosmetic Act (FFDCA) 21 U.S.C. § 346a.

in December 2001and presented to the public in a technical briefing in January 2002. The assessment was reviewed by the SAP in February 2002. Public comment was also solicited for ninety days. The comment period closed in March 2002.

OPP proceeded with the methodology and risk assessment development in a step-by-step process. The approach to the risk assessment was evaluated using a case study of three organophosphorus pesticides. That assessment was reviewed by the SAP (September and December 1999 see FIFRA SAP 2000a,b), who recommended that OPP proceed with a more comprehensive case study. OPP developed the hazard, dose-response and exposure assessment for 24 OP pesticides and brought it to the SAP for comment in September and December of 2000 (FIFRA SAP 2001a,b). Based on the comments, the hazard and dose-response assessment was revised and again reviewed by the SAP in September of 2001(FIFRA SAP 2001c). The SAP was very supportive of the approach, calling it both 'skillful' and 'creative.' The recommendations made by the September 2001 SAP were addressed in the Preliminary Risk Assessment. In February 2002, OPP brought the Preliminary OP Cumulative Risk Assessment to the SAP. Once again the panel was generally supportive of the preliminary document while suggesting some revisions. These revisions have been incorporated in this current document, the Revised OP Cumulative Risk Assessment.

Cumulative Risk Assessment is a complex analysis and OPP needs to emphasize that the results are not a collection of numbers or bright lines. Quantitative methods have been used throughout the analysis but the results need to be interpreted with a full understanding of the assumptions made and the uncertainties introduced by making these assumptions. As the regulatory managers and the stakeholders look for guidance in reading the document, it is especially important to consider the Risk Characterization Chapter of the Risk Assessment.

I. Revised OP Cumulative Risk Assessment

B. Hazard/RPF

1. Introduction

Since the passage of the FQPA, the Office of Pesticide Programs (OPP) has presented proposed guidance, tools and methodologies for conducting cumulative risk assessments to the FIFRA Scientific Advisory Panel (SAP). Specifically, the hazard and dose-response sections have been presented to the FIFRA SAP four times between 1999 and 2002 including the February 5-8, 2002 meeting on the methods used in the Preliminary Cumulative Risk Assessment (PCRA) of the Organophosphorus Pesticides (FIFRA SAP, 2000a, 2001a, 2001b, 2002a). Following the previous SAP reviews, constructive comments and recommendations have been incorporated into revisions and refinements of the hazard and dose-response assessment for the organophosphorus pesticides (OPs). Key recommendations from SAP reports have included the utilization of the exponential model for fitting the cholinesterase data, the derivation of relative potencies from several relatively consistent studies rather than a single study, and further exploration of low dose modeling issues. In collaboration with EPA's Office of Research and Development (ORD) National Health and Environmental Effects Research Laboratory (NHEERL), OPP released a Preliminary Dose-Response Assessment for OPs on July 31, 2001 (USEPA 2001b) followed by a revised dose-response assessment on December 3, 2001. At the February 5-6, 2002 meeting, the SAP was very supportive of the approach used in the PCRA for OPs. The panel commended the Agency for its progress in modeling of dose-response relationships of OP exposure to cholinesterase inhibition. The panel indicated that remaining issues concerning cumulative hazard and dose-response assessment reflect the evolving nature of the field and do not need to be specifically addressed in the cumulative risk assessment of OPs.

Revised relative potency factors (RPFs) for 33 OPs were released to the public on April 17, 2002 (http://www.epa.gov/pesticides/cumulative/pra-op/rpf_final.htm). EPA has calculated RPFs for four OPs not included in the hazard and dose-response assessment of the PCRA: chlorethoxyphos, omethoate, phostebupirim, and profenofos. After issuing its PCRA, the Agency identified computer programming errors in its statistical modeling procedure. EPA discussed them at the February 5-8, 2002 meeting of the FIFRA SAP. These errors impacted the curve-fitting procedure for some OPs. In addition, EPA received additional toxicology data for disulfoton, fenamiphos, phosalone, tetrachlorvinphos, and tribufos, which were used in the revision of the RPFs for these chemicals.

2. Methods

a. Overview

Before the cumulative risk of exposure to OPs can be quantified, the relative toxic potency of each OP must be determined. The determination of relative toxic potency should be calculated using a uniform basis of comparison, by using, to the extent possible, a common response derived from the comparable measurement methodology, species, and sex for all the exposure routes of interest (USEPA 2001a, 2002).

b. Endpoints and Toxicology Studies

i. Selection of Endpoints

As part of the hazard analysis, all relevant responses were evaluated to identify the most appropriate endpoint pertaining to the common mechanism of toxicity and to determine which endpoint(s) provide(s) a uniform and common basis for determining the relative potency of the cumulative assessment group. OPs exert their neurotoxicity by binding to and phosphorylating of the enzyme acetylcholinesterase in both the central (brain) and peripheral nervous systems (Mileson *et al.,* 1998). There are laboratory animal data on OPs for cholinesterase activity in plasma, red blood cell (RBC) and brain, as well as behavioral or functional neurological effects in submitted guideline studies. Measures of acetylcholinesterase inhibition in the peripheral nervous system (PNS) are very limited for the OP pesticides. As a matter of science policy, blood cholinesterase data (plasma and RBC) are considered appropriate surrogate measures of potential effects on PNS acetylcholinesterase activity and of potential effects on the central nervous system (CNS) when brain cholinesterase data are lacking (USEPA, 2000c). Behavioral changes in animal studies usually occur at higher doses compared to doses needed to inhibit cholinesterase. Also, behavioral measures are limited in terms of the scope of effects assessed and the measurements employed. **Plasma, RBC, and brain cholinesterase inhibition were considered potential endpoints for extrapolating risk to humans in the OP cumulative risk assessment.**

ii. Selection of Routes and Duration of Exposure for Potency Determination

Humans may be exposed to the OPs through diet, in and around residences, schools, commercial buildings, etc. Therefore, the potency of OPs needs to be determined for the oral, dermal, and inhalation routes of exposure. Cholinesterase inhibition can result for single or short-term exposures. The Revised Cumulative Risk

Assessment for OPs (RCRA) has evaluated both single-day and multiple sequential days (i.e., 7-day rolling average) exposures for integrating multiple sources of OPs.

Various toxicokinetic and toxicodynamic factors influence an individual OP's time to peak effect of inhibition, persistence of action following acute exposure, and the duration of exposure required to reach steady state inhibition. OPP has elected to estimate relative potencies and points of departure (POD) using measurements where cholinesterase inhibition in the laboratory animal is not changing with time. OPP defines this point where continued dosing at the same level results in no further increase in enzyme inhibition as steady state. The use of cholinesterase data for single-dose or short duration studies to model the comparative potency is problematic because the extent of inhibition is rapidly changing immediately following dosing. Measures of cholinesterase taken during this time will be highly variable and uncertain. Cholinesterase inhibition will continue to increase until steady state is reached. When the measurements are taken at steady state, the differences in toxicokinetics among the OPs are less likely to impact the assessment. At this point in the dosing scheme, it is possible to develop a stable estimate of relative inhibitory capacity (i.e., relative potency) between compounds.

OPP has elected to use data reflecting steady state conditions to estimate relative potencies for the OPs in the interest of producing RPFs that are reproducible and reflect less uncertainty due to rapidly changing, time-sensitive measures of cholinesterase. Although the data selected do not directly reflect the time frames of interest (single-day and multiple sequential days), they are preferred to short-term estimates for developing comparative potencies among OPs. OPP has shown previously that steady state is reached by approximately 21 to 28 days of exposure (USEPA, 2001b). No further analysis of the time course data was performed in the revised cumulative risk assessment. **The current focused on studies of a duration of 21 days or greater in order to use cholinesterase data that has attained steady state.** Twenty-one days of exposure was selected instead of 30 days because of the duration of exposure of available guideline toxicity studies; specifically, most dermal toxicity studies are 21 or 28 days in duration.

iii. Toxicity Database

As stated previously, relative potency should be based whenever possible on data from the same species and sex to provide a uniform measure of relative potency among the cumulative assessment group (USEPA, 2002). Under FIFRA, toxicology studies in various species (e.g., dog, mouse, rat and rabbit) are submitted to OPP. For the OP's,

toxicology studies in the rat provided the most extensive cholinesterase activity data for all routes, compartments, and both sexes. **Thus, the focus of this analysis was on cholinesterase activity data derived from male and (non-pregnant) female rats**. EPA used rabbit studies for five chemicals with residential/nonoccupational exposure potential because dermal toxicity data in rats were not available. The cholinesterase data considered in this analysis were extracted from the study types listed in Table I.B-1.

Studies used in this analysis were identified by their source MRID number. Studies submitted to OPP are reviewed for their quality of cholinesterase measurements and consistency of their experimental protocol with the OPPTS Guidelines (http://www.epa.gov/opptsfrs/home/guidelin.htm).

When assessing cholinesterase activity, it is important to carefully consider methodological issues that may affect the accuracy and variability of the data. There are many methods available for measuring cholinesterase activity. These methods include colorimetric, electrometric, titrimetric, radiometric, fluorimetric, gasometric, and immunochemical assays. The colorimetric method, based on the Ellman reaction, is the most commonly used method for measuring brain, plasma and erythrocyte cholinesterase activity (Ellman et al., 1961; USEPA 1992; ASCP, 1994). For this preliminary assessment, if the Data Evaluation Record (DER) for a particular study indicated that the study was acceptable, it was assumed that the methodology was also acceptable.

A comprehensive list of all the studies utilized in the present analysis is given in Appendix III.B.2. The cholinesterase data are available to the public at http://www.epa.gov/pesticides/cumulative/.

Table I.B-1. Test Guideline Studies Evaluated for Cholinesterase Activity.

Test Guideline Studies Evaluated for Cholinesterase Activity	
Study Type	**Guideline Type**
Oral	
90-day oral toxicity study in rat	OPPTS 870.3100 OPP 82-1
Chronic oral toxicity in rat	OPPTS 870.4100 OPP 83-1
Carcinogenicity in rat	OPPTS 870.4200 OPP 83-2
Combined chronic toxicity/carcinogenicity in rat	OPPTS 870.4300 OPP 83-5
Subchronic neurotoxicity study in rat	OPPTS 870.6200 OPP 82-7
Range finding oral toxicity study in rat	Not applicable
Other —Special studies	Not applicable
Dermal	
21/28-Day dermal toxicity in rat or rabbit	OPPTS 870.3200 OPP 82-2
90-Day dermal toxicity in rat	OPPTS 870.3200 OPP 82-2
Inhalation	
90-Day inhalation toxicity in rat	OPPTS 870.3465 OPP 82-4
21/28-Day inhalation toxicity in rat	OPPTS 870.3465 OPP 82-4
Inhalation carcinogenicity in rat	OPPTS 870.3320 OPP 83-5

c. Collection of Cholinesterase Activity Data

i. Oral Route

Oral relative potency values were needed for all OP pesticides included in the RCRA because of potential dietary exposures from food and drinking water and hand to mouth exposures associated with residential/nonoccupational uses. Numerous oral studies with comparable methodologies were available and suitable for quantitative dose-response analysis. An electronic spreadsheet is needed to perform quantitative dose-response analysis. Study type, duration of exposure,

number of animals per dose group, sex, compartment, and the measured effect for each dose group (mean cholinesterase activity, activity units, and standard deviation) were compiled into an electronic spreadsheet. In feeding studies, average compound intake (mg/kg/day) over the entire study was used. At least one oral toxicity study of the appropriate duration was available for all the OPs. Time of measurement was expressed as number of days on study where: number of days = number weeks x 7 and number of days = number months x 30.

ii. Dermal and Inhalation Route

Relative potency factors were needed for 10 OPs with residential exposure. Unlike the database of oral toxicity studies, the database of dermal and inhalation studies with cholinesterase measurements is limited. However, using the CEL approach is adequate for the RCRA. Comparative effect levels (CELs) have been used to compare the relative potency of the OPs. CELs are dose levels from a given study with a defined range of effects. The CEL was defined as the dose causing a maximum of 15% brain cholinesterase inhibition. Quantitative dose-response analysis for estimating a common benchmark response is the preferred method for determining relative potency.

d. Selection of Relative Potency Factors for the Female Brain Cholinesterase Data Set

A key component of cumulative hazard assessment is to select an endpoint pertinent to the common mechanism of toxicity that can be used to quantify cumulative risk. In the July 2001 dose-response assessment, OPP prepared a dose-response analysis for 25 OPs in which a large body of toxicity data on a common mechanism endpoint for these OPs – the ability to inhibit cholinesterase in plasma, RBC, and brain – was analyzed. To determine which compartment would provide a strong basis for determination of relative potency, OPP reviewed data in each compartment. In the July 2001analysis, RPFs based on the male RBC database were proposed. It was stated in that document that the RBC RPFs proved to be a reliable and sensitive endpoint considered protective of both the peripheral and central nervous systems for the majority of the chemicals. The major advantage of the RBC database was its large size compared to the whole brain ChE database; this large database allowed the examination of time course information and observation of a steady state response.

After considering the comments from the September 2001 SAP meeting in addition to the comments from the public and stakeholder groups, OPP has decided to use female brain ChE data for quantifying cumulative risk for OPs. OPP has decided to estimate cumulative risk based on RPFs and PODs from the female brain ChE database for

several reasons. Principally, compared to relative potency estimates based on RBC, estimates of relative potency based on brain ChE have tighter confidence intervals and therefore will confer less uncertainty on cumulative risk estimates. Also, these data represent a direct measure of the common mechanism of toxicity as opposed to using surrogate measures. The toxic potencies and PODs for brain cholinesterase inhibition for these OPs are generally similar to the RBC data for the oral, inhalation, and dermal exposures (USEPA, 2001b). The SAP recommended the Agency address the issue of repeated measures in its revised analysis. This issue concerning repeated cholinesterase activity measures only pertains to the plasma and RBC ChE data because blood can be collected several times from a single animal, whereas brain ChE can only be collected once. Finally, in the present analysis, although male and female rats were equally sensitive for 30 OPs, female rats were more sensitive to three OPs. Therefore, OPP has chosen to based its RPFs on female brain measurements.

In the RCRA, potency estimates have been recalculated only from the brain ChE database. The plasma and RBC databases were thoroughly examined in the July 2001 analysis (USEPA, 2001b). Re-analysis of the plasma and RBC databases using the revised methodology is unlikely to significantly change potency estimates from these compartments (USEPA, 2001c).

e. Determination of Chemical Potency: Oral Route

In their review of the September, 2000 pilot analysis, the SAP suggested that EPA consider Michaelis-Menton kinetics or the exponential model to fit cholinesterase data from OPs (FIFRA SAP, 2001a). Preliminary simulations using a subset of studies (one study per 24 chemicals) were performed using both the rectangular hyperbola (i.e., Michaelis-Mention kinetics) and the exponential function. The exponential model was selected over the rectangular hyperbola based on statistical criteria such as goodness of fit (USEPA, 2001b). Based on the results presented to the SAP in September, 2001, the panel indicated that no alternative to the exponential model would be more appropriate at the present time (FIFRA SAP 2001b).

i. Exponential Equations Used To Determine Potency

The simplified and general exponential equation used for modeling the effect of the OPs on cholinesterase activity is:

Equation I.B-1a

$$y = A\left[P_B + (1 - P_B)\mathrm{e}^{-m \times Dose} \right]$$

where ***y*** is cholinesterase activity,
Dose is the dose level of the OP, in mg/kg/day,
A is the background (similar to control) ChE activity,
m is the slope-scale factor,
and P_B is the horizontal asymptote (i.e., limiting value of minimum cholinesterase activity), expressed as a fraction of the background activity.

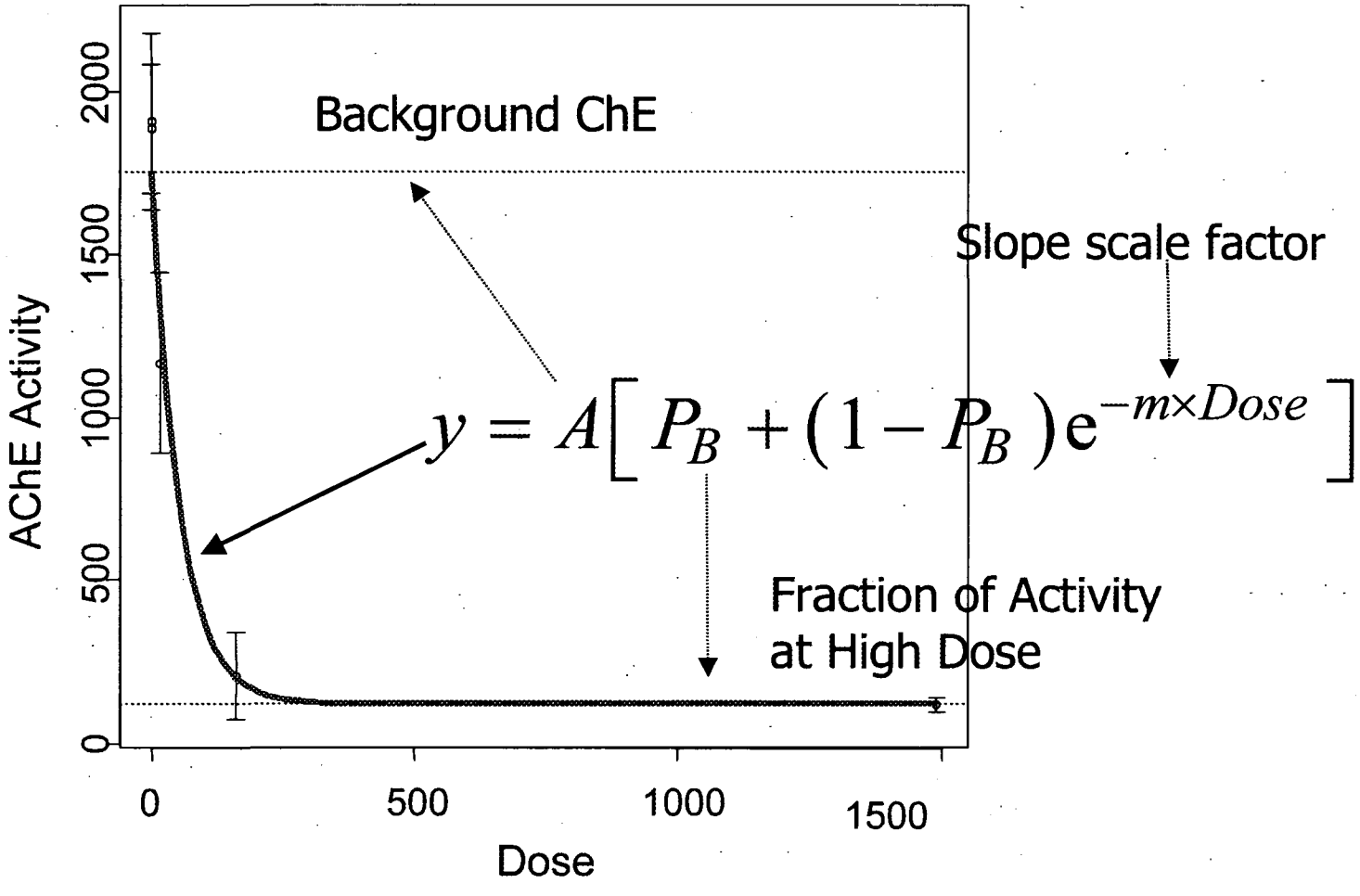
Both *y* (cholinesterase activity) and *dose* were extracted from the oral toxicity studies. P_B expresses the horizontal-asymptote as a fraction of background cholinesterase activity. P_B does not have any units. As described in detail in the technical appendix (III.B.1), Equation I.B-1a was reparameterized to Equation I.B-1b, where benchmark dose is an explicit parameter, to simplify the statistical calculations.

Equation I.B-1b

$$y = A\left[P_B + (1 - P_B)\,e^{-\frac{\log\left(\frac{1-P_B-BMR}{1-P_B}\right)}{BMD}\times Dose}\right]$$

where **A** is the level of cholinesterase activity in the absence of exposure to organophosphate (i.e., control),
P_B is the fraction of cholinesterase activity remaining at a very high dose of organophosphate,
BMR is the level of inhibition at which to estimate the benchmark dose (in this study, *BMR* is always 0.10),
BMD is the benchmark dose, and
Dose is the dose of organophosphate pesticide, generally in units of mg/kg/day.

Figure I.B-1. Plot of basic equation.



The exponential function in Equation I.B-1a/b decreases in a linear fashion in the low dose region (Figure I.B-1). Considerable discussion at the August 2001 Technical Briefing and the SAP meeting of September 5-6, 2001 centered around the potential for a flat region in the low dose portion of the dose-response curve. This potential low-dose flat region was explored and a revised equation was developed. This revised equation is a modified version of the exponential function in Equation I.B-1b which includes two additional variables, *S* (shape) and *D* (displacement). S and D together describe a low-dose flat region of the dose-response curve (Figure I.B-2). The second equation results from combining Equation I.B-1b with an equation which describes the relationship between administered dose and calculated internal dose (Equation I.B-2). The value *idose* replaces *Dose* in Equation I.B-1b. The SAP called this revised equation "elegantly simple" and pointed out that the equation improved fit for many OPs with little response at low dose levels. For ease of discussion, Equation I.B-1b will be called the '*basic*' model (low dose linear) and Equation I.B-2 will be called the '*expanded*' model (low dose flat).

Equation I.B-2

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

where ***idose*** is the scaled internal dose,
Dose is the administered dose level (mg/kg/day),
S controls the low-dose shape of the curve, and
D controls the ultimate horizontal displacement of the curve relative to the identity line (i.e., the line with *idose* = *Dose*).

As shown in Figure I.B-2, for the basic model, the low dose region decreases in a linear fashion. For the expanded model, the low-dose end of the dose-response curve has a more shallow slope (more flat). As *S* grows small, or *D* grows large, the estimated benchmark dose increases in magnitude. As *S* grows large, or *D* approaches 0, the relationship between *idose* and *Dose* approaches the line *idose = Dose. In other words, as S increases or D decreases, the shape of the expanded equation approaches the shape of the basic equation.* The technical discussion of the expanded model and its derivation are described in more detail in Appendix III.B.1.

Figure I.B-2 shows the relationship between the basic and expanded models and also how the shape and displacement variables impact the dose-response curve.

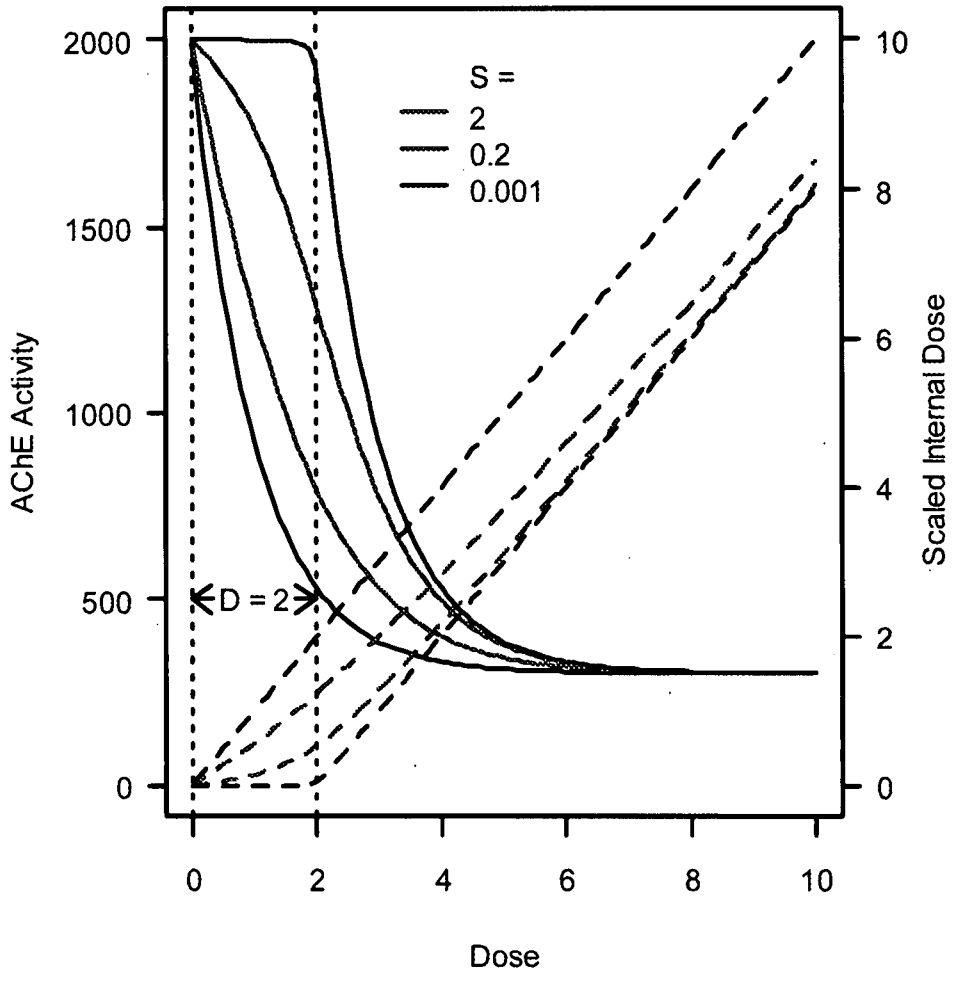


Figure I.B-2. Basic and expanded equations. The black solid curve is the basic equation of Equation I.B-2 with A = 2000, P_B = 0.15, and m = 1. The colored solid curves show the results of the expanded equation with 3 different values of S and D=2. The dotted curves shows the relationship between *idose* (blue, purple, and red) and *Dose* (black).

ii. Joint Analysis of OP Cholinesterase Data

In the joint dose-response analysis, the cholinesterase data for various time points for a specific chemical are modeled *together* all at once. For example, there are five measurements of female rat brain cholinesterase following exposure to methamidophos. All five datasets were analyzed together to determine the benchmark dose (although studies are plotted separately in Appendix III.B.2). This approach allows information about the shape of the dose-response curve to be "shared" among individual studies and results in benchmark dose estimates which are representative of a given OP. To perform the joint analysis of all the datasets for each chemical, several aspects of the data need to be accommodated . First, measurements of cholinesterase activities can have different units (mainly U/G, U/L, and ΔpH), which need to be accommodated in the same analysis. Model parameters may also differ between males and females. Finally, it is likely that model parameters vary randomly among studies and within a study. When more than measurement of brain cholinesterase was available, the approach to nonlinear mixed effects (nlme) modeling developed in Lindstrom and Bates (1990) was used to fit the cholinesterase data to Equations I.B-1b and I.B-2. Only one measurement of brain cholinesterase was available for four OPs; for these OPs generalized least squares (*gnls*) was used to fit the cholinesterase data. Profile likelihood plots were used to estimate the horizontal asymptotes, shape, and displacement parameters. All estimated parameters, including the shape and displacement parameters, were estimated separately for each OP and vary among OPs. The technical statistical methodology used to fit the cholinesterase data to the exponential model are not discussed here. The statistical methodology are discussed in detail in Appendix III.B.1.

Thirty-two OPs were fit to both the basic and expanded models. In cases where the expanded model resulted in a significantly improved fit ($P < 0.05$), the expanded model was used to estimate potency. The basic model was used to estimate the potency of the remaining OPs. Omethoate was modeled using only the basic model. At the time of public release for the revised RPFs only one measurement of brain cholinesterase in female rats with the appropriate duration of exposure was available for omethoate. In this dataset, ***all*** treatment groups exhibited reduced brain ChE activity compared to the control. Three other OPs have one dataset for female rat brain cholinesterase inhibition was available. For only one of these, dichlorvos, reduced cholinesterase activity was observed at all treatment groups. The expanded model did not improve the fit for dichlorvos; the basic model was used to estimate the potency. In addition, the potency of dimethoate, the parent chemical, of omethoate was estimated using the basic model. At this time, it is reasonable to assume that the expanded model would not improve the fit for omethoate.

iii. Use of BMD_{10} for Relative Potency Determination

Potency determinations of the OPs for the oral route exposure are based on the benchmark dose where cholinesterase activity is reduced 10% compared to background activity (BMD_{10}). The BMD_{10} was selected as the effect level for potency determination because this level is generally at or near the limit of sensitivity for discerning a statistically significant decrease in cholinesterase activity across the blood and brain compartments and is a response level close to the background cholinesterase.

At the February 5-8, 2002 meeting of the FIFRA SAP some members of the panel in addition to some public commenters discussed the Agency's selection of the BMD_{10} as the benchmark response level. In response to this discussion, the Agency analyzed the detection limits of the studies assessing female brain cholinesterase levels used in the RCRA of the OPs. This analysis has shown that generally these studies can reliably detect around 10% cholinesterase inhibition, that such levels were generally achieved in the studies, and that therefore, the Agency's use of the BMD_{10} as the benchmark response is appropriate. This analysis is described in detail in Appendix III.B.3

iv. Software Used in Oral Potency Determination

The programming code in R-language used to develop the relative potency factors and the PODs for the index chemical in the current analysis has been included in Appendix III.B.4.

In the July 2001 dose-response analysis, a computer program, OPCumRisk, was used to determine relative potency estimates and PODs for the index chemical. OPCumRisk was developed at ORD's NHEERL specifically for use in the July 2001 OP dose-response assessment and is available at http://www.epa.gov/scipoly/sap/index.htm. OPCumRisk is written in R (Ihaka and Gentleman, 1996), a freely distributable implementation of the S programming language available for download on the internet at http://www.R-project.org. Minor revisions recommended by the SAP have been incorporated into the OPCumRisk program (See Appendix III.B.3). The statistical methodology used in the present document has **not** been incorporated into the OPCumRisk program.

f. Determination of Chemical Potency: Dermal Route

Chemical potency was determined using CELs for the dermal route of exposure. These CELs are experimental dose levels which elicit a similar toxicological response to the selected endpoint.

Cholinesterase activity data were collected from dermal toxicity studies for nine chemicals with residential/nonoccupational exposure and the index chemical (methamidophos). Five OPs were tested by the dermal route in rats. Only rabbit studies were available for the other five OPs. Thus, it was not possible to compare cholinesterase activity data from dermal studies in only one species. Of the chemicals with potential dermal exposure, only three chemicals (acephate, disulfoton, and naled) had more than one dermal toxicology study which could be used for assessing relative potency. One chemical, dichlorvos, had no dermal exposure study. The requirement for a dermal toxicity study with dichlorvos was waived because the volatility of the chemical renders it technically difficult to conduct such a study.

Relative potencies of the chemicals with residential/non-occupational uses were determined by using CELs derived from data on inhibition of cholinesterase activity in female rat brain. The CEL was defined as the lowest dose where a maximum 15% brain cholinesterase inhibition (compared to control) occurred.

g. Determination of Chemical Potency: Inhalation Route

Chemical potency was determined using CELs for brain cholinesterase activity for the inhalation route of exposure. Cholinesterase activity data were collected from inhalation toxicity studies for seven chemicals with residential/nonoccupational exposure and the index chemical (methamidophos). Two inhalation exposure studies were available for acephate whereas only one suitable study was available for the other OPs. Although all of the inhalation studies were performed with the same species (rat), four different strains of rats were used. Furthermore, the exposure conditions varied among the chemicals tested. There were four whole-body exposure studies, one head-nose, and three nose only exposure studies. No inhalation toxicity study was available for three chemicals, bensulide, fenthion, and tetrachlorvinphos.

Relative potency was calculated from CELs for brain cholinesterase activity determined from inhalation toxicity studies. The CEL was defined as the lowest dose where a maximal response [brain cholinesterase inhibition] of 15% (compared to control) occurred.

h. Selection of the Index Chemical (Methamidophos)

The cumulative risk assessment guidance document (USEPA, 2002) states that the index chemical should be selected based on the availability of high quality dose-response data for the common mechanism endpoint and that it acts toxicologically similar to other members of the common mechanism group. High quality dose-response data allows the calculation of points of departure (POD) for oral, dermal, and inhalation exposures with confidence. A POD is a point estimate on the index chemical's dose-response curve that is used to extrapolate risk to the exposure levels anticipated in the human population. Thus, any error or uncertainty in an index chemical's POD value will be carried forward in the cumulative risk estimates. For the cholinesterase inhibiting OP pesticides, the ideal index chemical should exhibit high quality dose-response data in plasma, RBC, and brain for both sexes of a single species for all exposure routes of interest.

In the July 2001 dose-response assessment, methamidophos was selected as the index chemical for the OPs. The selection criteria and the potential candidates for the index chemical were discussed in detail in the July, 2001 document (USEPA 2001b). **Methamidophos remains the index chemical for the RCRA OPs because this chemical has a high quality database for the common mechanism endpoint of inhibition of acetylcholinesterase for the oral, dermal, and inhalation routes of exposure.**

i. Points of Departure (POD)

The oral, dermal, and inhalation PODs for the index chemical are based on the benchmark dose where cholinesterase activity is reduced 10% compared to background activity (BMD_{10}). The BMD_{10} was selected as the effect level for the POD because this level is generally at or near the limit of sensitivity for discerning a statistically significant decrease in cholinesterase activity across the blood and brain compartments and is a response level close to the background cholinesterase.

j. Calculation of Relative Potency Factors (RPF)

Oral RPFs were calculated from oral BMD_{10}s for female brain cholinesterase activity by the Equation I.B-3.

$$Oral\ RPF_{\text{Chemical X}} = BMD_{10\ \text{Index Chemical}} / BMD_{10\ \text{Chemical X}}$$

Equation I.B-3

where $BMD_{10\ \text{Chemical X}}$ is the BMD_{10} for Chemical X

and $BMD_{10\ \text{Index Chemical}}$ is the BMD_{10} of the index chemical.

CELs for brain cholinesterase activity measured in dermal studies were determined in order to calculate RPFs. Dermal RPFs were calculated using Equation I.B-4.

$$Dermal\ RPF_{\text{Chemical X}} = CEL_{\text{Index Chemical}} / CEL_{\text{Chemical X}}$$

Equation I.B-4

CELs for brain cholinesterase activity measured in inhalation studies were determined in order to calculated RPFs. Inhalation RPFs were calculated using Equation I.B-5.

$$Inhalation\ RPF_{\text{Chemical X}} = CEL_{\text{Index Chemical}} / CEL_{\text{Chemical X}}$$

Equation I.B-5

3. Results

a. Dose-Response Modeling: Oral Route of Exposure

The joint analysis using the exponential model served as good method for determining potency and provided confident estimates of the benchmark dose. The exponential model fits the cholinesterase data well. Plots of dose-response data, residuals, and profile likelihoods for all 33 OPs are given in Appendix III.B.2. BMD_{10}s and RPFs for the OPs are listed below.

i. Basic vs. Expanded Models

A joint analysis using the basic (low dose linear) and/or the expanded (low dose flat) equations of brain cholinesterase data for OPs was performed. The potency of 17 pesticides listed in Table I.B-2 were determined with the expanded model. The expanded model fit was significantly improved; i.e., the P-value of the likelihood test for the expanded model was ≤ 0.05 for all 17 chemicals. The potency of the remaining 16 were determined with the basic model.

Table I.B-3 shows the dose-response model parameters for the horizontal asymptote (P_B), shape (S), and displacement (D) parameters for each OP. These parameters vary among OPs.

Table I.B-2. Listing of OPs which were modeled with basic and expanded models

Listing of OPs which were modeled with basic and expanded models.		
Chemical	**Expanded vs. Basic**	**P value for the Improvement in Model Fit for Expanded vs. Basic**
Acephate	Basic	0.999
Azinphos-methyl	Expanded	3.04E-21
Bensulide	Expanded	0.0002
Chlorethoxyfos	Expanded	7.05E-24
Chlorpyrifos	Expanded	1.88E-13
Chlorpyriphos-methyl	Basic	0.96
Diazinon	Expanded	8.05E-21
Dichlorvos	Basic	0.77
Dicrotophos	Basic	0.998
Dimethoate	Basic	0.81
Disulfoton	Expanded	2.06E-10
Ethoprop	Basic	0.78
Fenamiphos	Basic	0.46
Fenthion	Basic	0.998
Fosthiazate	Expanded	2.73E-09
Malathion	Expanded	9.29E-13
Methamidophos	Basic	0.17
Methidathion	Basic	0.86
Methyl-parathion	Expanded	1.03E-07
Mevinphos	Expanded	0.0001
Naled	Basic	0.62
Omethoate	Basic	NA
Oxydemeton-methyl	Basic	0.9996
Phorate	Expanded	4.23E-28
Phosalone	Expanded	0.01
Phosmet	Expanded	5.20E-05
Phostebupirim	Expanded	0.001
Pirimiphos-methyl	Basic	0.99997
Profenofos	Basic	0.9999
Terbufos	Expanded	1.14E-32
Tetrachlorvinphos	Basic	0.39
Tribufos	Expanded	8.79E-13
Trichlorfon	Expanded	8.90E-06

Table I.B-3. Exponential model parameters for female and male brain cholinesterase data

Exponential model parameters for female and male brain cholinesterase data				
Chemicals	**Displacement[a] (D)**	**Shape[b] (S)**	**P_B Male[c]**	**P_B Female**
Acephate	--	--	0.295	0.286
Azinphosmethyl	0.597	0.001	0	0.082
Bensulide	22.066	0.110	0	0
Chlorethoxyfos	0.603	0.002	0	0
Chlorpyrifos	0.764	0.015	0.287	0.249
Chlorpyriphos-methyl	--	--	0.383	0.413
Diazinon	18.725	0.212	0.457	0.428
Dichlorvos	--	--	0.672	0
Dicrotophos	--	--	0.115	0.109
Dimethoate	--	--	0.331	0.364
Disulfoton	0.043	0.001	0.168	0.133
Ethoprop	--	--	0.304	0.313
Fenamiphos	--	--	0.720	0.750
Fenthion	--	--	0.230	0.200
Fosthiazate	11.560	0.006	0.128	0.098
Malathion	1415.734	2.913	0.800	0
Methamidophos	--	--	0.204	0.207
Methidathion	--	--	0.331	0.288
Methylparathion	0.351	0.007	0	0
Mevinphos	0.057	0.001	0.320	0.343
Naled	--	--	0.256	0.267
Omethoate	--	--	0	0.414
Oxydemeton-methyl	--	--	0.211	0.210
Phorate	0.235	0.002	0	0
Phosalone	4.502	1.222	0.090	0
Phosmet	1.379	0.027	0	0
Phostebupirim	0.097	0.005	0	0.052
Pirimiphos-methyl	--	--	0.769	0.610
Profenofos	--	--	0	0.496
Terbufos	0.211	0.005	0	0
Tetrachlorvinphos	--	--	0	0
Tribufos	1.775	0.046	0	0
Trichlorfon	28.437	0.189	0	0.400

a. *D* controls the horizontal displacement of the curve; b. *S* controls the low-dose shape of the curve; c. P_B is the horizontal asymptote, expressed as a fraction of the background activity. Parameters for S and D are only available for those chemicals with the expanded model

ii. Benchmark Dose Calculations

The BMD_{10}s for brain cholinesterase measured in male and female rats using the joint analysis procedures are listed in Table I.B-4 and shown graphically in Figures I.B-3 and I.B-4. Among the OPs, BMD_{10}s range widely over approximately five orders of magnitude.

Ratios of the male to female BMD_{10}s are plotted in Figure I.B-5. For 30 of 33 OPs the ratio is approximately one indicating that male and female rats exhibit similar sensitivity to the OPs for brain cholinesterase activity. For these three OPs (terbufos, tetrachlorvinphos, and trichlorfon) the females rats were ~2- to 7-fold more sensitive compared to male rats.

Table I.B-4. Oral BMD_{10}s and BMDLs (mg/kg/day) estimated for brain ChE activity

Oral BMD_{10}s and BMDLs (mg/kg/day) estimated for brain ChE activity				
Chemical	Female		Male	
	BMD_{10}	BMDL	BMD_{10}	BMDL
Acephate	0.99	0.53	0.77	0.41
Azinphos-methyl	0.86	0.79	1.14	0.98
Bensulide	31.91	30.44	40.88	37.11
Chlorethoxyfos	0.65	0.61	0.69	0.62
Chlorpyrifos	1.48	1.26	1.50	1.27
Chlorpyriphos-methyl	16.20	4.77	14.26	4.21
Diazinon	6.24	2.89	9.62	5.39
Dichlorvos	2.35	1.61	1.71	0.08
Dicrotophos	0.04	0.04	0.04	0.03
Dimethoate	0.25	0.22	0.35	0.31
Disulfoton	0.07	0.06	0.10	0.09
Ethoprop	1.37	0.70	1.35	0.69
Fenamiphos	1.96	0.69	1.73	0.63
Fenthion	0.24	0.21	0.18	0.15
Fosthiazate	1.28	0.32	1.48	0.38
Malathion	313.91	221.12	212.02	119.31
Methamidophos	0.08	0.07	0.07	0.06
Methidathion	0.25	0.17	0.24	0.16
Methyl-parathion	0.67	0.50	0.70	0.51
Mevinphos	0.11	0.10	0.15	0.13
Naled	1.00	0.82	1.00	0.82
Omethoate	0.09	0.07	0.14	0.12
Oxydemeton-methyl	0.09	0.09	0.07	0.07
Phorate	0.21	0.20	0.29	0.26
Phosalone	6.93	6.27	7.88	7.05
Phosmet	3.56	2.03	4.15	2.25
Phostebupirim	0.37	0.24	0.40	0.26
Pirimiphos-methyl	2.25	1.61	1.58	0.93
Profenofos	20.58	17.64	24.98	21.86
Terbufos	0.10	0.08	0.18	0.17
Tetrachlorvinphos	60.69	20.97	369.27	102.31
Tribufos	4.27	3.31	4.52	3.47
Trichlorfon	31.74	28.62	58.49	45.39

Figure I.B-3. BMD_{10}s (mg/kg/day) for female brain ChE activity for 33 OPs

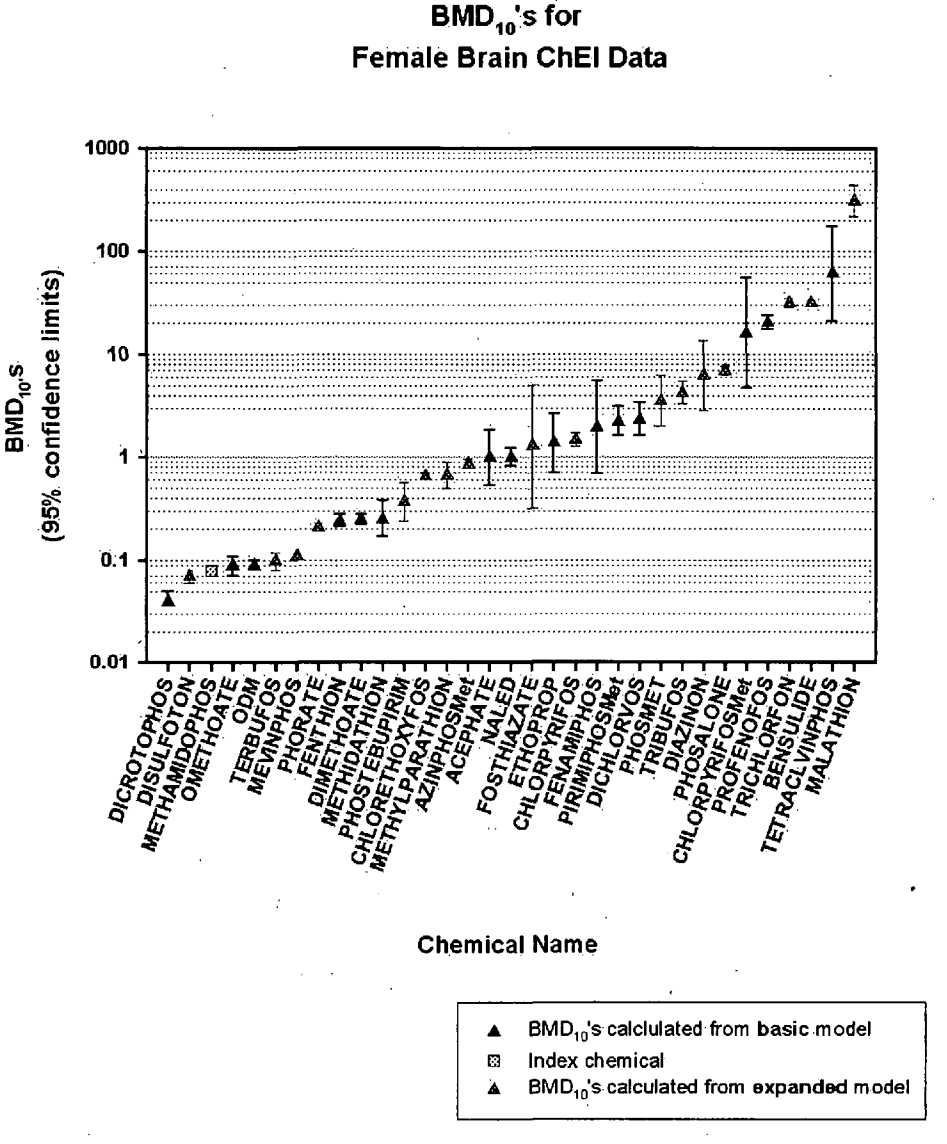


Figure I.B-4. BMD_{10}s (mg/kg/day) for male brain ChE activity for 33 OPs

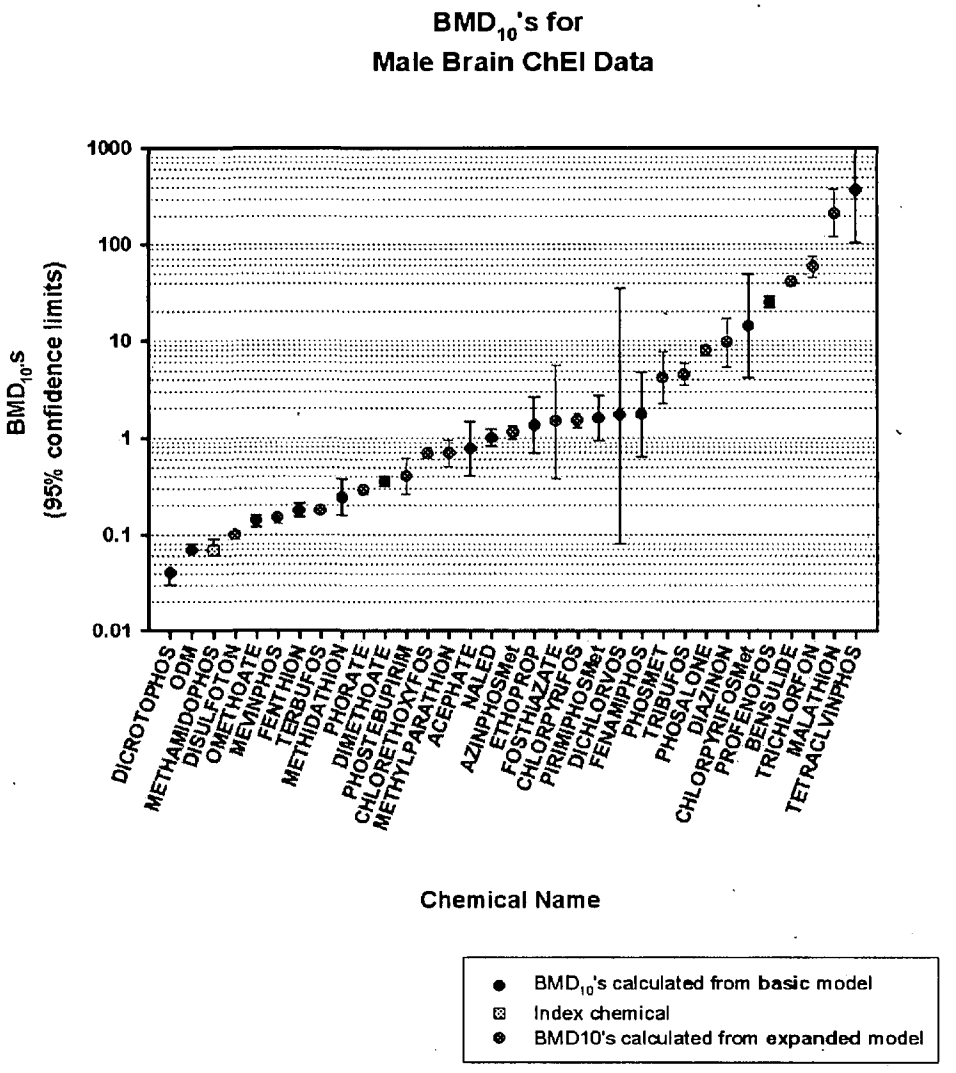
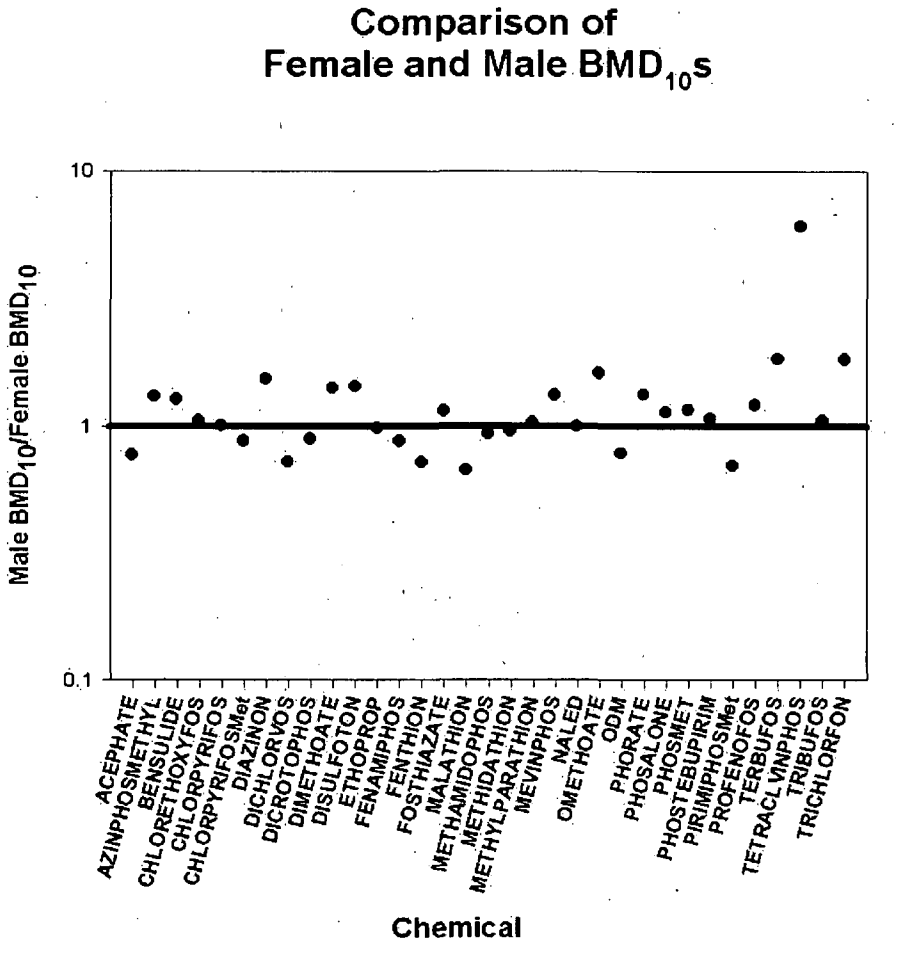


Figure I.B-5. Comparison of BMD_{10}s (mg/kg/day) for female and male brain ChE activity for 33 OPs



b. CELs Determined for Dermal Endpoints for OPs with Residential/Nonoccupational Exposure

Table I.B-5 lists CELs and the next higher dose levels for brain ChE inhibition from dermal exposure studies of OPs with residential/occupational exposure plus the index chemical, along with the level of ChE inhibition (compared to control values).

Table I.B-5. CELs for brain and RBC cholinesterase activity from dermal exposure studies (% cholinesterase inhibition compared to control value)

Chemical	Species	Male Brain CEL mg/kg/day	Male Brain Next Higher Dose mg/kg/day	Female Brain CEL mg/kg/day	Female Brain Next Higher Dose mg/kg/day
Acephate	rat	300 9%	>300* 9%	**300** **14%**	>300* 14%
Bensulide	rat	500[a] 0-9%	>500*[a] 0-9%	**500[a]** **2-10%**	>500*[a] 2-10%
Dichlorvos	Dermal exposure study waived due to volatility of compound.				
Disulfoton	rabbit	1.6 7%	3 55%	**1.6** **8%**	3 27%
Fenamiphos	rabbit	10 * 0%	>10 * 0%	**0.5** **0%**	2.5 18%
Fenthion	rabbit	100 13%	150 65%	**50** **13%**	100 24%
Malathion	rabbit	300[a] 2%	1000[a] 65%	**50[a]** **0%**	300[a] 19%
Methamidophos	rat	0.75 0%	11.2 41%	**0.75** **5%**	11.2 38%
Naled	rat	10 0%	20 60%	**10** **0%**	20 60%
Tetrachlorvinphos	rat	1000 0%	>1000 * 0%	**1000** **0%**	>1000 * 0%
Trichlorfon	rabbit	1000 0%	>1000 * 0%	**100** **4%**	300 18%

* Highest dose tested.

c. CELs Determined for Inhalation Endpoints for OPs with Residential/Nonoccupational Exposure

Table I.B-6 lists CELs for brain cholinesterase inhibition determined for inhalation toxicity studies for OPs with residential/nonoccupational exposure plus the index chemical, along with the level of cholinesterase inhibition (compared to control values).

Table I.B-6. CELs for brain and RBC cholinesterase activity from inhalation toxicity studies (% cholinesterase inhibition compared to control value)

Chemical	Method	Male CEL (mg/kg/day)	Male Next higher dose (mg/kg/day)	Female CEL mg/kg/day	Female Next higher dose (mg/kg/day)
Acephate	nose only	1.419 14%	1.419* 14%	**1.492** **13%**	1.492* 13%
Bensulide	No inhalation toxicity study was available for bensulide				
Dichlorvos	whole body	0.436 10%	0.436 10%	**0.458** **11%**	0.458 11%
Disulfoton	nose only	0.044 4%	0.384 24%	**0.047** **5%**	0.410 28%
Fenamiphos	nose only	0.928 0%	>0.928* 0%	**0.984** **0%**	>0.984* 0%
Fenthion	No inhalation toxicity study was available for fenthion				
Malathion	whole body	115 3%	514 17%	**121** **8%**	540 41%
Methamidophos	head/ nose	0.292 8%	1.432 29%	**0.310** **11%**	1.520 25%
Naled	whole body	0.354 0%	1.594 38%	**0.378** **4%**	1.702 46%
Tetrachlorvinphos	No inhalation toxicity study was available for tetrachlorvinphos.				
Trichlorfon	whole body	9.388 0%	27.44 21%	**3.574** **0%**	9.96 27%

*Highest dose tested.

d. Points of Departure for the Index Chemical (Methamidophos)

Table I.B-7 lists the PODs and no-observed-adversse-effect-levels (NOAELs) for the oral, dermal, and inhalation routes for methamidophos. The PODs for all three routes were calculated with dose-response modeling using the basic model of Equation I.B-1. OPP has used these endpoints in the RCRA.

Brain cholinesterase was only measured once (at study termination) in the methamidophos 21-day dermal and 90-day inhalation studies. Therefore only one data set was available for calculation of the PODs for these routes.

Within route of exposure, the BMD_{10}s for brain cholinesterase shown in Table I.B-6 were similar for males and females. The values of the BMDLs were close to the BMD_{10}s. This observation increases the confidence not only in the selection of methamidophos as the index chemical but also the utilization of the central estimate of the female data (BMD_{10}) for cumulative risk extrapolation rather than its lower limit (BMDL). It is notable that the BMD_{10} and BMDL values were similar to but slightly larger than NOAELs established for the oral (chronic NOAEL used for RfD derivation), dermal, and inhalation routes.

Table I.B-7. Points of departure for index chemical (methamidophos) by route of exposure for brain cholinesterase activity measured in female and male rats

Route of Administration	Sex	BMD_{10} (mg/kg/day)	BMDL (mg/kg/day)	NOAELs (mg/kg/day)
Oral[a]	F	**0.08** [d]	0.07	0.03*
	M	0.07	0.06	
Dermal[b]	F	**2.12** [d]	1.77	0.75
	M	1.88	1.41	
Inhalation[c]	F	**0.39** [d]	0.21	0.31
	M	0.30	0.20	0.29

[a]MRID nos. 41867201, 43197901, 00148452
[b]MRID no. 44525301
[c]MRID no. 41402401
[d]PODs for RCRA of OPs.
*NOAEL used for chronic RfD derivation in the single chemical assessment.

e. Relative Potency Factors (RPFs)

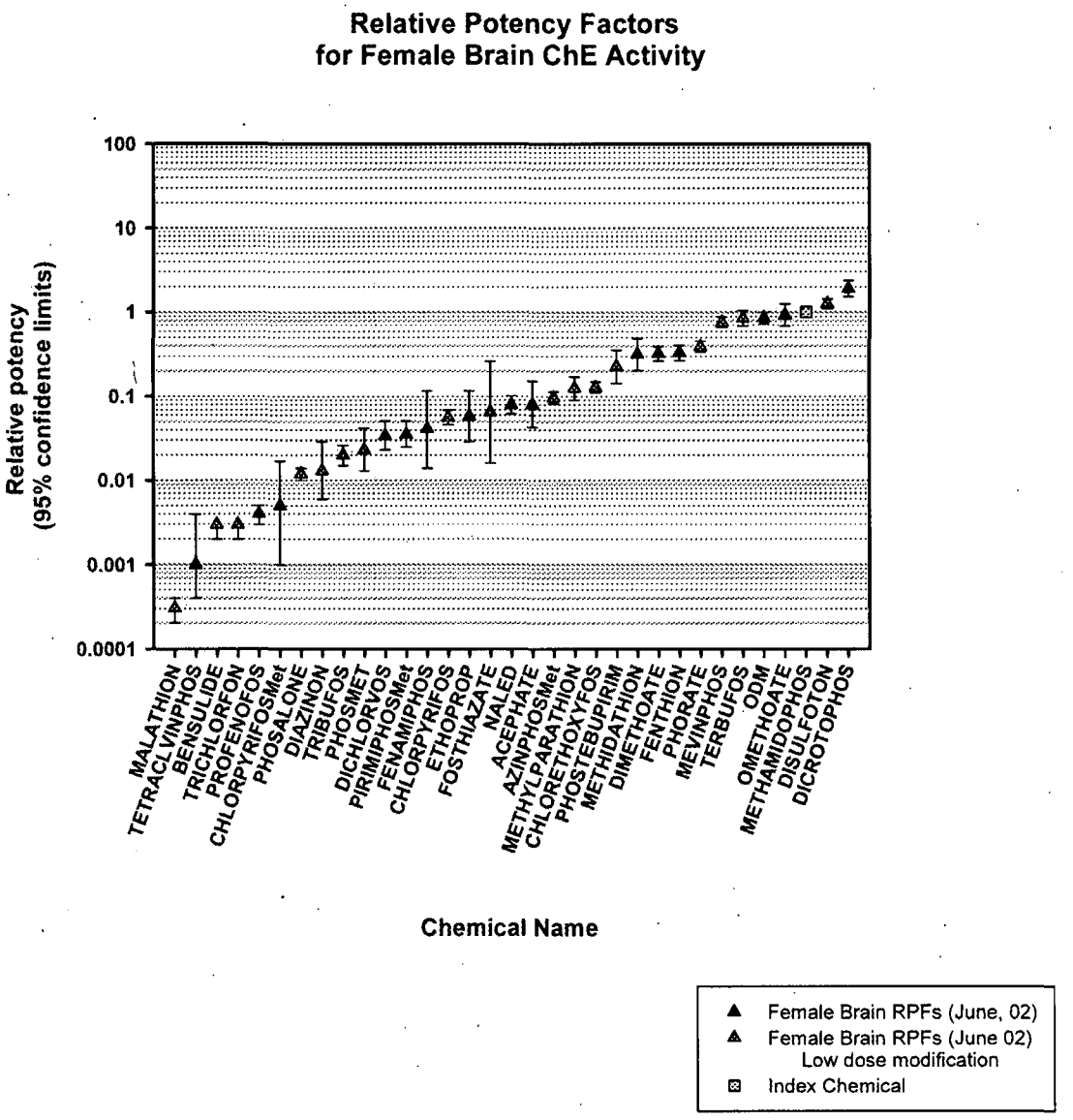
Table I.B-8 provides the RPFs for the oral, dermal, and inhalation routes of exposure based on brain cholinesterase in female rats which were used in the RCRA for OPs. Figure I.B-6 shows the oral RPFs with 95% confidence limits.

These values were calculated with Equations I.B-3, I.B-4, and I.B-5 for oral, dermal, and inhalation routes, respectively, and using methamidophos as the index chemical. BMD_{10}s for all of the chemicals are listed in Table I.B-4. Dermal and inhalation CELs are given in Tables I.B-5 and I.B-6. Although a model-derived oral RPF was determined for fosthiazate, this is a new OP that is not yet registered. Fosthiazate has no appropriate monitoring data to support characterization of exposure from food, and therefore, was not included in the quantification of cumulative risk.

Table I.B-8. Relative potency factors for the oral, dermal, and inhalation routes of exposure

Relative Potency Factors for Female Brain Cholinesterase Activity			
Chemicals	**Oral**	**Dermal**	**Inhalation**
Acephate	0.08	0.0025	0.208
Azinphos-methyl	0.10		
Bensulide	0.003	0.0015	
Chlorethoxyfos	0.13		
Chlorpyrifos	0.06		
Chlorpyrifos-methyl	0.005		
Diazinon	0.01		
Dichlorvos	0.03		0.677
Dicrotophos	1.91		
Dimethoate	0.32		
Disulfoton	1.26	0.47	6.596
Ethoprop	0.06		
Fenamiphos	0.04	1.5	0.315
Fenthion	0.33	0.015	
Fosthiazate	0.07		
Malathion	0.0003	0.015	0.003
Methamidophos	1.00	1.00	1.00
Methidathion	0.32		
Methyl-parathion	0.12		
Mevinphos	0.76		
Naled	0.08	0.075	0.82
Omethoate	0.93		
Oxydemeton-methyl	0.86		
Phorate	0.39		
Phosalone	0.01		
Phosmet	0.02		
Phostebupirim	0.22		
Pirimiphos-methyl	0.04		
Profenofos	0.004		
Terbufos	0.85		
Tetrachlorvinphos	0.001	0.00075	
Tribufos	0.02		
Trichlorfon	0.003	0.0075	0.087

Figure I.B-6. Relative potency factors for female brain ChE activity for 33 OPs



4. Discussion

a. Determination of Relative Potency

With the passage of the FQPA in 1996, EPA was faced with numerous challenges such as the reassessment of 66% of all tolerances by 2002 and notably the development of methodology for doing cumulative risk assessment. As part of the methodology development, EPA has participated in the public process with technical briefings and reviews by outside experts who make up the SAP. The SAP has offered constructive and thoughtful guidance in the development of the hazard and dose-response component of cumulative risk assessment. With each review, EPA has taken the recommendations into consideration and has made appropriate revisions or refinements. The analysis performed for the OPs represents an innovative and novel approach to hazard and dose-response assessment, and by taking advantage of the large database of oral toxicity studies in adult rats available to OPP, offer a comprehensive review of the common mechanism endpoint (i.e., cholinesterase inhibition) from available toxicity studies in adult animals. By incorporating dose-response information from multiple studies into one estimate of potency for the oral route, potency estimates are representative of the overall toxicity of each pesticide.

Adult cholinesterase data for many OPs has been extensively analyzed for plasma, RBC, and brain ChE response (USEPA 2001b, 2001c). OPP has generated an extensive database of ChE data that is available to the public. This large database has allowed OPP to investigate sex differences among rats, study-to-study variability for over 75 studies, time course data ranging from 21 days to > 2 years of exposure, and steady state response. The joint analysis allowed the exploration of low dose issues using a sophisticated model. The joint analysis using the exponential model resulted in high confidence RPFs and PODs that are representative of the OPs.

The data for the inhalation and dermal routes were less extensive compared to the oral route. Potency estimates using CELs from the dermal and inhalation studies are not as robust as those calculated for the oral route but are adequate for use in the cumulative assessment. It is also notable that the relative order of estimated potencies for all three routes of exposure are consistent with current knowledge about their toxicology.

The selection of methamidophos as the index chemical was supported by the SAP. Methamidophos had the highest quality database for the common mechanism endpoint in three routes of exposure and three biological compartments. The PODs calculated with methamidophos have narrow confidence limits which reduces overall uncertainty in the cumulative risk assessments. In this assessment, administered dose was used to estimate RPFs and PODs. At this time there are inadequate pharmacokinetic data for

these OPs to incorporate information about dose at the target site or species to species extrapolation.

b. Dose Additivity

The cumulative risk assessment for the OPs is based on the assumption of dose additivity. Dose additivity is the Agency's assumption when evaluating the joint risk of chemicals that are toxicologically similar and act at the same target site (USEPA 2001a). The SAP (FIFRA SAP, 2001a) indicated that substantial reliance would have to be placed on what is known about the mechanism of toxicity because it is very difficult to prove dose additivity at human exposure levels. They further pointed out that studies available on individual chemicals were usually not designed to address the issue of dose additivity.

The mathematical definition of dose addition requires a constant proportionality among the effectiveness of the chemicals (USEPA 2001a; Hertzberg et al.,1999). Thus, an important objective in the dose response assessment is to evaluate whether dose-response relationships are consistent with the assumption of dose additivity. There is some uncertainty surrounding the assumption. Two different versions of the exponential model have been used in this assessment. Approximately half of the pesticides were fit using a model with a flat low dose region while the remaining OPs were fit using a model which is linear in the low dose region. In addition, the OPs did not exhibit a common horizontal asymptotes (P_B); rather the P_Bs vary among chemicals. Both of these factors indicate that the dose-response curves are not parallel.

Dose additivity assumes that the common mechanism chemicals behave in a similar fashion (i.e., same pharmacokinetics and pharmacodynamics). In reality, these common mechanism chemicals may not behave ideally (i.e., the exact same pharmacokinetics and pharmacodynamics). Biotransformation of OPs is extremely complex and involves several metabolic systems in different organs (e.g., reactions involving cytochrome P450 isoenzymes, hydrolysis by esterases, and transferase reactions; see Nigg and Knaak, 2000). The differential activation and/or deactivation of OP pesticides has not been well documented in the literature, nor have the human metabolic pathways (Mileson et al., 1998). At this time, these pesticides can not be separated into subgroups based on pharmacokinetic or pharmacodynamic characteristics. Thus, current information on OP metabolism does not provide a sufficient basis to depart from dose additivity at low levels of exposure anticipated to be encountered environmentally.

The application of dose additivity requires the assumption of no interactions other than additive among the chemicals at low doses. There are a limited number of investigations of the toxicity of combinations of organophosphorus substances, not necessarily pesticides, that are known to

inhibit cholinesterase enzymes (For example see Dubois, 1961 and 1969; Frawley et al., 1957 and 1963; Calabrese, 1991; Cohen, 1984; Eto, 1974; Su et al., 1971; Casida et al., 1963; Keplinger and Deichman, 1967; Rosenberg and Coon, 1958; El-Sebee, et al., 1978; Seume and O'Brien, 1960; Singh, 1986; Mahajna et al., 1997; Serat and Bailey, 1974; Richardson, et al., 2001; Karanth et al., in press; Abu-Qare , et al., 2001a; Abu-Qare et al., 2001b). Most of the studies reviewed were high dose studies that investigated the acute lethality (LD_{50}) of combinations, mostly binary, and not the cumulative effects of low exposure levels from multiple OPs. A number of these studies were conducted using intraperitoneal (i.p.) administration which confounds interpretations of effects that may be expected by the oral, dermal, or inhalation routes.

Overall, the studies reported in the literature do not provide a basis for concluding that interactions between OPs will result in significant departure from dose addition at low doses. Nevertheless, this literature provides data showing that different types of interactions can occur between OPs and that the magnitude of the interaction appears to depend on the specific combination of OPs investigated, the dose-levels administered, and also the sequence of exposure (Singh, 1986; Pope and Padilla, 1990). In particular, the data available are not sufficient to establish the nature of interactive effects on cholinesterase activity that may be expected among OPs at low exposure levels.

The OPs all act on the same target site– namely, the inhibition of acetylcholinesterase by phosphorylation in nerve tissue, which elicits a variety of cholinergic effects. Dose addition is regarded as a reasonable and appropriate approach for estimating the cumulative risk associated with joint exposure to the OP common mechanism group. At this time, there is not sufficient basis to depart from dose additivity.

Although a biological or pharmacokinetic modeling approach would be preferred to determine the cumulative risk for these OPs, the input parameters for such an approach are not available. Thus, the pharmacokinetic (PK) characteristics of the OPs could not be incorporated in the dose-response assessment which would allow for a more refined estimate of the combined risk to humans. Therefore, OPP has applied simple dose addition and used an empirical curve fitting model (i.e., the exponential model) to determine RPFs and PODs.

c. Future Directions in Cumulative Dose-Response Assessment: Physiologically Based Pharmacokinetic (PBPK) Modeling

Physiologically based pharmacokinetic (PBPK) models, which describe the time course disposition of chemicals and their metabolites, are well suited to help assess cumulative risk. PBPK models are excellent tools to quantify the cumulative toxicity that can result from multiple exposures (multiple

exposures and multiple pathways) and from exposure to multiple chemicals with a common mechanism or mode of action. These models typically are systems of first order differential equations describing the mass balances and disposition of the chemicals and their metabolites in the body. While these models are excellent tools, numerous input parameters are necessary for each chemical. Organ specific thermodynamic parameters (such as tissue to blood equilibrium partition coefficients) are required for each pesticide entering the body and for each of its metabolites. Additionally, values for all of the metabolic rates governing all the biotransformation steps for each pesticide would be necessary. The complex processes for the common mechanism effect would be necessary. Using the OPs as an example, compound specific inputs such as binding constants and values for the rates of enzyme degradation, aging, and resynthesis would be needed.

ORD's National Exposure Research Laboratory (NERL) has formulated such a model that has been used to simultaneously model the disposition of three OPs and their metabolites (Blancato, et al., in review). Another PBPK model has been developed to describe the complex pharmacodynamics of acetylcholinesterase inhibition following OP exposure, based almost entirely on *in vitro* information (Gearhart, et al., 1994). Timchalk et al. (2002) developed a PBPK model for chlorpyrifos and and its major metabolites.

At present, these types of data/information on the majority of the OPs are not available to EPA. PBPK modeling techniques offer good promise despite the current limitations regarding the necessary input information. Continued development and testing of the models is necessary and should be pursued. Pharmacokinetic studies (*in vivo* and *in vitro* experiments to determine key values for PK parameters and the time course disposition of the compounds in the body) need to be done with many compounds to determine the key parameters of use in PBPK modeling. It is anticipated that data and methods will continue to improve and evolve as more experience is gained in this area.

I. Revised OP Cumulative Risk Assessment

C. Cumulative Risk From Pesticides in Foods

1. Introduction to Food

The cumulative dietary risk due to the use of Organophosphorus (OP) Chemicals on food crops was assessed using residue monitoring data collected by the United States Department of Agriculture's Pesticide Data Program (USDA-PDP) supplemented with information from the Food and Drug Administration Center for Food Safety and Applied Nutrition (FDA/CFSAN) monitoring data. The BMD10 for brain cholinesterase inhibition in female rats was chosen as the Toxicological Point of Departure (POD) for this assessment. Methamidophos served as the index chemical. The residue values for the other OP chemicals were converted to methamidophos equivalents by a Relative Potency Factor (RPF) approach. Residue data were collected on approximately 44 food commodities monitored by PDP between the years of 1994 and 2000. Food processing factors were applied to specific chemical/commodity pairs to extend these data for use on cooked and processed food/food forms in the analysis. The PDP residue data were further extended to other commodities identified as reasonable for translation of pesticide residue data per OPP/HED SOP 99.3 (USEPA, 1999b); see Appendix III.C.4. Other food commodities, not included in the PDP database, were incorporated using FDA monitoring data. The residue estimates incorporated in the assessment represent approximately 97 percent of the per capita food consumption for children aged 1 to 2 years (the most highly exposed age group) in the Continuing Survey of Food Intakes by Individuals for the years 1994-1998.

The residue data were compiled as distributions of cumulative residues of methamidophos equivalents and, after application of processing factors and FQPA factors, were summed on a sample-by-sample basis. These residue distributions were combined with a distribution of daily food consumption values *via* a probabilistic procedure to produce a distribution of potential exposures for multiple subpopulations in the CSFII 1994-1998 (Infants less than 1, Children 1-2, Children 3-5, Children 6-12, youth 13-19, Adults 20-49, and Adults 50+ years old). The most highly exposed age group was confirmed to be Children 1-2 years old.

2. Sources of Residue Data

a. USDA-PDP

The PDP program has been collecting pesticide residue data since 1991, primarily for purposes of estimating dietary exposure. The program is designed to focus on foods highly consumed by children and to reflect foods typically available throughout the year. Foods are washed and inedible portions are removed before analysis. This database is the primary source for residue data used in the current assessment, and data collected between 1994 and 2000 were included. A complete description of the PDP program and all data through 2000 are available on the Internet at http://www.ams.usda.gov/science/pdp. A summary of the PDP residue data on OP chemicals is shown in Appendix III.C.2. Appendix III.C.1 lists all of the food forms for which estimated residues were based on PDP data.

b. Market Basket Study of OP Residues in Apple Sauce

The Apple Processors Association sponsored a market basket study of OP pesticide residues in apple sauce samples collected in 1999. These data are incorporated in the current assessment for residue estimates on apple sauce and baby food apple sauce. The residue data on these samples are summarized in Appendix III.C.2.

c. FDA/CFSAN Surveillance Monitoring Data

The FDA Surveillance Monitoring Program is designed primarily for enforcement of EPA pesticide tolerances on imported foods and domestic foods shipped in interstate commerce. Domestic samples are collected as close as possible to the point of production in the distribution system. Import samples are collected at the point of entry into U.S. commerce. The emphasis in sample collection is on the agricultural commodity, which is analyzed as the unwashed, whole (unpeeled), raw commodity. Processed foods are also included in the program. A description of the program and residue data for recent years can be found on the Internet at http://vm.cfsan.fda.gov/~lrd/pestadd.html. Because the emphasis of this program is not on dietary exposure, it is being used in the current assessment mostly as a semi-quantitative check on the potential for residues and as support for data from other sources. The program has extensive data available on eggs and fish and these data support the judgement that the OP residues are negligible on these foods as consumed. Appendix III.C.1 indicates the food forms for which exposure estimates were supported by this program.

d. FDA/CFSAN Total Diet Study (TDS)

The TDS has provided data on dietary intake of food contaminants for about 40 years. A program description and residue data can be found at the same Internet site listed above for FDA Surveillance Monitoring Data. Foods are purchased in grocery stores, generally 3 or 4 times a year, prepared and cooked for consumption, and analyzed by highly sensitive multiresidue methods. Between 1991 and 1999 there have been 26 market baskets collected and approximately 260 foods analyzed for, among other things, OP pesticide contamination. A disadvantage of these data is that only one sample is analyzed of each food in each market basket. For this reason these data have been used primarily as semi-quantitative support for judgements on residues in foods. An exception is made in this assessment for the estimate for residues in meats other than poultry. Multiple forms and tissues of beef, pork, lamb, and meat byproduct cold cuts have been analyzed in all of the market baskets with only limited residues of OP pesticides on a few of the meats at low levels. In an effort to include residue estimates for all highly consumed foods, a conservative estimate for meat commodities was based on the TDS Data. A maximum residue level was used for each meat based on the TDS. The meat commodities included on this basis are identified in Appendix III.C.1 and the residue data are summarized in Appendix III.C.3.

3. OP Pesticides Included in Cumulative Assessment

All of the OP analytes detected in the PDP program are included in the current assessment. See Appendix III.C.2 for a complete summary of the analyses for OP pesticides and metabolites on each food commodity in the database. There have been significant numbers of analyses for 67 OP active ingredients, degradates, or metabolites between 1994 and 2000. A total of 39 of these OP analytes have been detected in at least one of the foods analyzed. After exclusion of data on pesticides that have been canceled or do not have food uses, and combining data for metabolites and degradates, there are positive analytical data being used for 20 OP pesticides. These are the following:

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

Naled has not been separately analyzed generally and residues from this use would be reflected in the dichlorvos analyses. Bensulide is not included in the PDP data; however, negligible residues would be expected in foods based on field trial data submitted for registration purposes. Cadusafos is not represented in the PDP data but the only registered use that could potentially result in food residues is as a nematacide soil application on bananas that are imported into the United States. Field trial data submitted for registration/tolerances purposes indicate that residues will not occur in the edible portion of the banana. Chlorethoxyfos is not included in PDP data but its only food use is soil application to corn crops at a low rate; therefore, significant residues in edible portions and processed foods from corn would not be expected. Dicrotophos, not included in PDP data, has one food use on cotton. Cottonseed oil is the only food commodity of cotton and it is not included in the current assessment, but the impact of the chemical on dietary (food) exposure is expected to be low due to the extent of refining and blending of the oil. Tebupirimphos (phostebupirim) has one food use on corn, mainly to control root worm. Significant contribution to cumulative food exposure is not expected. Profenofos is used on cotton, which is not included in the current assessment for the reasons stated above. Trichlorfon has no food uses except for an overseas use as pour-on treatment of beef cattle. Tetrachlorvinphos is used only on livestock or livestock premises. Potential residues from the two latter livestock uses are anticipated to be covered by the conservative cumulative residue estimate for meat commodities.

4. Foods Included in the Food Risk Assessment

The universe of foods included in the cumulative dietary exposure assessment is defined by the USDA CSFII for the years 1994-1996 with supplementary data on children obtained in 1998. The survey data, CSFII 1994-1998, is integrated into DEEM-FCID™. Appendix III.C.1 lists all of the foods in CSFII 1994-1998 in decreasing order of their relative per capita consumption by children 1-2 years old and children 3-5 years old. Each food is assigned a percent of relative consumption which was estimated in the following manner: the per capita consumption of each food was summed for all children in the survey in the two age groups. These consumptions were totaled for all foods in the survey and the individual sums for each food were expressed as a percent of the total. This measure of relative consumption is used as a partial indication of the potential significance of a given food in the diet of children.

According to the above described measure of relative consumption, the available PDP data were used either directly or with processing factors to estimate cumulative residues in foods accounting for about 88% of the per capita consumption of children 1-2 years old. PDP data were used for the top 10 ranked foods and for 24 out of the top 30 foods. Apple sauce, which was supported by special study data, account for about 1% of the consumption by children 1-2 years old.

Residues in other foods were estimated using translated PDP data according to HED SOP 99.3, (USEPA, 1999b) as summarized in Appendix III.C.4. Translations included only residues for chemicals registered on the food being simulated. These foods account for about 1% of the per capita consumption of children 1-2 years old.

Surveillance monitoring data from FDA include extensive analysis of eggs and fish with the implication that OP residues would not be expected to occur in significant amount on these two categories of foods. The TDS data from FDA indicate a similar situation for livestock meats. In this case a conservative estimate of residues was incorporated into the assessment, i.e., meats were assumed to always be contaminated with OP residues equal to the maximum values found in the TDS market baskets (see Appendix III.C.3 for a summary of TDS data used). These foods being supported by FDA data, i.e., eggs, fish, and meat, account for about 5% of the per capita consumption of children 1-2 years old.

PDP has analyzed high fructose corn syrup and found no OP residues but has not analyzed any other sugar or syrup sources. The FDA TDS has analyzed refined sugar and maple sugar and found no OP residues in 26 market baskets. A knowledge of the highly refined nature of sugars and syrups supported by the limited residue data mentioned above is the basis for assuming that negligible residues of OP pesticides would be expected to occur in sugars and syrups. Therefore, residues were assumed to be zero for these foods derived from sugarcane, sugar beet, and maple. These foods account for about 2% of the per capita consumption of children 1-2 years old.

The food forms not included in the current assessment account for almost 3% of the per capita consumption of children 1-2, distributed among many food forms. Table I.C-1 summarizes the relative consumption of foods in the assessment for children 1-5 years old. The information is provided in detailed form in Appendix III.C.1.

Table I.C-1. The Proportion of the Diet of Children (1-5 years old) Covered in the Cumulative Food Assessment

Source of Residue Estimate	Percent of Per Capita Consumption	
	Children 1-2	Children 3-5
PDP (RACs & processed)	88.4	85.0
Apple Sauce Study	0.9	0.7
Translation of PDP	1.1	1.3
FDA Monitoring and TDS	4.9	6.3
Assumed Negligible	2.0	3.1
Not Included in Current Assessment	2.7	3.6

5. Method of Estimation of Cumulative Dietary Risk

Dietary exposure was estimated using the Dietary Exposure Evaluation Model (DEEM-FCID™) software. A joint distributional analysis was conducted by combining representative data on concentrations of OP pesticides on foods with distributions of anticipated consumption of these foods by different segments of the U.S. population. The primary advantage of a joint distribution analysis is that the results are in the form of a simultaneous analysis (i.e., a distribution) of exposures that demonstrate both best-case and worst-case scenarios of exposure. The inputs were distributions or point estimates for residues, distributions for consumption, and a hazard endpoint. The output was a series of distributions of one-day dietary exposures and distributions of associated risks, i.e., margin of exposures (MOEs). The different components of the input data are discussed further in the remainder of this section.

a. Manipulation of Residue Data for Exposure Assessment

Commonly, the following two equations are used for estimating exposure and risk from a single chemical:

1) Exposure = Residue X Consumption

2) Risk = Hazard X Exposure

In the case of cumulative exposure assessment, the residue term in the first equation is changed to Index Equivalent Residue ($Residue_{IE}$), and the hazard end point in the second equation is based on the index chemical.

The calculated cumulative residue is a simple arithmetic addition of residues of different chemicals that have different toxicities (potency) and therefore simple addition of their residues is not appropriate. For that reason,

the amount of residue of each chemical is adjusted by multiplying by a ***RPF*** to get the equivalent residue of an index chemical. This new calculated residue is termed ***Residue***$_{IE}$ and the exposure value resulting from combining Residue$_{IE}$ and consumption is termed ***Index Equivalent Exposure (Exposure***$_{IE}$). The new central equation for exposure will then become:

$$\text{Exposure}_{IE} = \text{Residue}_{IE} \text{ X Consumption}$$

and in the risk equation (second equation) the toxic end point of the index chemical is used. The following discussion explains in more detail how this was accomplished for this cumulative risk assessment.

b. Generation of Cumulative Equivalent Residue (Residue$_{IE}$)

To determine a given one-day cumulative oral exposure to multiple OP chemicals, first an Residue$_{IE}$ for each residue value is calculated. On a given PDP sample, each residue value is multiplied by any applicable processing factor (PF) for that chemical on food sample of interest and the RPF for the same chemical to express it as a Residue$_{IE}$ for that chemical; this is step 1.

Step 1: **Residue$_{IE}$ (per chemical n) = Residue X PF$_n$ X RPF$_n$**

The cumulative Residue$_{IE}$ for all chemicals detected on one PDP sample will then be the sum of all the Residue$_{IE}$ for all the chemicals on that sample; this is step 2.

Step 2: **Cumulative Residue$_{IE}$ = $\sum$ Residue$_{IE}$** (per PDP sample)

For example, given 100 samples of apples, each analyzed for 22 OPs, there will be generated 22 Residue$_{IE}$ values for each sample. In step 2, each set of 22 Residue$_{IE}$ for a sample is summed to generate a cumulative Residue$_{IE}$ per one sample; hence 100 cumulative Residue$_{IE}$ points for 100 samples of apples are generated.

By summing on a sample-by-sample basis, the potential for capturing any co-occurrence on the same commodity is enhanced. Another very important advantage of this approach is that, using appropriate record keeping (see next section), the complete history of each cumulative residue value in the exposure assessment can be potentially traced back to its origins. All of the sample collection and analytical information associated with a given PDP sample and all arithmetic adjustments incorporated in producing a Residue$_{IE}$ can be traced in the process of sensitivity analysis or critical food commodity contribution analysis.

c. OPCRA Food Residue Database

The data manipulations necessary to prepare the PDP residue data for input into the risk equation are in principle very simple; however, the task of performing these calculations for multiple chemicals and food commodities is problematic. The residue data used in this assessment consist of approximately 1.5 million records of analytical data and sample information. The processing factors account for several thousand additional records of information. For this reason, and in anticipation of the need to make multiple uses of the data, to keep track of them, and work backward from the cumulative assessment results to determine contributors, all the data manipulations were conducted using relational database techniques. The OPCRA food residue database currently being used for this purpose consists of, among other things, four major data tables:

1. Residue data table(s); about 1.5 million records containing essentially all of PDP sample and analyses data for OP pesticides as well as other residue data compiled from FDA and the Apple Sauce Market Basket Survey.

2. Processing factor data table; containing all relevant processing factors for specific food form/chemical combinations. Appendix III.C.5 is extracted from these data.

3. RPF Table; containing the RPF for all chemicals of interest.

4. Translation Table; providing bridging links between PDP commodity codes, such as *AJ* (apple juice), and all corresponding DEEM™ food forms, such as *Apple, juice cooked:canned;cook meth N/S.* This table allows the assignments of translation of data between PDP commodities also, such as cantaloupe data to watermelon food forms. Appendix III.C.6 summarizes the links used in this assessment.

These four tables are linked through common fields, including pesticide codes and commodity codes. Calculation queries are coded into the database so that all the pertinent residue records can be extracted, each calculation outlined above can be performed, and the results can be sorted and stored in various formats for further analysis.

A cumulative residue calculation query performs the two-step process described earlier, extracting the various parameters needed from the four tables described above. The calculation is performed on all of the food samples that are of interest and the results are compiled in text files containing the cumulative distributions for each food commodity of interest.

Each text file contains a header with sample information (number of values, number of detects, number of zeros, average of residues) and all of the cumulative residue values for a single food form, sorted in descending order.

Residue distribution inputs to DEEM™ are converted to single average values for those foods that are highly blended before consumption.

By maintaining all of the calculation parameters in separate tables in the database, it is possible to repeat the above process with new inputs by simply replacing or adding data to the appropriate table. For example a specific chemical can be omitted from the entire process by assigning it a value of zero in the RPF table. Specific chemical/commodity combinations can be selectively omitted by entering a zero value for that pair in the processing factor table. These methods have been used extensively in the current assessment to adjust the inputs to reflect currently supported uses of OPs on food crops and to test the relative contributions of chemicals and commodities to the results of an assessment.

d. Generation of Exposure Values

The cumulative $Residue_{IE}$ values (text files described in the previous section) are treated as distributions of representative residues and linked to all appropriate food forms; cumulative residue values are then randomly picked and combined with a consumption record to generate a single exposure value which is termed $Exposure_{IE}$. This process (semi-Monte Carlo in nature and conducted by DEEM™ software) is repeated many times per each consumption record to generate a distribution of exposure values. This process has been described in public documents and proceedings of the FIFRA Science Advisory Panel (http://www.epa.gov/oscpmont/sap/2000/#february). For the food forms that are highly blended before consumption, the residue input consisted of the average of all the cumulative residues, i.e., a single average residue value was entered into the DEEM™ calculation.

e. Food Consumption Data

For this assessment, food consumption is being modeled on the USDA CSFII, 1994-1998. The consumption survey is included as an integral component of the DEEM-FCID™ software. The CSFII 1994-1998 contains survey data on 20,607 participants interviewed over two discontinuous days. It contains a supplemental children's survey conducted in 1998 in which an additional 5,459 children, birth through 9 years old, were added to the survey. This is the first dietary exposure assessment in which OPP has used this survey.

DEEM-FCID™ also has integrated new USDA/EPA recipes for conversion of foods reported eaten in the survey to food commodities on which residue data are available. These recipes, which are available to the public, replace proprietary recipes used in previous versions of DEEM™.

Separate assessments were conducted on the various segments of the population as represented in the CSFII 1994-1998. Among others, the current assessment included the following age groups:

- ❑ Infants less than 1 year old
- ❑ Children 1-2 years old
- ❑ Children 3-5 years old
- ❑ Children 6-12 years old
- ❑ Youth 13-19 years old
- ❑ Adults 20-49 years old
- ❑ Adults 50+ years old

The most highly exposed population group in this cumulative assessment is children 1-2 years old; subsequent analyses of the results reported in this document will emphasize results for this age group.

f. Hazard Data used in the Cumulative Food Assessment

Section II describes the hazard portion of this risk assessment in detail. Methamidophos was chosen as the index chemical for this assessment and relative potencies of the OP chemicals were based on female rat brain cholinesterase inhibition. The point of departure (BMD10) was 0.08 mg/kg body weight/day. The application of FQPA Safety Factors for this OP cumulative assessment is made for each individual chemical in the assessment. This is accomplished by incorporating these factors into the relative potency factors for each chemical in the assessment.

6. Results

The revised cumulative food exposure assessment for OP pesticides on food commodities was conducted for seven age groups, infants of less than one year, children 2-3 years old, children 3-5 years old, children 6-12 years old, youth 13-19 years old, adults 20-49 years old, and adults 50+years old.

Appendix III.C.7 contains a complete listing of the food forms in the DEEM-FCID™ software that were included in this assessment. This table also includes summary information on the residue distributions that were prepared from the OPCRA food residue database as input for each food form. Although most of the data inputs in this table are defined as residue distributions (rdf files), for highly blended commodities, a single average residue was estimated. The actual DEEM™ input file and necessary rdf files will be made available on CD ROM and on the internet for any interested party.

The most highly exposed age group in this assessment is Children 1-2 and the subsequent results reported in this chapter will focus on this group. Figure I.C-1a is a cumulative plot of the exposure distribution for this age group. Figure I.C-1b expands the portion of the cumulative distribution between the 99th and the 99.99th percentile. There are 4192 person-days (approximately half that many individuals with two reported days of food consumption) represented in the consumption records for this age group.

Figure I.C-1a. Cumulative Distribution of Food Exposure for Children 1-2 yrs

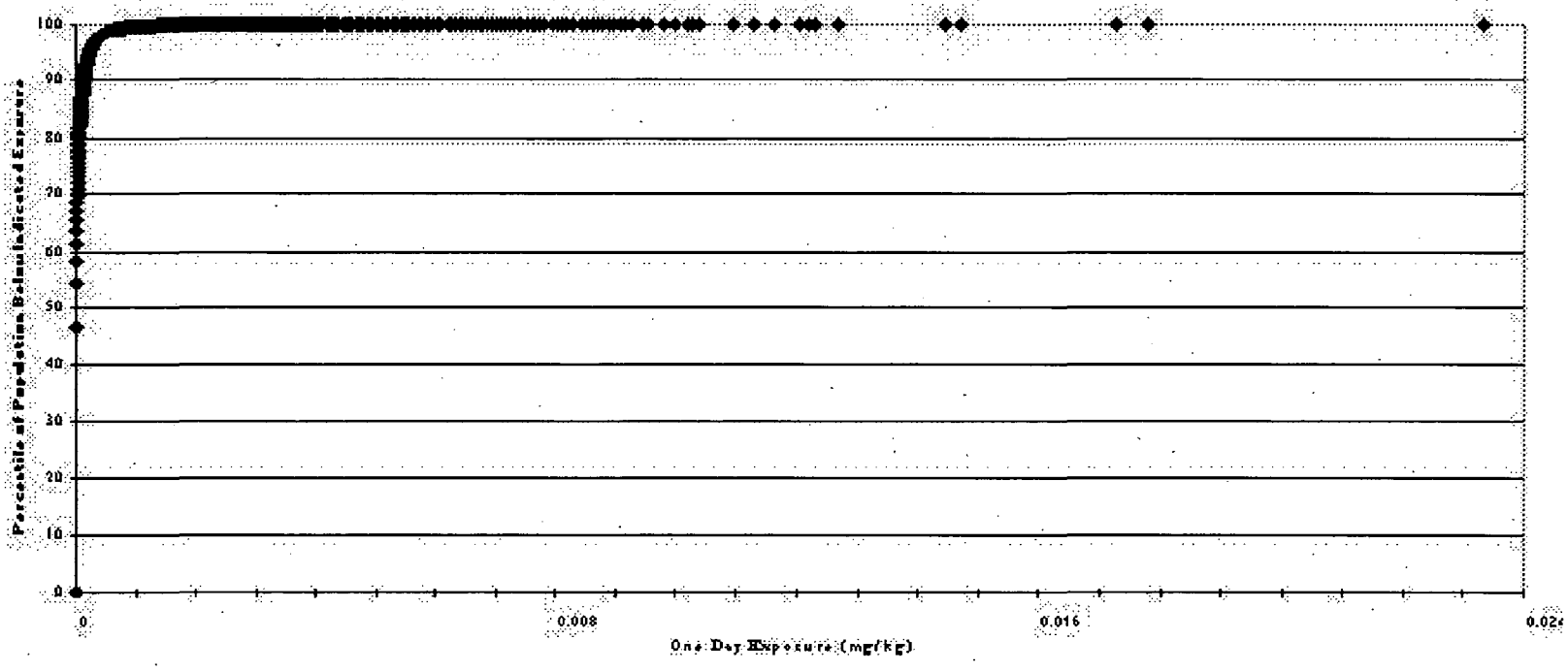
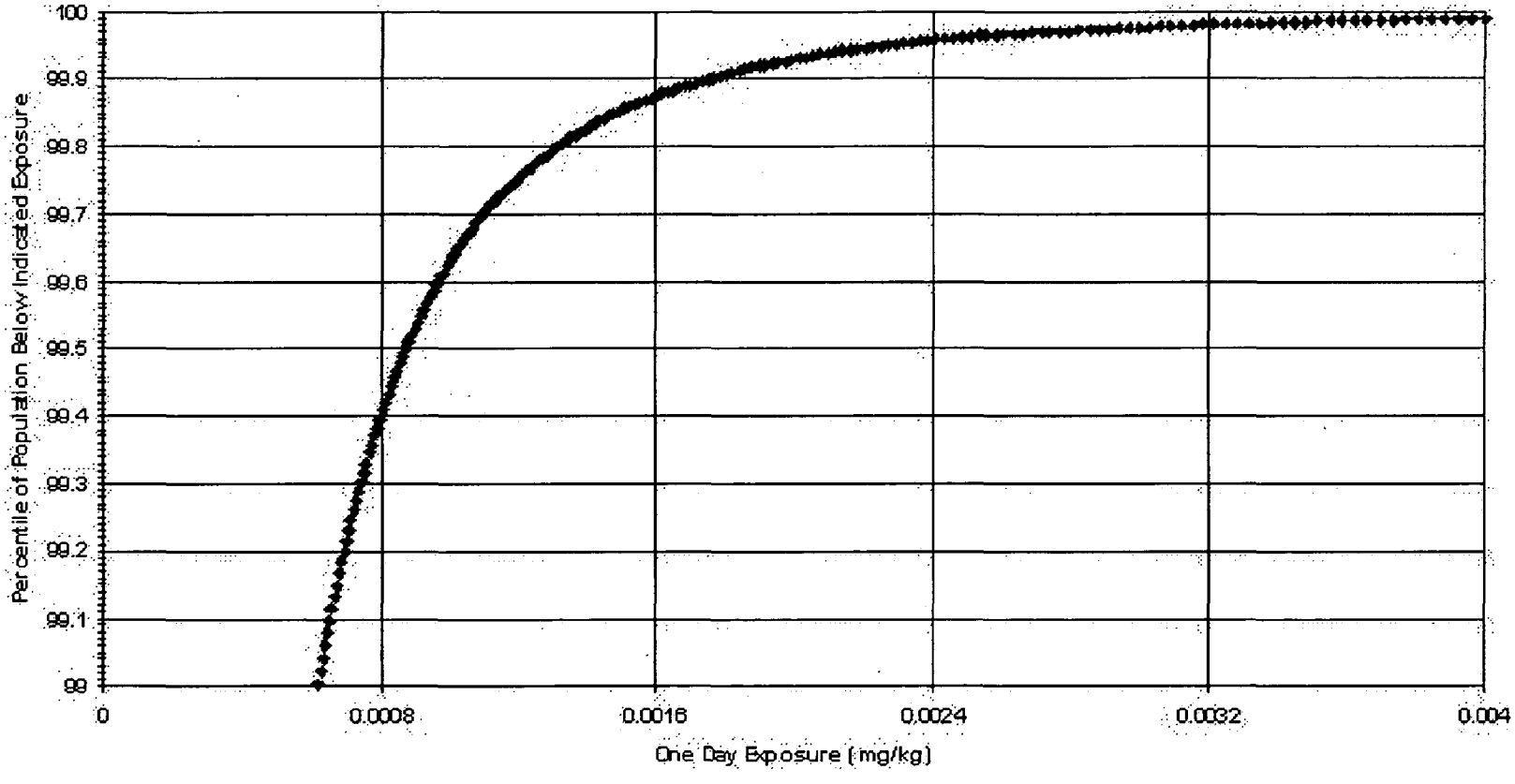


Figure I.C-1b. Cumulative Distribution of Food Exposure for Children 1-2 yrs - 99th percentile to 99.99th percentile of Exposure



a. Analysis of Significant Presence in The Upper Portion of the Distribution

The DEEM software has a provision for analyzing the foods and food forms that are contributing to the upper portions of an exposure distribution, up to a maximum interval of 5 percentile. This provision was used in the current assessment, in combination with the chemical/commodity specific information maintained in the database described above, to assess both foods and chemicals present in the tail of the distribution. The data summarized here were obtained by examination of the exposure distribution interval from the 99.8th percentile to the 100th percentile. Table I.C.2 lists all of the food forms appearing at or above the 99.8th percentile from a Monte Carlo assessment of the exposure of children 1-2 years old.

Table I.C-2. Partial Summary of Foods and Food Forms Occurring in the Top 0.2 Percentile of Exposure to an Exposed Sub-population in OP Cumulative Risk Assessment.*

[Monte Carlo Iterations =1000. Number of actual records in this interval = 8247. N=number of appearances in all records (including duplicates).]

Food	Food Form	N	Fraction of Total Exposure
Grape	Uncooked; Fresh or N/S; Cook Meth N/S	2600	0.33
Pear	Uncooked; Fresh or N/S; Cook Meth N/S	1549	0.16
Apple, fruit with peel	Uncooked; Fresh or N/S; Cook Meth N/S	2177	0.13
Apple, juice	Uncooked; Fresh or N/S; Cook Meth N/S	1510	0.10
Tomato	Uncooked; Fresh or N/S; Cook Meth N/S	584	0.05
Grape, raisin	Uncooked; Dried; Cook Meth N/S	376	0.04
Bean, snap, succulent	Cooked; Frozen; Boiled	397	0.03
Pepper, bell	Uncooked; Fresh or N/S; Cook Meth N/S	337	0.03
Bean, snap, succulent	Cooked; Canned; Boiled	383	0.02
Potato, tuber, w/o peel	Cooked; Fresh or N/S; Boiled	155	0.02
Spinach	Cooked; Frozen; Boiled	39	0.01
Bean, snap, succulent	Cooked; Fresh or N/S; Cook Meth N/S	58	0.01
Squash, summer	Cooked; Fresh or N/S; Boiled	33	0.01
Bean, lima, succulent	Cooked; Frozen; Boiled	76	0.01
Celery	Uncooked; Fresh or N/S; Cook Meth N/S	136	0.01
Cucumber	Uncooked; Fresh or N/S; Cook Meth N/S	42	0.01
Bean, lima, succulent	Cooked; Canned; Boiled	64	<0.01
Spinach	Cooked; Fresh or N/S; Baked	22	<0.01
Cucumber	Cooked; Canned; Cook Meth N/S	28	<0.01
Potato, tuber, w/peel	Cooked; Fresh or N/S; Fried	32	<0.01
Pepper, bell	Cooked; Canned; Cook Meth N/S	32	<0.01
Bean, snap, succulent	Cooked; Fresh or N/S; Boiled	110	<0.01
Bean, snap, succulent	Cooked; Fresh or N/S; Boiled/baked	31	<0.01
Potato, tuber, w/o peel	Cooked; Frozen; Fried	36	<0.01
Pepper, bell	Cooked; Fresh or N/S; Cook Meth N/S	46	<0.01
Potato, tuber, w/o peel	Cooked; Fresh or N/S; Fried	22	<0.01
Tomato	Cooked; Fresh or N/S; Boiled/baked	32	<0.01
Potato, tuber, w/o peel	Cooked; Fresh or N/S; Baked	23	<0.01
Apple, juice - babyfood	Cooked; Canned; Cook Meth N/S	37	<0.01
Apple, juice	Uncooked; Frozen; Cook Meth N/S	22	<0.01
Strawberry	Uncooked; Frozen; Cook Meth N/S	15	<0.01
Bean, lima, succulent	Cooked; Fresh or N/S; Boiled	36	<0.01
Bean, snap, succulent	Cooked; Fresh or N/S; Fried	13	<0.01
Cherry, juice	Uncooked; Fresh or N/S; Cook Meth N/S	11	<0.01
Bean, snap, succulent- babyfood	Cooked; Canned; Cook Meth N/S	19	<0.01
Tomato	Cooked; Fresh or N/S; Boiled	94	<0.01
Spinach	Uncooked; Fresh or N/S; Cook Meth N/S	7	<0.01
Peach	Uncooked; Fresh or N/S; Cook Meth N/S	42	<0.01
Grape, juice	Uncooked; Fresh or N/S; Cook Meth N/S	8	<0.01
Tomatillo	Uncooked; Fresh or N/S; Cook Meth N/S	7	<0.01
Apple, juice	Cooked; Canned; Cook Meth N/S	94	<0.01
Tomato, juice	Cooked; Canned; Cook Meth N/S	5	<0.01

Food	Food Form	N	Fraction of Total Exposure
Potato, tuber, w/peel	Cooked; Fresh or N/S; Baked	4	<0.01
Pepper, bell	Cooked; Fresh or N/S; Fried	21	<0.01
Cucumber	Uncooked; Cured etc; Cook Meth N/S	3	<0.01
Bean, snap, succulent	Cooked; Frozen; Baked	5	<0.01
Apple, peeled fruit- babyfood	Cooked; Canned; Cook Meth N/S	6	<0.01
Lettuce, head	Uncooked; Fresh or N/S; Cook Meth N/S	48	<0.01
Potato, tuber, w/peel	Cooked; Fresh or N/S; Boiled	5	<0.01
Broccoli	Cooked; Frozen; Boiled	3	<0.01
Celery	Cooked; Fresh or N/S; Boiled	64	<0.01
Potato, tuber, w/o peel	Cooked; Frozen; Baked	6	<0.01
Squash, summer	Cooked; Frozen; Boiled	2	<0.01
Squash, summer	Cooked; Fresh or N/S; Boiled/baked	1	<0.01
Tomato	Cooked; Fresh or N/S; Cook Meth N/S	11	<0.01
Spinach	Cooked; Fresh or N/S; Boiled/baked	1	<0.01
Grape	Cooked; Fresh or N/S; Cook Meth N/S	26	<0.01
Tomato	Cooked; Fresh or N/S; Baked	49	<0.01
Apple, sauce	Cooked; Fresh or N/S; Boiled	34	<0.01
Orange	Uncooked; Fresh or N/S; Cook Meth N/S	24	<0.01
Grape	Cooked; Canned; Cook Meth N/S	30	<0.01
Tomato, puree	Cooked; Canned; Cook Meth N/S	39	<0.01
Orange, juice	Uncooked; Fresh or N/S; Cook Meth N/S	17	<0.01
Strawberry	Uncooked; Fresh or N/S; Cook Meth N/S	2	<0.01
Celery	Cooked; Fresh or N/S; Cook Meth N/S	30	<0.01
Potato, chips	Cooked; Fresh or N/S; Fried	3	<0.01
Pepper, bell	Cooked; Fresh or N/S; Baked	19	<0.01
Orange, juice	Uncooked; Frozen; Cook Meth N/S	8	<0.01
Celery	Cooked; Dried; Boiled	3	<0.01
Celery	Cooked; Canned; Cook Meth N/S	17	<0.01
Pear	Cooked; Fresh or N/S; Cook Meth N/S	25	<0.01
Broccoli	Cooked; Fresh or N/S; Boiled	2	<0.01
Grape, raisin	Cooked; Dried; Cook Meth N/S	10	<0.01
Potato, tuber, w/o peel	Cooked; Fresh or N/S; Cook Meth N/S	2	<0.01
Pepper, non-bell	Uncooked; Fresh or N/S; Cook Meth N/S	8	<0.01
Celery	Cooked; Canned; Boiled	9	<0.01

*This table was prepared as part of the evaluation of the potential outliers and potential contributors and does not represent a judgement about the threshold of concern.

To evaluate the presence of chemicals in the tail of the distribution, all of the food forms in the above table were linked with the corresponding residue distributions that had been generated for the cumulative assessment. The individual chemical contributors to these distributions were extracted from the OPCRA food residue database used to generate the distributions. Thus the relative percent contributions of food forms derived from DEEM were combined with the relative percent contributions of chemicals to each food form's residue distribution to give an estimate of the relative contribution of each chemical to the interval being examined. These data were further reduced by combining all food forms to the crop level, for example, fresh grapes, raisins, and grape juice were all combined under the crop name grapes, and so on. All metabolites, degradates, and isomers were combined for each active ingredient in that assessment. The linkage of the DEEM output and the OPCRA food residue database information on chemical/food form specific contributions are summarized in Appendix III.C.8.

The most significant chemical presence in the exposure interval between the 99.8th percentile and 100th percentile is dimethoate/omethoate with a relative contribution of approximately 48% of the exposure, followed by azinphos methyl at 27%, acephate and its metabolite methamidophos at 11%, methamidophos, as active ingredient, at 5%, phosmet at 2.5%, phorate at 2.2%, and mevinphos at 1.8%. The most significant food crops are: apples, grapes, green peppers, pears, potatoes, spinach, succulent beans, and tomatoes.

7. Discussion

a. Changes Since the Preliminary Assessment

A preliminary cumulative assessment was published on December 3, 2001. Since that time a number of changes have been made in the input data, some of them as a result of public comments. All of these changes are captured in the data summaries included in the Appendices to this document. A summary of the major changes or categories of changes is provided in this section.

- Processing factors were updated. Several factors were added or changed based on public comments on the preliminary assessment. Appendix III.C.5 provides a summary of the processing factors currently being used. It should be noted that the absence of a processing factor in Appendix III.C.5 or a factor of zero indicates that the specific food form/chemical pair does not contribute to any residue distribution estimates. In some cases the absence of a factor is simply due to the fact that there are no detectable residues of that chemical in the database but in other cases it is due to the fact that a specific use is being excluded from the assessment because it is not being supported. Several commodities are not entered in the table at all because the residue

analyses conducted on these foods were uniformly below detectable levels. Therefore, one must not use this table as a means of determining the uses included in the assessment. The appropriate starting point for this determination is Appendix III.C.7, which lists every food form included in the assessment. A factor of zero in the processing factor table in some cases is due to a correction of a former entry and in some cases, such as for chlorpyrifos on apple and grape commodities, is a means of adjusting the assessment to account for mitigation negotiations. In the example of chorpyrifos, the use patterns are being altered to allow only pre-bloom applications, which are expected to yield essentially no detectable residues. The PDP data set contains many detects due to foliar applications; therefore, the processing factor was used as a use flag that was lowered to zero for this assessment. The residue data are still in the database and can be reactivated by raising the use flag.

- Apple sauce residue data have been added to the data set based on MRID 45432001: Data are from The National Food Laboratory and were sponsored by Apple Processors Association. The data have been incorporated in the PDP Data set in the OPCRA food residue database.

- Relative Potency Factors have been revised. Among the revisions, omethoate now has a factor different from that of dimethoate.

- FQPA Factors of 3 have been applied (via RPF adjustments) to all chemicals in the assessment except methamidophos, dimethoate/omethoate and chlorpyrifos, which have their FQPA factors reduced to 1.

- The bridging and translation of residue data from source to CSFII food forms have been updated. Several adjustments and corrections were made in these assignments. Among these was the changing of all tomato processed food forms to be derived from canned tomato residue data instead of fresh tomato residue data. All of the translations for the current assessment can be seen in Appendix III.C.6.

- Some inappropriate residue data were removed from the assessment. Lettuce residue data from 1994 were removed completely from the assessment because they contained residues from use patterns of methamidophos and mevinphos that are not current. Lettuce residues are now based solely on data from 1999 and 2000.

- Fenamiphos and chlorpyrifos-methyl have been removed from the assessment based on planned phase-outs. Appendix III.C.9 should be consulted for the complete summary of OP pesticide uses or import tolerances that are currently being supported in the reregistration process. It is important to note that this appendix provides the scope of use patterns that are being considered as having potential for producing OP

residues on foods. This list is based on reregistration actions up through March of 2002. If an OP use is not listed in this appendix then it is not considered in the current assessment.

- Tolerance exceeding residues were added back to the residue data as a result of discussion with SAP after release of the preliminary assessment. These violative residues are not a significant contributor to the assessment.

b. Major Assumptions in the Revised OPCRA for Foods

The following discussion of input assumptions is provided as a revision to the same discussion that was included in the preliminary assessment. The assumptions are revised to reflect their current status and thus some of the points covered in the previous section may be restated here.

The processes for exposure and risk assessment in the Office of Pesticide Programs (OPP) have been undergoing a rapid evolution. A number of choices and assumptions made in the conduct of the current assessment may differ from previous single-chemical assessments. The following discussion is intended to provide some background on the impact of choices that are unique to this assessment.

i. Some PDP Residue Data Were Excluded

The assessment includes only chemical/crop combinations currently being supported for registration in the United States or with import tolerances (see Appendix II.C.9). Therefore, residues representing canceled and phased-out uses are excluded. That is, residues in the OPCRA food residue database that do not represent supported section 3 registrations, SLN uses, or supported import tolerances, are excluded from the assessment. In a change from the preliminary assessment of 12/3/01, we are not excluding violative residues, i.e., tolerance exceeding residues, from the assessment. The criteria listed in this paragraph are intended to ensure that the cumulative assessment simulates the residue pattern that will result from ongoing mitigation actions in the reregistration of OP pesticides. Although this may appear to underestimate the food exposure as reflected by available residue data, it should be kept in mind that these data reflect past patterns of residue occurrence. The inclusion of violative residues in the assessment has no significant effect on the overall results of the assessment. Violative residues are rare in residue monitoring data.

ii. Composite Samples Were Used to Estimate Residues in Single-Servings as Consumed

Only the residue data from composite samples were utilized in this assessment. A single composite sample may contain several individual serving of some foods. For purposes of the present assessment, it is assumed that residues reported on composite homogenates adequately reflect the residues in any given single-serving contained in that homogenate. Therefore, no attempt was made to "decomposite" residue values to simulate residues that might be present in the single-servings contained in the PDP composite sample. PDP has conducted single-unit sampling for apples, pears, and peaches since 1998. A comparison of the residue levels on these single-servings to the residues on comparable composite samples indicate that use of composite samples will not result in a significant under- or overestimation of residues.

iii. PDP Samples Were Assumed to Reflect Residues in Foods Prepared for Consumption

The PDP generally collects foods at wholesale distribution centers and stores them frozen until analysis. Foods are washed and inedible portions are removed before analysis but these foods are not further cooked or processed. Processing factors (see Appendix III.C.5) were applied to the residue data in this assessment. These factors were taken from the most recent single-chemical dietary exposure assessments for the OPs. Information on these factors is somewhat limited; therefore, some storage or process related dissipation of residues may not be accounted for. In response to the preliminary assessment we have had several public comments with suggestions for improvements in the processing factors. These suggestions have been incorporated in the current assessment as appropriate. The processing factors in Appendix III.C.5 reflect these changes. The processing factors still probably result in some overestimation of residues in processed foods for which factors are not available, but the impact on this assessment of this possibility appears to be minimal according to the results reported here. Most of the food forms that appear to be significantly present in the upper ends of the exposure distribution are either uncooked food forms or are supported by residue data on food forms that have been processed in a similar manner.

iv. Residue Data Were Assumed to Reflect Co-occurrence of OPs in Single-day Diets

One reason for conducting the assessment of PDP residue data on a sample-by-sample basis is to maintain the connections in multi-analyte occurrences on these samples. In other words, it is assumed that the PDP sampling and analysis protocols capture the co-occurrence of OPs. Appendix III.C.10 demonstrates the extent of this measured co-

occurrence in the PDP program between 1994 and 1999. It can be seen in this table that a majority of PDP samples were reported as containing no detectable residues at all. For those that contained detectable residues, single residues were most prevalent but many multiresidue samples were found. The maximum number of OP analytes reported on a PDP sample is 5 (this occurred on only 5 samples during the period 1994-1999).

In addition to considering co-occurrence of different OPs on one food, the potential exists for co-occurrence from residues of one or more OPs on different foods consumed in one-day. This assessment is using residue data collected over a seven year period, 1994 through 2000. This is necessary in order to maximize the number of food commodities in the assessment but this raises issues of lack of co-occurrence. Co-occurrence in the food is important from the standpoint of all the food consumed in the same time period. One may question if it is appropriate to model exposure based on bananas grown in 1994 and apples grown in 1998. On the other hand, the consistency in appearance of residues in the monitoring data over time suggest that the uncertainty in this choice is probably not more significant than those in other aspects of the model.

A related choice in selection of residue data was to include all available data for a given food. This has resulted in data sets that span time periods of less than one year to as much as four years of data. At the time of the preliminary assessment we were exploring the impact of using reduced data sets for foods with a suggested maximum of 2 years of data for any given commodity. A decision was made to continue using the complete data set in the absence of specific information that a given subset of the data were inappropriate to consider for currently supported uses or import tolerances. Therefore, the complete data set is still being used (1994-2000 PDP) with the exception of data from 1994 on lettuce. These samples contained residues of methamidophos and mevinphos that could have resulted from applications that were not representative of current use patterns. The use of the complete data set from 1994 through 2000 increases the probability that variations in climate and pest pressures may have been captured in the residue distributions.

v. It Was Assumed That All OPs of Concern on an Analyzed Food Sample Were Accounted for in the Residue Analysis

All residue analyses are subject to the limitations of the sensitivity of the analytical methods. Many of the samples analyzed are reported as being below the analytical method reliable limit of detection (LOD). It has been usual practice in Agency assessments on individual pesticides to assume that residues in non-detectable samples are present at ½ LOD of the analytical method in samples that were harvested from treated fields. Thus, for purposes of estimating residues in samples reported as <LOD, a proportion of the samples equal to the estimated percent crop treated is assigned a residue level of ½ LOD and the remaining samples, which are assumed to come from untreated crops, are assigned a residue value of zero. This procedure becomes problematic for a cumulative assessment. It is not enough to simply estimate the percent crop treated for each of the pesticides in the cumulative assessment; it is also important to consider the potential for co-occurrence of residues of multiple residues on the same crop.

In the current assessment it is assumed that all OP residues reported as non-detectable are absent from the sample, i.e., they are assigned a value of zero. In a complex analysis such as this cumulative analysis, in which there are abundant samples with detectable residues, the assumption of zero for non-detects would not be expected to impact greatly the outcome of the exposure assessment at the highest percentiles. This was tested in an earlier stage of the assessment and reported in the case study that was presented to the SAP in December of 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 greatest number of detectable residue findings on a given food. The most prevalent detected chemical was chosen because it is reasonable to assume that chemical would also have the greatest number of residues below the limit of detection. Under the conditions of the case study the two extremes showed essentially no significant difference in exposure above the 95th percentile of exposure. At the lower percentiles of exposure the impact of input for non-detectable residues on cumulative exposure became apparent; however, the overall exposure levels were so low they would not be considered to be of concern.

vi. PDP Residue Data Were Translated in Some Cases to Foods for Which No Residue Data Were Available

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 these commodities (USEPA, 1999b). 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 of data become more difficult to make. In the current assessment, translations of the residue data were made using the translation scheme in HED SOP 99.3 (USEPA, 1999b) in order to ensure representation of the maximum number of commodities possible. The allowable translation are summarized in Appendix III.C.4. In making these translations the only residues included were those that could occur on the simulated food from current registrations of OP pesticides. The uncertainty in this scheme is not expected to have a major impact on the assessment because the foods being translated comprise a relatively small portion of the per capita consumption by children (See Appendix III.C.1 for confirmation of this fact). An analysis of foods in the higher percentiles of exposure in this assessment has confirmed that translated foods do not significantly impact that portion of the distribution.

vii. The Food Exposure Portion of This Cumulative Assessment is Considered to be Constant Throughout the Year and Across Regions

It is currently assumed that the food distribution and storage systems in the United States result in essentially a national distribution of the major foods in our diet that is constant throughout the year. 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 should reflect the foods as available to the consumer. This applies to imports also. For the water portion of dietary exposure it is recognized that the potential for residues is not constant nationwide. The national food estimate is combined with regional water assessments to provide a series of regional dietary assessments.

viii. Some Residue Data are Under Consideration But Not Included in This Assessment

A task force of pesticide producers has provided the Agency with an OP pesticide market basket survey. The results of this market basket survey, conducted in 1998, were submitted to the Agency in 2001. In this survey 13 foods were analyzed for 29 OP analytes. Samples were taken from grocery stores and single-serving size homogenates 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 assessment using market basket survey data are in general agreement with a similar assessment using PDP data. The impact of these data on the OP cumulative risk assessment are not included in this assessment.

I. Revised OP Cumulative Risk Assessment

D. Residential OP Cumulative Risk

1. Introduction

The Office of Pesticide Programs (OPP) has used a calendar based model (Calendex™) to address the temporal aspects of the residential use of pesticides in 7 geographic regions throughout the United States. These regions, based on major crop growing areas and their influence on surface and ground water, also present an opportunity to consider the unique climate patterns, pest patterns and potential socioeconomic patterns that influence residential pesticide use and expected exposure.

Calendex™ allows the OPP to delineate the critical timing aspects of seasonal uses of Organophosphate (OP) insecticides that result in exposure to pesticides. Calendex also enables OPP to identify potential co-occurrences from multiple sources. This includes the exposure from home lawn and garden treatments, pesticides used on golf courses and applications made by governmental entities for the control of public health pests such as wide area mosquito sprays.

In nearly all cases, the residential exposure scenarios were developed using proprietary residue and exposure data. Exposure factors such as breathing rates and durations of time spent indoors or outdoors were taken from various references including US EPA/ORD/NERL Consolidated Human Activity Database (CHAD), and the Agency's Exposure Factors Handbook (USEPA, 1997a). In this assessment, the full range of exposure values – expressed as uniform, log-normal or cumulative distributions -- are used, where appropriate, rather than relying solely on measures of central tendency. While the dietary and drinking water assessment address only the oral exposure route, the residential assessment considers the dermal and inhalation exposure routes as well as the oral route based on the mouthing behavior of young children.

EPA registered labels, while useful for establishing site/pest relationships and recommendations for applications, generally cannot provide the temporal aspects of regional pesticide use. Thus, OPP has relied on other sources of pesticide use information, including the National Home and Garden Pesticide Use Survey (NHGPUS) data and information available in State Cooperative Extension Service publications. These data resources were comprehensively used to identify information such as frequency of applications, the type of application equipment used, and the type clothing worn while making those applications. State Cooperative Extension Service recommendations were used to establish regional windows of pesticide applications based on the observed appearance of insects such as white grubs on lawns. For example, the timing for the treatment of white grubs occurs during mid-July in southern Texas (Region F-

Lower Midwest) and mid-August in areas such as New York (Region D – North East/ North Central).

2. Scope of Regional Assessments

The residential and drinking water assessments were developed for 7 distinct geographic Agricultural Production Regions (Figure I.D-1). EPA included ten OP pesticides with residential uses and potential for significant exposures in its assessment. Not included in the cumulative assessment were certain OP uses that result in low exposure and uses for which risk mitigation actions have been taken.

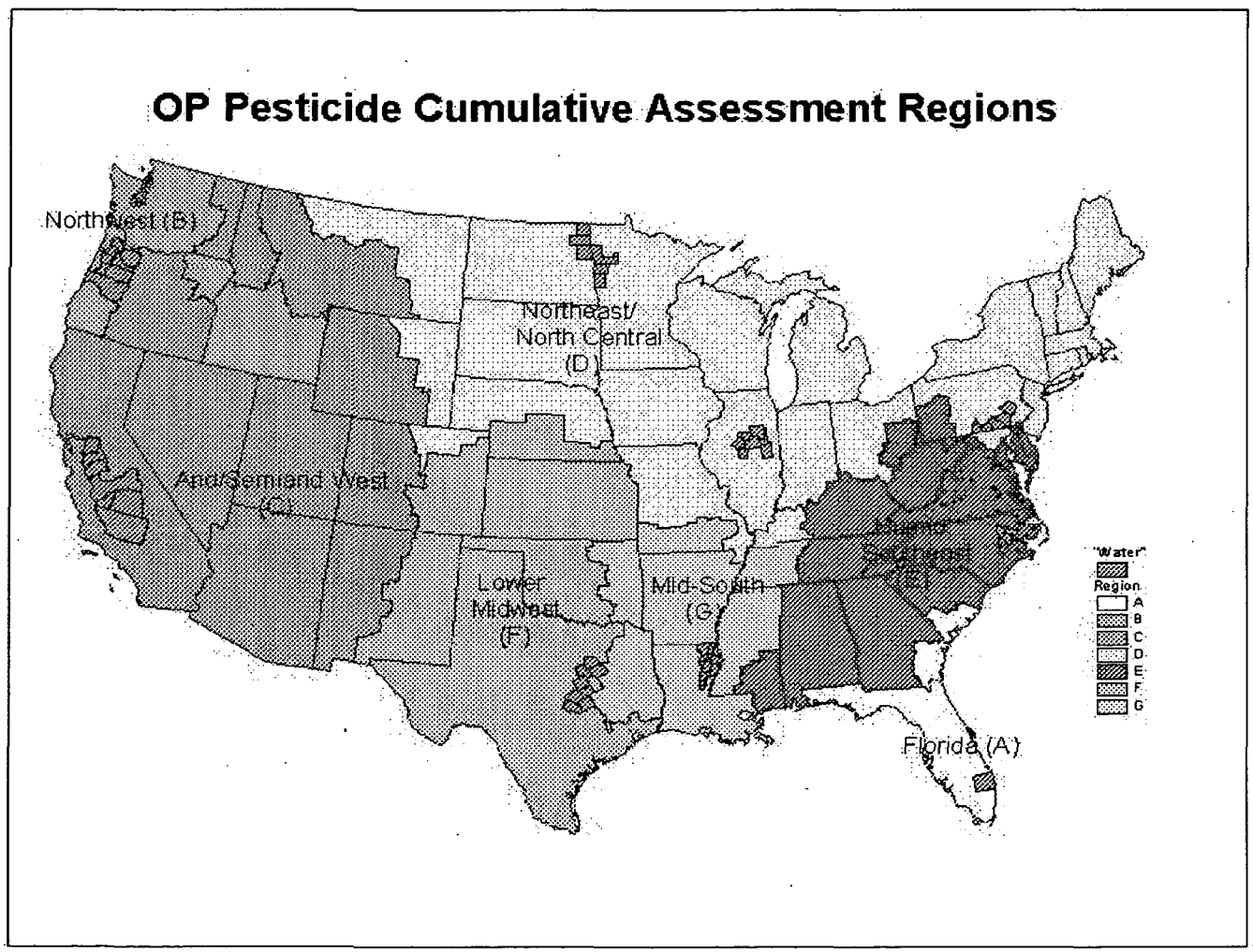
Two OP pesticides are currently registered for use on pets, tetrachlorvinphos (TCVP) (shampoo/dip and flea collar) and Dichlorvos (DDVP) (flea collars). OPP had insufficient data on DDVP or TCVP exposure for flea collar uses to include them in a calendar-based probabilistic assessment. However, OPP did assess TCVP through the shampoo/dip and powder use and these results are incorporated in this cumulative assessment.

Other OP uses were not included because they resulted in low exposures or because their single chemical REDs showed low risk. These low exposure uses include ant baits, paint additives and post application residential exposure from sod farm application of pesticides. Ant baits are contained inside enclosed packages. The treatment of individual fire ant mounds has very low applicator exposure and the reentry or significant play on fire ant mounds is unlikely. Low exposure is expected also because the treatments often take more than one day to produce results.

In case of paint additives, the diazinon additives in outdoor paints result in low potential for exposure because of the complexity of the paint/pesticide matrix as well as the dilution of airborne concentrations in the outdoor environment. For sod farm uses, post application exposure is mitigated by rapid dissipation of residues, residue removal during harvesting (cutting, rolling or stacking), and transportation. Installation of the sod requires considerable site preparation which is followed by watering in, further lowering potential for significant exposure in a post application scenario. OPP believes that children are unlikely to enter the lawn area immediately following the sod installation.

Finally, for wide-area public health treatments, the more significant uses such as fenthion, malathion and naled were included. Chlorpyrifos use for mosquito control was not included because very low exposures were estimated in the single chemical, screening level assessment.

Figure I.D-1. OP Pesticide Cumulative Assessment Regions



3. Residential Scenarios

The Residential Scenarios addressed in this document represent critical OP uses that have the potential for significant exposure or risk when considered in a cumulative assessment. These are:

- ❑ Golf course and lawn care applications,
- ❑ Home gardens,
- ❑ Wide area Public Health sprays,
- ❑ Pet Treatments (includes aerosol, liquid, and powder uses.), and
- ❑ Impregnated pest strips (limited to closets and cupboards.).

Table I.D-1. Summary of Changes Between December 3, 2001 Preliminary Cumulative Risk Assessment and Revised Cumulative Risk Assessment

Uses Included in the Preliminary Assessment That Have Been Removed from the Final Assessment	
Use Scenario	**Rationale for Change**
DDVP Crack and Crevice	Registrant is presently generating data
DDVP Pest Strips (currently under mitigation)	This assessment was limited to use of a small pest strip in closets and cupboards only. The uses in attics, basements, and garages were not considered in this assessment.
Malathion Lawn Spray	Registrant is no longer supporting this use.
Malathion Golf	Registrant is no longer supporting this use.
Malathion Vegetable Garden Dust	Registrant is no longer supporting this use.
Trichlorfon Lawn Care Spray – Applicator Scenario	This use has been limited to professional application by lawn care operators only. Only post-application scenarios will be considered.
Uses Included in the Final Assessment That Were not Included in the Preliminary Assessment	
Use Scenario	**Rationale for Change**
TCVP Aerosol, Powder, Pump Spray	Pet collars were not included in this assessment and are believed to pose less risk than the aerosol, powder, and pump spray uses considered in this assessment.

a. Golf Course and Lawn Treatments

Golf Course

Five OPs are registered for use on golf course fairways, greens and tees and/or residential lawns. Of the five pesticides, four may be applied on golf courses (Malathion golf course use is no longer supported by the registrant and was thus not included in the assessment). These pesticides are acephate, bensulide, fenamiphos, and trichlorfon. Acephate is used for surface feeding insects, like the chinch bug, which invade primarily warm season grasses such as St. Augustine grass. Bensulide is used for germinating weeds such as crabgrass on fairways, greens, and tees. Fenamiphos is a nematicide and is also watered. Trichlorfon is used for sub surface or thatch dwelling insects such as white grubs.

Lawn Treatments

On lawns, two pesticides may be applied by homeowners or by professional LCO. These pesticides are bensulide and trichlorfon. Bensulide is an herbicide used to control germinating weeds, and trichlorfon is labeled for insects such as white grubs, which damage turf when present in significant numbers. Both of these pesticides need to be watered in for effective control. Malathion is also registered for use on lawns applied as surface sprays to control nuisance pests such as fleas; however, this use is no longer supported by the registrant and was not included in the assessment.

b. Home Gardens

The home garden scenarios include ornamental and edible food gardens (including home fruit orchards). Due to the wide variety of plant/pest relationships that can exist in any given region, it was assumed that applications could be made throughout the growing season for a given area. Acephate and disulfoton are insecticides that have systemic properties and appear to be more widely recommended in the cooperative extension publications. However, malathion continues to be recommended for aphids by most cooperative extension services. In addition to use on ornamental gardens, malathion is also registered for use on home vegetable gardens and orchards.

c. Public Health Uses

Residential exposure from aerial and ground based applications for the control of public health pests made by regional or state personnel was addressed in this assessment. Malathion, fenthion and naled are applied to control mosquitoes. Fenthion is also applied to control black flies.

d. Indoor Uses

DDVP is the sole OP pesticide with indoor registrations. DDVP is used as both a crack and crevice spray and as a pesticide impregnated pest strip for the control of flying insects. Since OPP is currently in negotiations with the registrant regarding the use of DDVP crack and crevice applications, this scenario was not evaluated. The DDVP pest strip scenario, however, was

evaluated but was limited to use of smaller strips to control insects in closets and cupboards in which strip replacement occurred every 4 months.

e. Pet Uses

TCVP was evaluated in this assessment as an aerosol, pump, or powder flea and tick treatment for pets. TCVP is also available in impregnated from in pet collars. This assessment considered only TCVP pet treatment using the aerosol, pump, or powder form (and not the impregnated collar form), as these uses are believed to result in equal or higher exposures than the pet collar use. This is based on the assumption that shampooing a dog will result in greater exposure than merely securing a collar around a dog's neck. Post application exposure to the collar is also expected to be lower due to a smaller area being treated (area around the neck rather than the whole body).

4. Exposure Routes Considered

The routes of exposure considered in this cumulative assessment varied depending on certain application and post-application exposure activities which were determined to be age group-specific. The results of exposure are described in detail below:

Post-Application Oral Route of Exposure: Oral ingestion via hand-to-mouth activity of children was the only oral route of exposure considered in the residential portion of this assessment. Specifically, oral hand-to-mouth ingestion was considered only for the age groups Children 1-2 and 3-5 for their activities on treated lawns. OPP acknowledges that there is very limited data on exposure to very young children; in general, however, children ages six and older no longer exhibit mouthing behavior to the degree seen in younger children such as placing hands and /or objects into the mouth. In addition, while OPP recognizes that non-dietary pathways other than through hand-to-mouth activities do exist such as ingestion of soil and mouthing of grass, these latter two pathways are not considered because they had little impact on the exposure assessment when they were addressed in the individual chemical OP risk assessments.

Post-Application Dermal Route of Exposure: The dermal route of exposure was considered for both children and adults; however, the calculation for children adjusted by the appropriate surface area to body weight ratio. Children are considered in a separate group from adults because of the potential for additional exposures that result from a higher skin surface area to body weight ratio. In general children six and older have a surface area to body weight ratios that are similar to adults.

Post-Application Inhalation Route of Exposure: The inhalation route of exposure was considered for adults and children.

5. Data Sources

Three basic types of data were considered in this assessment: pesticide use data, residue concentration and dissipation/decay data, and residue contact and exposure factor data. Together, this information can be used to predict the potential for co-occurrence of exposure events in aggregate and cumulative

assessments. These data are described in more detail below and in Table I.D-2 (by application scenario).

Pesticide Use Data: Pesticide use information is critical to establishing windows of potential exposure when using a calendar-based exposure model. This information is needed to predict what pesticide will be used, the amount of pesticide which will be used, when the application will be made, how many times the pesticide will be applied (and for how long), and whether the applicator will be a professional or not. Other data such as frequency of applications, types of application equipment used, and types of clothing worn while making the applications are also used in developing exposure scenarios.

Several references were used to determine the application timing for lawn care pesticides and to estimate the number of pesticide users. To determine the percent of households that employ professional lawn care operators (LCO), the Agency used the 1996-1997 National Gardening Survey (Butterfield, 1997) conducted by the Gallup polling organization. For specific chemicals, regional percent of lawns treated were taken from the National Home and Garden Pesticide Use Survey (NHGPUS) (USEPA, 1992). Two other data sources, Kline Professional Markets for pesticides and Kline Consumer Markets for pesticides, were also used to check/confirm the NHGPUS estimates/data.

Residue Concentration Data: Residue concentration data and associated pesticide decay/dissipation parameters are used to define the sources and magnitude of exposure resulting from human contact.

Exposure Factor (Contact) Data: Exposure factors such as the amount of time spent in an area, whether the exposure is occurring indoors or outdoors, and whether the residue source is a golf course or a lawn (and if the latter, its size) are critical for estimating exposures to a given substance.

For example, an important variable for estimating home-owner applicator exposure is the size of the lawn. OPP considered the average and median lawn sizes reported in a journal article by Vinlove and Torla (1995). The means and medians were ~13,000 ft^2. However, the authors noted problems, interpreting the data since it is based primarily on low income houses and consists of adjustments of the lot size by the house's foundation (footprint) only. The data do not consider other structures such as decks or other green space such as gardens, which can reportedly reduce the lot size by up to 50%. Similar lawn sizes were noted in an extensive survey conducted by the Outdoor Residential Exposure Task Force (ORETF) with similar problems encountered with respect to confounding variables such as decks and other green spaces. For this assessment, OPP used a uniform distribution for lawn size bounded by 500 ft^2 and 15000 ft^2.

Another important variable for addressing post-application exposure from home lawn treatment is the duration of time spent on lawns. In this OP CRA, cumulative distributions of durations on lawns of up to two hours were used to address adult exposure on lawns. These data are presented in Table 15-64 in EPA's Exposure Factors Handbook; however, OPP notes that the percentiles above the 95^{th} have the same values (121 minutes). A similar cumulative distribution was given for children ages one to four. In order to be protective of children and to address the uncertainty of the upper percentiles of the exposure

factor data, OPP selected a cumulative distribution from the Exposure Factor Handbook's Table 15-80 with a bound of 3.5 hours for children.

This distribution represents the amount of time spent outdoors. This allows for the time that children spend outdoors not only at home but also in parks and near schools.

6. Lawn Care Exposure Data

a. Lawn Applicator Dermal and Inhalation Exposure Data

Residential applicator exposure was assessed for the applicator scenarios used in this assessment (i.e., commercial/professional applicator exposures were not included in the assessment). Both dermal and inhalation exposures were considered. Briefly, dermal exposures were calculated as the product of the Unit Exposure (mg/lb ai handled), application rate (lbs ai/ft^2), and area treated (ft^2). Unit exposure and area treated were inserted in the calculation as a log normal distribution and uniform distribution respectively, and application rate as a point estimate. Inhalation exposures to applicators were entered in the assessment as a uniform distribution bounded by high and low measured values.

Data concerning Unit Exposures (UE) (through both the dermal and inhalation routes) were generated by the ORETF. Specifically, this data consisted of exposure data from 30 volunteers using a push-type rotary spreader to apply 50 lbs of dacthal product to treat 10,000 ft^2 of turfgrass. Exposure data from these studies were used to generate normalized values expressed as milligrams exposure per pound of active ingredient of a pesticide handled (referred to as UE). Volunteers participating in these exposures studies were adult non-professionals who use pesticides on their own gardens and lawns. Many of the volunteers selected as subjects in these studies were members of garden clubs. All volunteers made their applications without specific instruction from the study investigators. Unit exposures from these studies were available for various clothing scenarios that consider individuals wearing short pants and short sleeved shirts, to long pants and long sleeved shirts. For this assessment, OPP assumed that all applications were performed using short pants.[1] Based on the Unit Exposure values generated in this study, UE's used in this assessment for the dermal and inhalation exposures were as follows: (i) for dermal exposure, a lognormal distribution with arithmetic mean of 0.69 mg/lb ai handled and arithmetic standard deviation of 0.36 mg/lb ai handled, truncated at the estimated 99th percentile of 1.93 mg/lb ai handled and (ii) for inhalation exposure, a uniform distribution bounded by the low and high measures values of 0.00019- and 0.0096 mg/lb ai handled, respectively.

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[1] A survey conducted by Doane and Gallup (Johnson et al., 1999) on behalf of the ORETF identified 70% of those who treat their lawns wear short sleeved shirts while applying granular formulations. Likewise, 32% reported wearing short pants while applying granular formulations. Sensitivity analysis performed by OPP demonstrated that significant differences in Unit Exposures existed only between long pants and short pants, and that no significant differences existed between any of the other clothing scenarios (i.e., short- vs. long-sleeves did not impact estimated exposures). However, these significant differences in unit exposure between long pants and shorts had negligible effect on total MOEs, and thus, for this assessment, OPP assumed that all applications were performed using short pants.

Table I.D-1. Pesticides and Use Scenarios Considered in the Residential/Non-Occupational Regional Assessments

Pesticide	Golf Course	Lawn Care	Home Gardens	Public Health	Pest Strip	Pet Uses
Acephate	Used in Regions A, E, F, and G	None	Edible Foods: None Ornamentals: All Regions	None	None	None
Bensulide	Used in Regions A, C, D, E, F, and G	Used in Region F	Edible Foods: None Ornamentals: None	None	None	None
DDVP	None	None	Edible Foods: None Ornamentals: None	None	All Regions	None
Disulfoton	None	None	Edible Foods: None Ornamentals: All Regions	None	None	None
Fenamiphos	Used in Regions A, C, E, F, and G	None	Edible Foods: None Ornamentals: None	None	None	None
Fenthion	None	None	Edible Foods: None Ornamentals: None	Used in Regions A, and G	None	None
Malathion	None	None	Edible Foods: All Regions Ornamentals: All Regions	Used in Regions A, D, E, F, and G	None	None
Naled	None	None	Edible Foods: None Ornamentals: None	Used in Regions A and D	None	None
TCVP	None	None	Edible Foods: None Ornamentals: None	None	None	All Regions
Trichlorfon	Used in Regions C, D, E, F, and G	All Regions	Edible Foods: None Ornamentals: None	None	None	None

The application rate used in the assessment was taken as a point estimate equal to the maximum (label) application rate. For lawn size, OPP selected a uniform distribution of lot sizes ranging from 500 to 15,000 ft^2. This range considers smaller lawns for residences such as town houses. Information in a survey conducted by the ORETF also indicates that many pesticide users make spot treatments of insecticides. The upper bound of 15,000 ft^2 (~1/3 acre) appears reasonable given the type of application equipment assumed to be used by residential applicators (rotary granule spreaders). Information on frequency and timing of applications for pesticides were obtained from Representative Cooperative Extension Service publications and are described in each of the region specific section in Part II of this assessment.

Table I.D-2. Scenario-Specific Residential Exposure Data Inputs

Parameter		Value	Assumptions	Input Format	Data Source
Hand Pump Sprayer for Ornamentals					
Unit Exposure	-inhalation	0.002-0.0142 mg/lb ai handled	hand pump sprayer	Uniform Distribution	ORETF (Merricks, 1997)
	-dermal	mean of 78.2 and a SD of 75.7 mg/lb ai handled	hand pump sprayer	Lognormal Distribution	
Distribution includes wearing short pants and short sleeved shirt and were truncated at the 99th percentile.					
Area Treated		500-2000 ft^2	median home 2250 ft^2 assumed all one floor, with 2.5-10 ft. ornamental bed width	Uniform Distribution	US Census
Application Rate		label directions	rate per gallon treating 500-1000 ft^2	Uniform Distribution	(Merricks, 1997)
Treatments per Season		1-4	two-week intervals (on average based upon survey and label directions)	Cumulative Distribution	ORETF
Malathion on Edible Food Crops/Gardens and Home Orchards					
Area treated		135-8000 ft^2		Log Normal Distribution	ORETF with the National Garden Survey
Time Spent in Garden		0.083 -1 hour		Uniform Distribution	ORETF
Transfer coefficients		100-5000 cm^2/hr	activities=harvesting and maintenance of edible food crops. Accounts for a wide variety of gardens and activities	Uniform Distribution	(Korpalski and Bruce, 2000)
Number of applications		1-5	1 app.=32.6%, 2 app.=36.5%, 3 app.=14.3%, 4 app.=12.2%, 5 app. =4.4%	Cumulative	ORETF with the National Garden Survey

Parameter		Value	Assumptions	Input Format	Data Source
Ornamental Granular Incorporated Treatment-Disulfoton					
Unit Exposure	-inhalation	0.00001 mg/lb ai	Based on 1/2LOQ	point value	(Merricks, 2001)
	-dermal	mean of 0.18 and a SD of 0.29 mg/lb ai (trunc. at 99th%tile)	Distribution assumes the applicator is wearing short pants and short sleeved shirt.	Lognormal distribution	(Merricks, 2001)
Application rate		label		point value	
Frequency of application		1-3	1 app.=63%, 2 app.=32%, 3 app.=5% at six-week intervals		ORETF with the National Garden Survey
DDVP-Pest Strips					
Concentration in Air		0.005- 0.11 mg/m^3 over 120 days	samples taken at 1, 7, 14, 28, 56, and 91 day intervals and adjusted proportionately to account for smaller strips than measured in Collins and DeVries, 1973.	uniform distribution reflecting the range each sample day	Collins and DeVries, 1973

b. Post-application Dermal and Non-Dietary Exposure Data

i. Dermal Exposure-Residue Contact Data

The fate of pesticides applied to turf, and subsequent human contact, is a key variable for assessing post-application dermal exposure and can be an important exposure pathway to consider as part of a cumulative assessment. This exposure pathway was evaluated here in the OP Cumulative Risk Assessment by using data from a number of available studies (described in more detail below). Briefly, post-application dermal exposure (mg pesticide) is calculated by multiplying the transfer coefficient (cm^2/hr) derived from literature and other studies by the time spent on the lawn (hr) and the residue concentration on the lawn (mg/cm^2). For this assessment, the transfer coefficient and the time spent on lawn were represented by a distribution of values while the residue concentration on the lawn was represented by a time series of concentration values (which accounted for residue degradation over time). The transfer coefficients used in this equation were developed by dividing the hourly dermal exposure (µg/hr) obtained from a set of activities by the measurement commonly referred to as turf transferable residues (TTR) ($\mu g/cm^2$). Since none of the dermal exposure studies used to estimate hourly exposure in the above chemical specific residue studies permitted direct calculation of the TTR, the transfer coefficients for this assessment were instead for this assessment developed by assuming a transfer efficiency of 0.5% for granular formulations and 1% for spray formulation. This was done for two reasons:

- to make use of available dermal exposure measurements in the above studies which are not influenced by TTR method, and
- to make use of the available residue dissipation data for which there are no corresponding dermal exposure transfer coefficients.

The values of 0.5% and 1% are within the range of efficiency for the existing chemical specific TTR data. To account for the additional uncertainty of assuming a certain transfer efficiency to develop the transfer coefficients, TTR data having transfer efficiencies lower than 0.5% (granular) or 1% (spray) were adjusted upwards to make up the difference in efficiency. If the transfer efficiency of the TTR data was higher than 0.5% for granular formulations or 1% for spray formulations, they were not adjusted.

For a more detailed discussion of the relationship of transfer coefficients and TTRs please refer to the "Overview of Issues Related to the Standard Operating Procedures for Residential Exposure Assessment" presented to the FIFRA Scientific Advisory Panel on September 21, 1999.

Using the above-indicated calculation methodology, several exposure studies were used to assess post application dermal exposure to individuals reentering treated lawns. Separate studies are available, and used, for kids and adults. These studies are described in additional detail below:

Children's Exposure: Two studies were used to assess exposure to kids under granular and spray application scenarios. One study (Black,1993) investigated dermal exposure values of young children who are exposed to a non-toxic substance used to represent a spray application scenario. In this study, children performed unscripted activities on turfgrass treated with a non-toxic substance used as a whitening agent in fabrics. The subjects of the study were 14 children aged four to nine years old. The children performing the unstructured activities were provided toys and were observed in the treated area for a period of one half hour. Activities recorded included the following classifications:

- Upright (standing, walking, jumping and running)
- Sitting (straight-up, cross legged, kneeling, crouching and crawling)
- Lying (prone or supine)

Dermal exposure was measured by fluorescent measurement technology described in Fenske et al., (1986). Measurements on various body parts were expressed as μg/body part (e.g., hand, face, etc.) and as concentration ($\mu g/cm^2$). These concentrations were normalized to represent the surface area of children three to four years of age for use with a standardized body weight of 15 kg. Standard surface area values were taken from the Agency's Exposure Factors Handbook.

In a second study (Vaccaro, 1996) in which a granular formulation was used, seven adults performed structured activities intended to mimic a child's activities. These activities included:

- Picnicking
- Sunbathing
- Weeding
- Playing frisbee
- Playing touch football.

The subjects performed these activities for a period of four hours beginning after the turf had dried. Turf had been treated earlier with a granular form of chlorpyrifos and exposure was estimated in the study by monitoring the amount of a chlorpyrifos metabolite – 3,4,5, 6-TCP – excreted over the following period of 6 days. This method directly measures internal dose and was used to back-calculate a generic "to the skin" transfer coefficient by using chemical specific dermal absorption data for chlorpyrifos (Nolan et al., 1993) These data were further adjusted to account for differences in surface area of adults vs. children.

The transfer coefficients (cm^2/hr) for children estimated from these two studies are summarized below in Table I.D-3:

Table I.D-3. Transfer Coefficients for Dermal Exposure to Lawn and Public Health Uses for Children 1-6 Years of Age

Vacarro - Granular (scripted)	Black - Spray (unscripted)
714	2844
1042	3594
1042	3776
1485	4051
1736	4103
2758	4357
4785	4902
	6812
	8395
	8746
	9119
	9885
	10713
	16008

A lognormal distribution was used to fit these transfer coefficients values and an arithmetic mean and standard deviation for each distribution was calculated[2]. Specifically (for children's exposures) the OP cumulative assessment used a distribution for the transfer coefficient defined as a lognormal distribution with an arithmetic mean of 7265 cm^2/hr and a standard deviation of 4621 cm^2/hr for the spray application. For the granular application, the distribution used to define the transfer coefficient was a lognormal distribution with an arithmetic mean of 2225 cm^2/hr with a standard deviation of 2162 cm^2/hr. In each case, the lognormal distribution was truncated at the calculated 99th percentile of the distribution (i.e., 23,769 cm^2/hr for the spray application and 10,623 cm^2/hr for the granular application) in order to avoid a distribution which contained values that were well-beyond those that are deemed reasonable.

Adult Exposures: The Vaccaro study data discussed above were also used to assess exposure to adults under granular and spray application scenarios. These data are presented below in Table I.D-4:

[2] See Appendix 3 of "Guidance for Submission of Probabilistic Human Health Exposure Assessments to the Office of Pesticide Programs [draft dated 11/4/98] available at http://www.epa.gov/docs/fedrgstr/EPA-PEST/1998/November/Day-05/6021.htm for more information.

Table I.D-4. Transfer Coefficients for Dermal Exposure to Lawn and Public Health Uses for Adults 18 Years of Age and Older

Vacarro - Spray (scripted)	Vacarro - Granular (scripted)
3348	1229
6770	2813
7217	2813
8779	4010
9895	4688
11243	7446
13169	12920
13243	

A lognormal distribution was used to fit these transfer coefficients values and an arithmetic mean and standard deviation for each distribution was calculated (see footnote 2 in this chapter). Specifically (for these adult exposures), the OP cumulative assessment used a distribution of values for the transfer coefficient characterized by a lognormal distribution with an arithmetic mean of 9,784 cm^2/hr and a standard deviation of 5,515 cm^2/hr for the spray application. For the granular application, the distribution used for the transfer coefficient was characterized with a lognormal distribution with an arithmetic mean of 6,370 cm^2/hr with a standard deviation of 7,789 cm^2/hr. In each case, the lognormal distribution was truncated at the calculated 99th percentile of the distribution (i.e., 28,907 cm^2/hr for the spray application and 37,250 cm^2/hr for the granular application).

ii. Non-Dietary Exposure Data Hand-to-Mouth Behavior

The assessment also incorporated exposure from hand-to-mouth activity by children on lawns. Briefly, exposure through this pathway is calculated as the product of the following factors: hand-to-mouth contact frequency (hr^{-1}), surface area of inserted hand parts (cm^2), saliva extraction efficiency (unitless), wet hand adjustment factor (unitless), and hours spent on lawn (cumulative distribution)[3].

[3] The cumulative distribution used for hours spent on lawn by children was obtained from the Exposure Factors Handbook and represents a cumulative distribution for "do-ers" only, i.e., a cumulative distribution for only those children that reported spending at least SOME time on the lawn (i.e., it does not consider that some children on any given day DO NOT spend time on the lawn). Thus, the cumulative distribution assumes that some time is spent on the lawn by each child. To the extent that this overestimates time spent on the lawn, this overestimates exposure by this pathway. On the other hand, this cumulative distribution for time spent on the lawn is not stratified by season. To the extent that children spend time on the lawn during the seasons when applications occur, this may underestimate exposure. On balance, however, OPP believes that the distribution used is a reasonable, yet conservative estimate of time spent on the lawn during the relevant portions of the year.

Surrogate data to evaluate non-dietary ingestion through hand-to-mouth behavior in young children consist, in part, of observations reported in Reed et al., 1999 concerning the frequency of hand-to-mouth activity. This study addressed the mouthing behavior and other observations of children situated indoors, ages three to six at day care (n=20) and children ages two to five at home (n=10). The children were video taped and the frequency of hand-to-mouth events were enumerated after the taping. The hourly frequencies of the hand-to-mouth events reported were a mean of 9.5 events per hour, a 90th percentile of 20 events per hour and a maximum of 26 events per hour. These data were used to construct a uniform distribution to represent the frequency of hand to mouth activity bounded by a low value of 0 events/hr and a high value of 20 events/hour.

The observations reported by Reed, and discussed above, are based on children in real world settings. However, they provide little information regarding the characterization of the hand-to-mouth event, residue transfer efficiency, or extraction efficiency of the residues on the hands by saliva during the mouthing event. For these values, additional assumptions and studies to address the transfer efficiency of turf residues by wet hands are needed. Variables addressing this exposure pathway are discussed in the following below:

- Based on previous conversations with the SAP, each hand-to-mouth event has been estimated to equal one to three fingers or 6.7-20 cm^2 per event. To account for the fact that a child may touch nothing between successive events, and the fact that the event may not result in insertion of fingers at all (Kissel et al., 1998), a uniform distribution of 0 to 20 cm^2 per event was assigned.

- Hands wet from saliva are reportedly more efficient at residue transfer than dry hands. A uniform distribution of transfer efficiency multipliers of 1.5 to three times was selected to address the increased efficiency of wet hands. Wet hands had higher transfer efficiencies than dry hands and other TTR methods addressed in a study performed by Clothier et al., 1999. The TTR methods used in the study had similar efficiencies as the chemical specific lawn residue data (TTR data) used in this assessment.

- To address the removal of residues from the hands by saliva during the mouthing event several studies were considered. The removal efficiency of residues on hands by saliva and other substances (e.g., ethanol) suggests a range of removal efficiencies from 10% to 50% (Geno et al.,1995; Fenske and Lu 1994; Wester and Maibach 1989; Kissel et al.,1998). Thus a uniform distribution of 10% to 50% was used in this assessment.

- The time spent on the lawn was estimated as a cumulative distribution ranging from 0.25 hours to 3.5 hours. This data was obtained from the Exposure Factors Handbook and represents children aged 1 to 4 years old. To be protective of children and to address the uncertainty of the upper percentiles of the exposure factor data, OPP selected a cumulative distribution from Exposure Factors Handbook Table 15-80 with a bound of 3.5 hours for children. This distribution represents the

amount of time spent outdoors. This allows for the time that children spend outdoors not only at home but also in parks and near schools.

The percent contribution to total exposure via non-dietary ingestion continues to be difficult to quantify. This includes the variables discussed above as well as issues regarding the utility of using children's hand-to-mouth frequencies based on indoor activities for outdoor exposure scenarios. There are also differences in mouthing behavior based on active and quiet play with increased mouthing likely to be during activities of quiet play. Limited data evaluated by Groot et al.,1998 suggests there can be longer durations of mouthing activities for children aged six to 12 months (exceeding 160 minutes per day) than children 18 to 36 months (up to 30 minutes per day). However, children in this age group are not likely to be engaged in the higher post application lawn activities which OPP is currently modeling. Additional data for very young children (under the age of two) are needed in addition to delineating the frequency differences between hand-to-mouth events for children engaged in active and quiet play. The Agency recognizes this is an evolving field of study and that additional research is also needed to evaluate the distribution of behaviors across different age ranges with a view towards the influence of factors such as socioeconomic status.

7. Home Garden Applicator and Post Application Exposure Data

The US EPA National Home and Garden Pesticide Use Survey (1992), as well as various proprietary data sources were used to estimate dermal and inhalation exposure of individuals applying OPs to ornamental gardens, fruit and vegetable gardens, and home orchards. In addition, post-application dermal exposures were assessed for individuals harvesting or performing post application maintenance activities in home fruit and vegetable gardens and orchards. Both applicator and post-application scenarios are described in additional detail below.

Applicator Exposures: As described for dermal lawn applicator exposure, dermal exposures to applicators in home garden scenarios were similarly calculated as the product of the Home Garden Unit Exposure (mg/lb ai handled), application rate (lbs ai/ft^2), and area treated (ft^2). Both Unit Exposure and area treated were inserted in the calculation as a distribution, while application rate was entered as a uniform distribution .

For spray applications, Unit Exposure was estimated from a surrogate study with volunteers applying carbaryl to shrubs and trees using a small tank sprayer. This data was used in developing unit exposures for application of acephate and malathion to ornamentals. These data are presented below in Table I.D-5:

Table I.D-5. Applicator Unit Exposures for Using a Hand Pump Sprayer μg/lb ai handled for Ornamental Uses of Acephate and Malathion (also for home Vegetable/fruit Gardens (malathion only)

Replicate	Short-Sleeved Shirt, Short Pants	Inhalation
2	25348.3	2.3
4	51515.8	2.7
6	125828.3	2.0
8	26598.1	2.1
10	354396.6	3.2
12	55550.5	2.9
14	118695.9	2.3
16	173841.6	9.3
18	45160.0	5.7
20	39757.8	9.2
22	46075.7	2.1
24	14886.1	2.3
26	35911.5	2.3
28	81656.0	2.0
30	76548.2	14.2
32	74890.0	6.6
34	46498.0	2.1
36	36582.8	13.4
38	25014.7	2.0
40	63485.8	10.8

For dermal exposures, distributions for Unit Exposure through acephate and malathion ornamental uses (log normal with an arithmetic mean of 78 mg/lb ai handled, a SD of 76 mg/lb ai handled, truncated at 99th percentile value of 372 mg/lb ai handled, for application rate (uniform distribution specific to pesticide being assessed and detailed in Part II of this document), and for area treated (uniform distribution with a minimum value of 500 ft^2, and a maximum value of 2000 ft^2) were used. This latter value is based on US census data indicating a median house area of 2,225 ft^2. For this assessment, it was assumed this area was for one floor having a perimeter of ~200 linear feet. The ornamental beds were assumed to be 2.5 to 10 feet wide.

For granular disulfoton applicator exposures through the dermal route, chemical specific data measuring exposure of individuals using a shaker can of disulfoton granules to the soil around roses followed by soil incorporation are

available and were used in the OP CRA. Distributions for dermal unit exposure for applications to shrubs were developed from the following data in Table I.D-6:

Table I.D-6. Dermal Unit Exposures (μg/lb ai handled) for Applicator Using Disulfoton on Shrubs and Flower Beds

Replicate	Shrub
1	134
2	304
3	187
4	150
5	35.3
6	172
7	45.1
8	16.3
9	94.6
10	360
11	41.1
12	245
13	13.9
14	69.9
15	161

Note: all inhalation replicates were non-detect/loq - LOQ = 1.5 μg.

Specifically, a lognormal distribution with an arithmetic mean of 0.18 mg/lb ai handled, a SD of 0.29 mg/lb ai handled, and a truncation point at 1.31 mg/lb ai handled (99th percentile) was used for dermal Unit Exposure and a point estimate was used for application rate. This point estimate for application rate was specific to pesticide of interest and is detailed in Part II of this document. A uniform distribution was used for area treated bounded by a minimum value of 10 ft^2, and a maximum value of 2000 ft^2. As described above, this value is based on US census data indicating a median house area of 2,225 ft^2. For this assessment, it was assumed this area was for one floor having a perimeter of ~200 linear feet. The ornamental beds were assumed to be 2.5 to 10 feet wide.

Based on ORETF-submitted data, applicator inhalation unit exposures were represented by a uniform distribution for acephate and malathion ornamental uses, and as a point estimate for disulfoton ornamental use. Specifically, Unit Exposures for acephate and malathion ornamental uses were represented by a uniform distribution with a lower bound value of 0.002 mg/lb ai handled and an upper bound value of 0.0142 mg/lb ai handled (which represent the minimum and maximum measured values as per Table I.D-5 above) ; application rate was represented by a uniform distribution specific to the pesticide of interest and detailed in Part II of this document; and area treated was considered as a

uniform distribution with a minimum value of 500 ft^2, and a maximum value of 2000 ft^2 based on US census data indicating a median house area of 2,225 ft^2. For this assessment, it was assumed this area was for one floor having a perimeter of ~200 linear feet.

For applicator inhalation exposures for disulfoton, point estimates were used for unit exposure (0.00001 mg/lb ai handled) and application rate. The point estimate for inhalation Unit Exposure represents ½ the LOQ, since all measured inhalation unit exposures were less than the analytical limit of quantitation. The point estimate for application rate is specific to disulfoton and detailed in Part II of this document in the regional assessments. A uniform distribution with minimum value of 500 ft^2, and a maximum value of 2000 ft^2 was used to represent area treated. This value is based on US census data indicating a median house area of 2,225 ft^2. For this assessment, it was assumed this area was for one floor having a perimeter of ~200 linear feet.

Post-Application Exposures: Post-application exposure while harvesting or performing post application maintenance activities in home fruit and vegetable gardens and orchards was assessed using a wide range of transfer coefficients to account for the diversity of gardens and types of activities. Specifically, post application exposure was estimated as the product of a transfer coefficient (cm^2/hr), time spent in the activity (hrs), dislodgeable residue concentration (mg/cm^2), and the dermal absorption factor (unitless).

For the above calculation, the transfer coefficient was characterized as a uniform distribution ranging from 100 to 5000 cm^2/hr to account for and reflect a wide range of tasks for gardeners. The time spent harvesting or performing post-application maintenance activities was represented by a uniform distribution ranging from 0.0833 hr/day to 1 hr/day. These estimates of time spent in the garden performing post application activities (as well as the frequency of applications) were based on survey data performed by the Outdoor Residential Exposure Task Force (ORETF). Dislodgeable residue concentrations (expressed in mg/cm^2) were expressed as a time series of values collected from chemical-specific dislodgeable residue data obtained from studies performed in California (for Western regions) and Pennsylvania (for Eastern regions) and detailed in the region specific sections in Part II of this document. Timing and frequency aspects (on both a regional and chemical-specific) of post-application gardening activities were based on information available in representative state cooperative extension service publications, and regional use data was based on information available in the National Home and Garden Pesticide Use Survey and Kline Professional Markets Reports (1997-1998).

8. Golf Courses Post Application Exposure Data

The potential dermal exposure of individuals playing golf on treated golf courses was estimated using chemical-specific turf residue data and transfer coefficients derived from surrogate dermal exposure data. Specifically, post-application exposure to residues from golf courses (in mg) was calculated as the product of transfer coefficient (cm^2/hr), the time spent golfing (hr), and the turf residue value (mg/cm^2). The percent of the population playing golf and the percent of golf courses that are treated with any specified OP was also considered and incorporated into the assessment.

The surrogate data used to derive transfer coefficients were based on two measurements of four individuals playing golf on two golf courses treated with chlorothalonil (Ballee, 1990), and the exposure of golfers (four volunteers) to flurprimidol (Moran et al., 1987). The data are presented below in Table I.D-7:

Table I.D-7. Golfing Transfer Coefficients ($\mu g/cm^2$) for Post Application Dermal Exposure:

Chemical	Transfer Coefficient
Chlorthalonil	391
	329
	561
	547
	592
	533
	385
	508
	756
	522
Flurprimidol	264
	278

For both studies, an assumed transfer efficiency of 1% was used to calculate the transfer coefficients, since the studies were conducted using spray-able formulations. Based on these two studies, a lognormal distribution with an arithmetic mean of 483 cm^2/hr and an arithmetic standard deviation of 185 cm^2/hr was used to represent the transfer coefficient. This distribution was truncated at the calculated 99th percentile value of 1066 cm^2/hr. The exposure duration for individuals playing golf was assumed to be a uniform distribution bounded at the low end by two hours and at the upper end at four hours. The four-hour value was obtained from a 1992 survey conducted by the Center for Golf Course Management.

To establish the percent of individuals playing golf, the above-mentioned 1992 study was used. It was reported here that an average of 12.2% of the population plays golf. To determine the likelihood of playing golf on a treated golf course, percent of golf courses treated data provided by Doane's GolfTrak (1998-1999) was used. These data indicated anywhere from 5 to 85% of golf courses are treated with any specified OP depending upon the identity of the OP and the region of use. Additional details concerning the chemical- and region-specific use patterns used in the estimation of exposures through this pathway are present in Part II of this document.

9. Public Health Post Application Exposure Data

Assessment of post-application exposure to public health sprays was conducted in a manner similar to the method used to assess post-application exposure to lawn chemicals. That is, 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. What differs between the public health spray scenario and post application lawn exposure scenario is the source strength of the residues deposited on the lawn from the public health sprays. The amount of residues that contact and may be present on the lawn can be predicted from the application rate for the various public health sprays and the application specifics, such as equipment type and spray nozzle settings. The percent of the application rate that is deposited on lawns following ground applications of public health sprays is based on a study by Tieze, et al. (1995) which measured the percent of the mosquito spray that is deposited on lawns following ground applications. These deposition values ranged from 3.8 to ~5%. For aerial applications, the percent of the application rate that is deposited on lawns were calculated using the spray drift model AgDrift which were reported (an discussed) in the individual risk assessments for malathion, naled and fenthion. These values ranged from approximately 15 to 30%. To address the uncertainty regarding the percent of use by ground equipment and or aerial equipment, a uniform distribution for deposition bounded by 3.8% and 30% was used. Inhalation exposure to public heath mosquitocide use was not addressed since there are no refined models to address this scenario. It is also expected that near-infinite dilution based on the outdoor location mitigates this exposure.

Timing aspects and estimates of percent of use are based on conversations with representatives of Florida Mosquito Abatement Districts (Whichterman) Florida A&M (Dukes) and Health Canada (Dr. Burke) for Black Fly. For other regions having public health spray uses, a spray schedule of once every two weeks was assumed for the summer season. Additional region-specific details regarding the application and timing of treatments and chemical-specific details regarding degradation are presented in Part II of this assessment.

10. Indoor Uses Inhalation Exposure Data

The only OP pesticide registered for indoor use is DDVP. This was assessed as a resin impregnated pest strip limited to unoccupied areas such as closets and cupboards. Exposures through crack and crevice treatments with DDVP were evaluated in the Preliminary Cumulative Risk Assessment, but not evaluate here in the Revised OP Cumulative Risk Assessment (Revised OP Cumulative) since OPP is currently in negotiations with the registrant regarding crack and crevice use.

Furthermore, estimated exposures through the DDVP pest strips were modified in this revised CRA to account for additional mitigation actions being taken and/or negotiated by the Agency. Specifically, use is expected to be limited to unoccupied areas such as closets and cupboards with the corresponding size of the pest strip reduced to account for the smaller spatial

volume being treated[4]. Exposure while handling the impregnated pest strips is expected to be minimal.

Thus, only post-application inhalation exposure was estimated for adults and children, with applicator exposure considered negligible and not evaluated.

Briefly, post application inhalation exposures (expressed in mg) were calculated in the OP CRA using the following equation:

$$E = C_{air} \times BMR \times H \times VQ \times MET\_TIME$$

E = Exposure through the inhalation pathway (mg)

C_{air} = residue concentration in air (mg/m^3),

BMR= Basal Metabolic rate (MJ/hr) which is specific to a CSFII individual's age, sex, and weight

H = 0.05 m3/MJ, a constant representing the volume of oxygen consumed (at standard temperature and pressure) in the production of 1 MJ of expended energy.

VQ= 27 (unitless), a conversion factor reflecting the ratio between the amount of air breathed to the amount of oxygen obtained

MET_TIME (hr) which represents a distribution reflecting the sum (over a day) of the product of an unitless activity-specific metabolic factor and the amount of time spent in that activity (summed over all activities in a day).

The residue concentration in air (C_{air}) is represented by a time series of calculated concentrations in homes using reduced -size DDVP pest strips in closets and/or cupboards. Specifically, use of a smaller pest strip was assumed to produce a proportionately smaller air concentration. Thus, the air concentrations in this revised CRA were estimated by multiplying the measured concentration values found under a "whole-house" scenario following use of an 80 gram (as per Collins and DeVries, 1973) by either 0.26 or 0.066 to represent use of Pest Strips of 21 g or 5.25 g size.[5]

The BMR term in the above exposure equation is calculated internally by the Calendex software and represents a point estimate specific to and calculated for each individual in the CSFII based on his self-reported age, sex, and weight. Both H and VQ in the above equation are constants as described above. The

[4] Mitigation actions that are currently being negotiated do permit uses in additional unoccupied areas such as attics, basements, and garages, but for purposes of this cumulative assessment exposures through these uses were not assessed.

[5] (21g or 5.25g)/80g

MET_TIME variable is represented by an age group-specific empirical distribution and accounts for the fact that an individual's breathing rate and the specific activities an individual engages in on any given day are NOT independent. That is, this factor (or term) accounts for the interrelationship that exists between the activities that an individual engages in and the breathing rate with which that activity is connected.[6] The genesis and derivation of this MET_TIME variable is discussed in additional detail below.

The MET_TIME term: As indicated earlier, OPP in the OP Preliminary Risk Assessment assumed *independence* between a person's daily activities, the place in which these activities are conducted, and the amount of time spent in these activities. OPP has refined these assumptions in this Revised CRA by using information on each of the activities that an individual engaged in on that day; as well as the location and duration spent in each micro environment (activity-location combination). Thus, this revised CRA appropriately considers the implicit relationship between a specific activity and its and duration. Specifically, OPP obtained information on time-activity data from the US EPA ORD Consolidated Human Activity Database (CHAD) (http://www.epa.gov/chadnet1/). This is a recently constructed meta-database of time use survey data in which time and activity by each individual survey participant is recorded in a chronological diary format. The database, in total, consists of 22,968 person diary days from 10 different time use surveys; there are 875,339 records in total, with each record containing detailed information for each micro environment (activity-location). Since MET values vary by activity, it is possible to calculate breathing rates for each distinct micro environment (reading the newspaper, preparing meals, eating, cleaning the house, etc.) which are weighted by the amount of time spent in that microenvironment. Therefore, an individual who reported spending 24 hours indoors in bed (illness) will have lower indoor inhalation exposure than if that individual had spent 24 hours indoors engaged in various physical activities (8 hours sleeping, 2 hours preparing meals, 2 hours exercising, etc.). In this manner, the calculated total indoor inhalation would be consistent with the information available in the time use diaries.

OPP generated a set of random MET values for each of the 875,339activities reported by respondents in the CHAD database which were consistent with the CHAD-defined distributional form of the activity category. These distribution functions were developed based on a compilation and review of the published literature. For example, the MET value for 'Sleep or nap' (CHAD activity code 14500) follows a lognormal distribution, with mean 0.9, standard deviation 0.1; minimum 0.8 and maximum 1.1. The MET values for 'Prepare and clean-up

[6] In the preliminary OP CRA, an average daily indoor 'breathing rate' factor (MET) was assumed for each individual. This MET factor was assumed to be uniformly distributed and bounded by 1 and 2 (i.e., MET ~U(1,2)). The time spent indoors (representing the duration of exposure) was drawn *independently* using the empirical distribution published in the Exposure Factors Handbook. That time spent indoors and average breathing factors are related was not explicitly considered. As discussed in the main body of this document, OPP has refined this calculation using the time-use surveys available from CHADS/NHAPES in a more comprehensive manner.

food' (CHAD activity code 11110) are exponentially distributed, with mean 2.8, standard deviation 0.9, minimum of 1.9 and maximum of 4. [7]

OPP then multiplied each generated MET value by the corresponding duration during which that activity was undertaken to maintain any correlation between time spent indoors and corresponding activities. For each individual, this MET x Time variable was summed over all records in that individual's daily diary, in which the activity occurred indoors. This value is used in the equation above to calculate that individual's daily indoor exposure. For each age cohort (Age <1, 1-2, etc), a frequency distribution of this MET x Time variable was calculated. The table I.D-8 below presents these distributions for each of the age cohorts. There was no information on respondent age for 224 of the 22,968 person-days. Included in this distribution were individuals (n=74) who did not report spending any time indoors (perhaps camping, or on vacation). Specifically, the table below represents for each of six age groups (children 0-1 years old, children 1-3 years old, children 4-5 years old, etc.) the cumulative distribution of the MET_TIME variable (e.g., 95% of children 1-3 years old have MET_TIME values of 56 or less, 98% of children in this age group have MET_TIME values of 65 or less, etc.). It was this cumulative distribution that was used for MET_TIME variable in the above equation.

Table I.D-8. Distribution of MET Time Values, By Age Group

Cum Pct	0-1	1-3	4-6	7-12	13-17	18+
N	563	2,171	2,088	3,930	1,192	12,800
25%	26	25	19	16	15	15
50%	33	32	25	20	18	21
75%	41	41	32	25	23	29
90%	50	51	41	32	28	40
95%	54	56	47	37	33	49
98%	59	65	53	44	39	58
99%	65	69	59	49	42	67
100%	70	115	101	84	120	130

Use information for the number of households using DDVP pest strips indoors was taken from the National Home and Garden Pesticide Use Survey, 1991. The use of pest strips was assumed to occur year round with these

[7] The amount of information available for specific activities varied across the different activities. These studies also varied with regards to the methodology and instruments used to measure MET corresponding to the different activities.

replaced once every 16 weeks. Based in part on information provided in the National Home an Garden Survey, two percent of the homes were assumed to use DDVP pest strips. Further, it was assumed that in those homes that used pet strips, one 5.25 g strip was placed in a cupboard and one 21 g strip was placed in a closet.

11. Pet Uses

The Cumulative Risk assessment also considered exposures through flea and tick treatments. There are several products containing TCVP which are available in aerosol, pump spray, and powder form. TCVP is also available in impregnated form in pet collars. Exposure assessments were performed for both applicators and non-applicators (i.e., post-application exposures). For applicators, both dermal and inhalation routes were considered. For post-application exposures, only the dermal and oral (hand-to-mouth) routes were considered. Each of these routes is discussed in additional detail below.

Applicator Exposure Dermal and Inhalation: The data for the applicator assessment scenarios are based on studies submitted to the Agency which involved application of a flea and tick products to dogs. In this OP CRA, applicator exposure was calculated as the product of Unit Exposure (in mg/mg ai handled), application rate (mg ai handled/lb of animal), animal weight (in lbs of animal), and number of pets treated. Each of these terms was represented in the calculation as a distribution. Unit Exposure (in mg/mg ai handled) was represented by a cumulative distributions for powder and aerosol/pump spray formulations. This empirical cumulative distribution is presented in Table I.D-9 for powder an aerosol/pump spray applications

Table I.D-9. TCVP Applicator Unit Exposure (mg/mg ai handled) for Pets

		Powder		Aerosol & Pump Spray	
		Dermal	Inhalation	Dermal	Inhalation
Dog	Pct	(mg/mg ai handled)	(mg/mg ai handled)	(mg/mg ai handled)	(mg/mg ai handled)
1	6.7%	0.0016667	0.0000004	0.0028700	0.0000001
2	13.3%	0.0017328	0.0000005	0.0043400	0.0000080
3	20.0%	0.0021848	0.0000007	0.0050300	0.0000090
4	26.7%	0.0022796	0.0000013	0.0053300	0.0000110
5	33.3%	0.0023325	0.0000025	0.0054400	0.0000150
6	40.0%	0.0023699	0.0000028	0.0056000	0.0000150
7	46.7%	0.0024669	0.0000028	0.0058800	0.0000170
8	53.3%	0.0028417	0.0000049	0.0061700	0.0000230
9	60.0%	0.0030423	0.0000052	0.0077300	0.0000230
10	66.7%	0.0034921	0.0000068	0.0093800	0.0000280
11	73.3%	0.0040102	0.0000081	0.0098400	0.0000280
12	80.0%	0.0040917	0.0000110	0.0099600	0.0000280
13	86.7%	0.0050375	0.0000114	0.0102200	0.0000460
14	93.3%	0.0052139	0.0000220	0.0143200	0.0000470
15	100.0%	0.0149053	0.0000238	0.0270900	0.0000550

Application rate in this equation was represented by a uniform distribution depending upon the formulation, as follows:

- for powder, the application rate was represented by a uniform distribution bounded by 21 and 25 mg ai handled/lb of animal ;
- for aerosol, the application rate was represented by a uniform distribution bounded by 11 and 15 mg ai handled/lb of animal; and
- for pump spray, the application rate was represented by a uniform distribution bounded by 9 and 10 mg ai handled/lb of animal.

Animal weight and number of pets were each represented by a empirical cumulative distribution. Animal weights were drawn from an empirical distribution represented in Table I.D-10 and which ranged from 3 to 148 lbs/pet.

Table I.D-10. Pet Applicator Exposure Variable Dog Weights

Cum. PCT of Dogs	Dog Weight (lbs)
1%	3
10%	11
20%	16
30%	20
40%	23
50%	30
60%	43
70%	55
80%	70
90%	80
95%	89
99%	108
100%	148

Source: Boone, Tyler, Chambers: 1999 SoT Poster session; Carbaryl Study MRID 446584-01; and MRID 446584-01.

Pet owners were assumed to treat between one and four pets of identical size as per the information presented in Table I.D-11.

Table I.D-11. Applicator Exposure Variable Number of Dogs Treated

Cum. PCT of Dog Owner-Apps	Number of Dogs
50%	1
75%	2
90%	3
100%	4

Applicator exposures through the inhalation route were calculated in a similar manner to the applicator dermal exposures described above, except that Unit Exposure (in mg/mg ai handled) were specific to inhalation exposures. These empirical unit exposures through inhalation are also presented in Table I.D.9, above. All other terms relating to application rates, animal weights, and number of pets treated remained as described earlier.

Frequency, timing, and probability of TCVP applications to pets were also considered in the OP Cumulative Risk Assessment. Based on the US EPA Home and Garden Pesticide Use Survey, less than one percent of the homes reported using TCVP products for flea and tick treatment on pets. In addition, this survey reported that between 13 and 19 percent of all households reported using a pet collar for control of fleas and tick. This estimate, however, includes **all** pet insecticide collars, not just those that contain TCVP. These use estimates are consistent with proprietary marketing data published by Kline, Incorporated. Since recent estimates for use of TCVP pet collars are not available, the percent of households applying TCVP flea and tick treatments was set in the OP CRA at 15 percent, and was assumed to be equally split (at 5% each) between each of the three (powder, aerosol, and pump spray) TCVP formulations to account for use of both the flea and tick treatments and the TCVP impregnated collars. This is believed to be protective, since high-end exposures from flea and tick treatments are expected to be higher than high-end exposures from pet collars. The household applicators were assumed to reapply TCVP flea and tick treatments every 8 weeks, with use occurring all year in the Southern regions (A,C, E, F, and G), and between April through mid-August (three applications) in the Northern regions (B and D).

Post-Application Exposure – Dermal and Oral (Hand-to-Mouth): Dermal and oral (hand-to-mouth) post-application exposures from TCVP flea and tick treatments were also considered in the OP CRA. Dermal exposures scenarios were considered to be applicable to both adults and children while non-dietary oral exposure scenarios (oral hand-to-mouth) were assumed to apply only to infants and children ≤6 years old.

Dermal Post-Application exposure: Dermal Post-Application exposure (to adults an children) was calculated as the product of Residue concentration (mg/cm^2), the Transfer Coefficient (in cm^2/hr), and the Time spent (in hrs/day). Residue concentration values on the application day were estimated from the

Day 0 residue measurement from a study conducted by Hartz for TCVP Reregistration purposes. Residues measured on Day 0 (4 hours after treatment) ranged from 0.224 mg to 0.413 ug/cm^2 for the powder formulation, 1.1 to 1.9 ug.cm^2 for the aerosol formulation, and 1.2 to 3.5 ug/cm^2 for the pump spray formulation. This information is presented below in Table I.D.12:

Table I.D-12. Post-Application Residues on Day 0 (day=0.167), (Empirical Distribution)

Obs	Powder (ug/cm^2)	Aerosol (ug/cm^2)	Spray (ug/cm^2)
Applicator A	0.413	1.603	2.433
Applicator B	0.224	1.947	1.348
Applicator C	0.395	1.750	1.416
Applicator D	0.299	1.559	3.595
Applicator E	0.230	1.061	1.267

Memo S. Hanley to D. Fuller, March 22, 2002, Re-Issue: HED's Review of Determination of the Dislogeability of Tetrachlorvinphos (TCVP) from the Fur of Dogs Following the Application of an Insecticide Powder; Pump Spray or Aerosol; MRID 454855-01. C Code 083701; DP Barcode D277543, Submission S597121. Tables 5b, 6b, 7b; 8 and 9 (half life).

These residues were assumed in the OP CRA to persist for a period of 32 days with a half life of 3 days (both as estimated from the submitted study). Thus, residue value inputs for dermal post-application exposures were assumed to be a time-series of concentrations values represented initially by a measured Day 0 value which is dissipated over a 32 day period in a manner consistent with a half-life of 3 days.

The Transfer Coefficient used in this assessment of dermal post-application exposures to adults and children was derived from a carbaryl groomer exposure study in which sixteen different veterinary technicians treated/handled eight dogs each, over a two to five hour time period. These transfer coefficients are presented in Table I.D-13 for adults and children and were derived assuming an average transfer efficiency of 2.97% (calculated as the average transfer efficiency of powder (0.62%), aerosol (3.3%) and pump spray (5%)) and an allometric scaling factor to estimate transfer coefficients specific to children.

Table I.D-13. Post-Application Transfer Coefficients for Dermal Exposure to Pet Fur Residues (Empirical Distribution)[1]

Groomer μg exposure	Duration: hrs	μg/hr	ai deposited μg/cm²	Dislodged: 2.97 % efficiency assumed [2] ug/cm²	Transfer Coefficient (adults) Cm²/hr	Transfer Coefficient (children) Cm²/hr[3]
8796	2.88	3054	37.5	1.114	2742	1016
6199	2.58	2403	31.0	0.921	2610	967
1408	3.07	459	18.6	0.552	831	308
2914	2.48	1175	36.4	1.081	1087	403
5667	3.08	1840	32	0.950	1936	717
2527	3.18	795	19	0.564	1409	522
2,348	2.93	801	15.9	0.472	1696	628
2961	2.72	1089	7.75	0.230	4731	1752
1135	4.03	282	14.8	0.440	642	238
14872	3.88	3833	28.8	0.855	4481	1660
1026	3.17	324	16.6	0.493	657	243
13490	4.05	3331	56.98	1.692	1968	729
4275	4.92	869	25	0.743	1170	433
4461	3.45	1293	42.25	1.255	1030	382
1511	3.03	499	8.87	0.263	1894	702
777	3.00	259	48.6	1.443	179	66
				Average	1817	673

[1]Source Carbaryl Groomer Exposure Study (activity - wash/dip/groom). Each vet tech treated/handled 8 dogs: held small dogs w/arms and torso; some dogs climbed on person's shoulders while grooming etc.
[2]Average transfer efficiency 2.97% =(powder (0.62%) + aerosol (3.3%) +pump spray (5%))/3;.
[3]The transfer coefficients derived from this study were adjusted by an allometric scaling factor based on the relative size of children to adults to derive an appropriate transfer coefficient for children Adult:Child surface area ratio - 2.7:1 (avg. Adult 3169: avg child 1174)

Finally, the time spent in this activity was assumed to follow a triangular distribution with minimum value of 0.0333 hours, a most likely value of 0.108 hours, and a maximum value of 1.025 hours (as per Freeman et al, JEAEE, 2001, 11:501-509).

Oral (Hand-to-Mouth) Post-Application Exposure: Post-application exposure through the oral (hand-to-mouth) route was also assessed (for children only) in

the OP CRA. Specifically, exposures through the hand-to-mouth route were calculated as the product of the Residue value (in mg/cm^2), the surface finger area (cm^2), the frequency of events (hr-1) and the time spent (hr). The residue value was obtained from TCVP residue studies. Surface finger area (per event) was assumed to follow a uniform distribution bounded by 0 and 20 cm^2. The frequency of events was assumed to follow a triangular distribution with a minimum value of 0.4 hr-1, a most likely value of 9 hr-1, and a maximum value of 26 hr-1. The time spent with the pet was assumed to follow the same distribution described above for dermal post-application exposures.

As under the Dermal and Inhalation Exposure Scenarios discussed above, applications were assumed to re-occur every 8 weeks, with use occurring all year in the Southern regions (A,C, E, F, and G), and between April through mid-August (three applications) in the Northern regions (B and D).

12. In Summary

In summary, this assessment relied upon the best available data from all sources that could be identified. Sources included chemical specific and task force generated data, as well as data from the scientific literature. When available, regional distinct residue dissipation data were used for the lawn and garden uses. Additional Region-specific information is presented in Part II of this document.

I. Revised OP Cumulative Risk Assessment

E. Water OP Cumulative Risk

1. Introduction: Incorporating Water Exposure Into the OP Cumulative Assessment

FQPA, passed in 1996, imposed an expansion of the risk assessments for food use pesticides by requiring that the Agency perform cumulative risk assessments, i.e., that the Agency assess the risks from different pesticides having a common mechanism of action and focusing on the likelihood that a person will be concurrently exposed to multiple pesticides from multiple sources (food, drinking water, and residential uses). Ideally, data to support the water side of this exposure calculation would provide information on multiple pesticides, and their transformation products, collected from drinking water sources, both surface and ground water, throughout the U.S. at a sufficient frequency to reflect daily and seasonal patterns of pesticide occurrence in water. However, due to the great diversity of geographic-, climatic-, and time-dependent factors that affect pesticide contamination in water, this approach is not possible. For the organophosphorous (OP) pesticides cumulative assessment, the Office of Pesticide Programs (OPP) must rely on both available monitoring data and modeling to develop sufficient data for use in the exposure assessment.

Because drinking water is local, the national exposure assessment for drinking water must address localized areas of the country where exposure to OPs may occur due to drinking water contamination. The methods described in this chapter account for the fact that pesticide concentrations found in drinking water are not random, but are in large part determined by the amount, method, timing and location of pesticide application, the physical characteristics of the watersheds in which the community water systems (CWS) are located, and other environmental factors (such as rainfall) which cause the pesticide to move from the location where it was applied.

OPP is using a probabilistic, calendar-based approach to appropriately match and subsequently combine estimates of pesticide residues in food with estimates of pesticide residues in drinking water to determine reasonable approximations of the amount of OP pesticides ingested in the diet on a daily basis. This approach looks at each individual day of the year and allows appropriate temporal matching of exposures through food and drinking water on a daily basis. Each single day assessment serves as a "building block" for the construction of multiple consecutive day average exposures. This method accounts for the temporal aspect of exposure to OPs due to expected seasonal pulses and seasonal use-patterns.

To realistically estimate exposures, the assessment must take into account which OPs can and do occur together in time and place to account for co-occurrence. Only those exposures which are likely to occur in the same location, in this case a watershed, are combined. Those exposures that are likely to occur on different days and in different locations will be separated. Although multiple OP pesticides may be registered for use on the same site, they may not necessarily be used at the same time.

Risk is a function of both hazard and exposure, and estimation of the exposure portion for drinking water requires data on concentrations of the pesticides in the drinking water and consumption of drinking water for different demographic populations on a daily basis. Drinking water is locally derived and concentrations of pesticides in source water fluctuate over time and location for a variety of reasons. Pesticide residues in water fluctuate daily, seasonally, and yearly as a result of the timing of the pesticide application, the vulnerability of the watershed to pesticide runoff, spray drift and leaching, and changes in the weather. Changes in concentrations also result from the method of application, the location and characteristics of the sites where a pesticide is used, the climate, and the type and degree of pest pressure. Given the data needs and the number of variables that can affect the outcome of the predictive model, it is apparent that the development of daily distributions of concentrations of co-occurring OPs in drinking water for various regions of the US is far-reaching in scope and complexity.

The goal of the drinking water exposure assessment is to provide estimates of distributions of residues (concentrations in drinking water) for use in probabilistic exposure assessment that account for

- daily and seasonal variations in residues over time due to time of application(s) and runoff/leaching events
- year-to-year variations due to weather patterns
- variability in residues from place to place, resulting from the source and nature of drinking water and from the regional / local factors (soil, geology, hydrology, climate, crops, pest pressures, usage) that affect the vulnerability of those sources
- the potential for co-occurrence of more than one OP in location and time only when this is likely to happen

The section that follows discusses briefly what we know about OP occurrence in drinking water sources from available monitoring data and how OP residues in drinking water may be affected by conventional drinking water treatment processes. Based on the needs of the probabilistic cumulative exposure assessment and the information gained from this assessment of monitoring data, OPP designed a drinking water assessment that provides multiple years of daily residue concentrations from drinking water sources in twelve regions across the country. These methods, and a characterization of the results of this assessment, follow the monitoring assessment.

2. What We Know About OP Occurrence in Drinking Water

The drinking water exposure assessment for the OPs would ideally be performed using direct drinking water data, or at least using extensive surface- and ground-water monitoring data as a surrogate. With few exceptions, the quantity, quality and relevance of available monitoring data analyzed in each of the individual OP risk assessments were considered inadequate to support a drinking-water exposure assessment. For many of the OPs, limited or no monitoring data are available. For some OPs, no detections were reported from a limited monitoring set, but it is unclear whether these non-detects signify a lack of transport, or insufficient or non-targeted sampling.

The first part of this section briefly summarizes available surface-water and ground-water monitoring studies that included multiple OP pesticides. Additional monitoring data that focused only on a single OP pesticide are summarized in the individual chemical risk assessments (available through the Office of Pesticide Programs web site at http://www.epa.gov/pesticides/op/status.htm). This is followed by a review of published literature and registrant-submitted studies on the effects of water treatment on OP residues in drinking water. The section concludes with an evaluation of the extent to which the monitoring data fulfill the needs of the cumulative water exposure assessment.

a. Summary of Monitoring Information

Evidence from the available monitoring studies confirms that OP pesticides do occur in drinking water sources. The frequency of detections is generally low, except for chlorpyrifos, diazinon, and malathion, and the magnitude 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.

These OP pesticides can occur together in the same water source at the same time. Chlorpyrifos, diazinon, and malathion are most likely to occur together. However, other OP pesticides may also occur with one or more of these three in local areas. The USGS NAWQA study detected multiple OP pesticides in the same water samples at the same time in almost all of its study units. In some instances, up to 7 of the 11 OP pesticides included in the monitoring study were detected together (see Appendix III.E.1).

In general, surface water sources are more likely to be vulnerable to OP contamination than are ground water sources. OP pesticides are found in streams draining through predominantly urban/residential as well as agricultural watersheds. Chlorpyrifos, diazinon, and malathion are frequently detected in urban streams. While the residential uses of chlorpyrifos and diazinon are being cancelled, residential uses for malathion remain.

Although monitoring for OP pesticides 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.

b. Surface Water Monitoring

Available monitoring has shown that OP insecticides contaminate surface-water resources from both agricultural and urban use. Maximum contaminant levels (MCLs) under the Safe Drinking Water Act have not been developed for the OP pesticides, and OPs will be included on the Unregulated Contaminant Monitoring List for the first time in 2002. As a result, States and public water supplies (PWS) have not often included OPs in surface-water monitoring. Therefore, with the exception of results from the pilot USGS-EPA Reservoir Monitoring Study, few studies include analyses of OP insecticides in raw and finished drinking water.

Available surface-water monitoring for OPs represents a range of surface-water bodies, from agricultural drainage ditches to outflow samples from the largest rivers in the nation. Monitoring data from bodies such as small streams may not represent direct drinking water sources, but can give an indication of possible surface-water concentrations in high OP-use areas. Sampling from streams that are used for drinking-water supply gives an indication of possible concentrations in drinking water. Without direct data at a drinking water intake downstream, however, a risk assessor cannot assume potential exposure at concentrations above or below that detected.

i. Sources of Surface-Water Data

Although the number of "ambient" surface-water monitoring studies which have included OP pesticides as analytes is extensive, extensive monitoring data is not available for all OPs. The largest available source of surface-water monitoring for OPs, the **USGS NAWQA Program**, includes only nine active OPs: chlorpyrifos, diazinon, malathion, phorate, methyl parathion, disulfoton, terbufos, azinphos-methyl and ethoprop. Two other OPs – fonofos and parathion – included in the study have been voluntarily cancelled.

The NAWQA program includes monitoring data for 76 pesticides and covers "more than 50 major river basins and aquifers covering nearly all 50 states" (Figure I.E-1) (http://water.usgs.gov/nawqa/nawqa_home.html). Results of the individual NAWQA study units are highlighted in the appropriate regional assessments and in more detail in Appendix III.E.1.

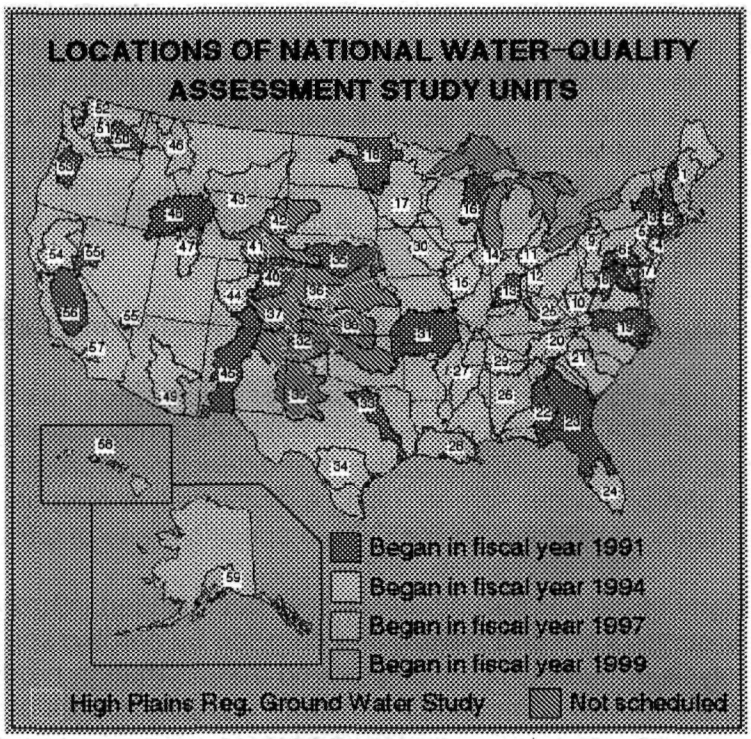


Figure I.E-1. Location of USGS NAWQA study units (Source: USGS).

The USGS **National Stream Quality Assessment Network (NASQAN)** program monitors water quality in the Rio Grande, Mississippi, Columbia, and Colorado Rivers, four of the nation's largest rivers. This study monitors for the same OPs included in NAWQA. NASQAN was designed to measure the mass flux of constituents such as pesticides and nutrients in these rivers, and so the 41 sampling stations are located at the mouths of these rivers, at the confluence of tributaries entering the

rivers, and at the intake and outflow of reservoirs along their path. Any detection of OPs in these studies is significant because detection in such large water bodies indicates that a large mass of the pesticide has run off to surface water. The relatively small number of stations and relatively infrequent sampling make it more difficult to connect detections in this study to specific OP uses.

State surface-water monitoring programs are most likely to include analytes required by the Safe Drinking Water Act, but may include OPs if consistent with budget priorities and local needs. When available, State monitoring programs are important additions to NAWQA data for a full understanding of possible OP exposure in drinking water. State programs are described in detail in Appendix III.E.2.

The USEPA Office of Pesticide Programs (OPP), USEPA Office of Ground Water and Drinking Water (OGWDW), and USGS National Water Quality Assessment (NAWQA/USGS) initiated a **reservoir monitoring project** to assess pesticide concentrations in untreated and finished drinking water derived from surface water reservoirs. Twelve drinking water reservoirs were selected from a list of candidate drinking water reservoirs which were potentially vulnerable to pesticide contamination. Vulnerable reservoirs are considered to be located in small watersheds with high pesticide use areas and high runoff potential. A summary of the results of this study occurs later in this section and in more detail in Appendix III.E.3.

ii. Completeness of the Surface-Water Monitoring Data Set

Monitoring data is most extensive for chlorpyrifos, diazinon and malathion, the three OP pesticides most frequently detected in agricultural and urban surface waters. States that did include more OPs generally did so as part of a wider screen, using a multi-analyte method, rather than specifically monitoring for the OPs in specific areas of OP use.

Many of the OP parent compounds not included in broad surface-water surveys are short-lived, and degrade by aerobic soil metabolism, photolysis or hydrolysis to longer-lived transformation products. Some of these short-lived compounds transform into degradates of toxicological concern that are more persistent and mobile than the parent compounds. The transformation of disulfoton to its sulfoxide and sulfone degradates is an example. Unfortunately, the toxic transformation products are, by and large, not included in monitoring studies.

Detection of pesticides in surface water is most likely when the sampling corresponds at least roughly to the timing and location of pesticide use. Several monitoring studies illustrate this:

- A series of studies by the California Department of Pesticide Regulation (CDPR) and the USGS investigated OP contamination from winter use as a dormant spray to tree fruits and tree nuts. The frequency and concentrations of OP detections in these studies were both relatively high. Among OPs detected in these studies were methidathion and dimethoate, which are rarely included in other monitoring programs.

- Diazinon and chlorpyrifos in urban streams represents the OP contamination most frequently detected in NAWQA surface water, followed by detection of malathion in urban streams. Since urban uses of these pesticides can occur year-round, and every NAWQA study monitored streams in watersheds dominated by urban or mixed land use, these studies were targeted to the timing and location of these uses.

- A study in the USGS San Joaquin River Basin (SJRB) further confirmed the importance of timing of sampling. Sampling three times per week in this study was more likely to detect higher concentrations than once per week. Sampling once per week was more appropriate for determining the median concentration.

iii. Effects of Study Design

In general, the surface-water studies which included OP pesticides as analytes were not specifically designed to correspond with times and locations of agricultural OP use. For instance, the same suite of nine OPs was included in NAWQA sampling programs nationwide. Azinphos-methyl was detected in surface water in the NAWQA Lower Susquehanna River Basin study unit, an area where azinphos-methyl is used in orchards. NAWQA also included azinphos-methyl as an analyte in three study units that it identified as part of the "Corn Belt." Surface-water sampling in the Lower Illinois River Basin study was specifically targeted to "two watersheds with greater than 90 percent row-crop agriculture and the basin inflow and outflow sites." Azinphos methyl is not used on corn, and it was not detected in any surface-water samples from these three study units. The USGS notes this effect of design in its analysis of OP occurrence in surface water and ground water from 1992 to 1997, reporting that azinphos methyl and ethoprop were not widely distributed in NAWQA and NASQAN studies, but that they "were detected in 43 and 69 percent, respectively, of samples from a few small agricultural watersheds in western irrigated valleys."

The design of the available programs determines their utility for the cumulative drinking water exposure assessment. While the NAWQA program samples in almost all states, a good number of the studies were designed to answer locally important questions for each river basin, and are not uniformly designed. The USGS Pesticide National Synthesis Project elaborates on why the studies are not specifically designed to produce a statistically representative analysis of national water-quality conditions (http://wwwdwatcm.wr.usgs.gov/ccpt/pns_data/data.html).

In comparison to NAWQA, NASQAN includes relatively few sites and samples each year, and is designed to allow an assessment of mass flux from some of the largest rivers. State studies were even more limited, and were most likely to include diazinon and chlorpyrifos in monitoring programs, if OPs were included at all. States that did include more OPs generally did so as part of a wider screen, using a multi-analyte method, rather than specifically monitoring for the OPs in specific areas of OP use.

iv. USGS-EPA Reservoir Monitoring Project

The USGS-EPA Reservoir Monitoring Study (Blomquist et al., 2001; available through the USGS web site at http://md.water.usgs.gov/nawqa/OFR_01-456.pdf) was designed to evaluate potential concentrations of a variety of pesticides and transformation products in untreated and treated drinking water derived from reservoirs. This study included twelve reservoirs covering a range of pesticide use areas across twelve states (Figure I.E-2). The study focused sampling during the period of the year with highest pesticide runoff vulnerability and variability in the post pesticide application season. Each reservoir was sampled quarterly for one year, as well as biweekly for a 4 month post-application period. Two sites were sampled at weekly intervals for 6 months post-application-season to improve the estimate of peak concentrations for short-lived compounds. Additional data collected for each site provided information on watershed properties, water treatment information, and reservoir characteristics.

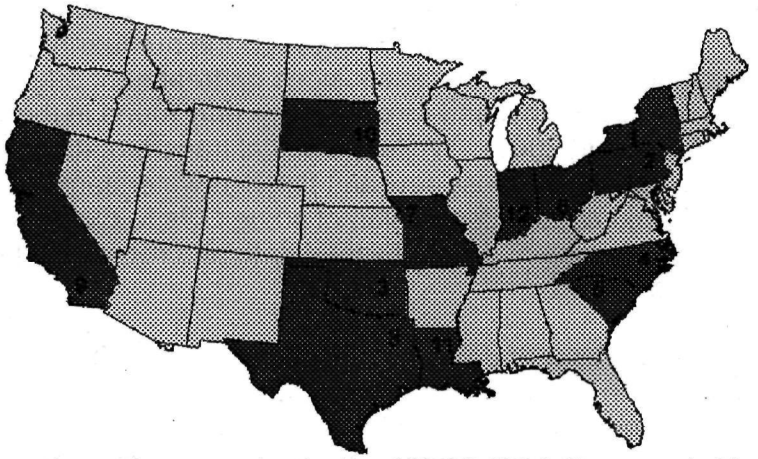


Figure I.E-2. Location of reservoirs in the USGS-EPA Reservoir Monitoring Project

While both untreated (raw) and treated (finished) water samples were taken at each sample time, the sampling scheme does not account for the travel time of the pesticide and its transformation products through the water treatment plant. Therefore, the occurrence and magnitude of pesticides in raw and finished waters cannot be directly correlated. This will likely exaggerate variability in removal efficiencies and limit direct linkage of degradation and formation patterns of pesticides during water treatment.

The pilot reservoir monitoring study provides two years of sampling, with 602 to 626 samples for each of 31 active OP parent and transformation products included in this cumulative assessment. This program included some rarely-monitored OPs, such as tribufos, phostebupirim, profenofos and dicrotofos, and rarely analyzed transformation products.

Thirteen of these 31 compounds were detected in either raw or finished drinking water samples, in spite of extreme drought conditions in 6 of the 12 watersheds in 1999 (see Appendix III.E.3 for details). Diazinon, the most frequently detected OP, was found in 35% of 323 raw water samples but in none of the 227 finished water samples. Although the lack of truly paired raw and finished water samples precludes definitive conclusions, these results suggest that diazinon may be removed by the treatment process. However, the likely transformation product, diazoxon, was not included as an analyte in the pilot program.

Results for other OPs suggest that parent OP compounds are transformed during water treatment. For instance, malathion was detected in raw water samples (2%) while malaoxon was detected in finished water samples (5%). Chlorpyrifos was detected in 5% of raw water samples; neither chlorpyrifos nor its oxygen analog were detected in

finished water. Azinphos-methyl and its oxon were both found in raw and finished water but the difference between the number of detections for each is insufficient to draw conclusions on treatment effects, especially since azinphos methyl and its oxon were only found in the same reservoir once (Missouri in 2000). While the actual transformation process is difficult to assess because raw and finished water samples were not temporally paired, the conversion of some OPs to oxon transformation products is consistent with published data and recent studies submitted by OP registrants.

A small number of detections of other transformation products are consistent with expectations based on the environmental fate properties of the parent chemicals. Fenamiphos and disulfoton were not detected in this limited sampling program, but both the longer-lived sulfoxide and sulfone transformation products were detected in one or two samples each. While their detection in raw water is an indication that drinking water contamination is possible, detections were few enough that the lack of detections in finished water is not a clear indication of removal by treatment.

Diazinon was detected in 10 of 12 reservoirs, and chlorpyrifos was detected in 6, which likely reflects their widespread use. No other OP was detected in more than three reservoirs in this limited sampling. Azinphos-methyl had the highest concentration detected of all parent products (0.114 ug/l in South Carolina raw water). Azinphos-methyl was found in 46% and 32% of samples taken in South Carolina in 1999 and 2000. Azinphos-methyl oxon was detected at a maximum concentration of 0.263 ug/l in Oklahoma, and was detected in 20% of samples in New York and Missouri in 2000. Malaoxon had the highest concentration detected of all analytes with maximum detections in Louisiana of 0.556 ug/l in 2000, and 0.204 ug/l in 1999.

Phostebupirim, which is very rarely included in any monitoring studies, was detected in 10% and 8% of 1999 raw water samples in Missouri and Pennsylvania, respectively. The concentrations were low (0.003 to 0.007 ug/l), but serve as a reminder that OPs may be transported to surface water bodies, even if few monitoring data are available to confirm this.

Although the reservoir monitoring study was not specifically targeted to high OP-use areas, it included more OPs than any previous study. Therefore, it is useful for considering the possibility of exposure to multiple OPs. Of 314 *intake samples* considered, 137 (44%) had one or more detectable OPs. Of the 137 with detectable OPs, 16 (12%) included more than one detected OP. Of 67 *outfall samples* considered, 17 (25%) had one or more detectable OPs, two of those samples (12%) having more than one OP detected. Of 218 *finished samples* considered, 24 (11%)

had one detectable OPs, and none of the finished samples considered here had more than one OP detected.

The pilot reservoir monitoring program confirmed the utility of sampling for a wide range of OPs and transformation products in drinking water, using low levels of detection. Continued and expanded monitoring should improve understanding of potential drinking water exposure, and of the effects of degradation in the field and from drinking water treatment.

c. Ground Water Monitoring

Due to the chemical properties of most of the OP insecticides, drinking-water exposure through contamination of surface-water resources is generally more likely than through contamination of ground water. However, even in regions where surface water is the predominant source of drinking water for most of the population, a significant portion of homes derives drinking water from relatively shallow domestic wells. In some areas of the country, where soils are especially permeable and depth to unconfined ground water particularly shallow, domestic wells represent some of the drinking-water sources most vulnerable to pesticide contamination.

Most OPs were described as unlikely to leach to ground water in the individual risk assessments completed over the last few years. This is due mainly to the relatively short aerobic soil-metabolism half-life of many OPs. However, there are some important exceptions. Several OPs are described as having the potential to contaminate ground water, but lack the data to sufficiently evaluate the magnitude of this risk.

Fenamiphos and its degradates, fenamiphos sulfoxide and fenamiphos sulfone, are the best examples of this problem. These chemicals have been detected at high levels in ground-water studies conducted in Florida, and to a lesser extent in California. Concentrations of fenamiphos and its transformation products detected in the Central Ridge area of Florida ranged as high as 246 ppb (204 ppb fenamiphos sulfoxide) in a retrospective ground-water study.

However, recent ground-water monitoring which includes fenamiphos is scarce. The USGS undertook a fenamiphos ground-water study at seven golf courses in Florida, and reported maximum detections of < 1.0 ug/l each for fenamiphos and its transformation products. The State of Florida reports that its database includes only two wells with detections of fenamiphos sulfoxide in its ground-water database. California collected samples from 40 drinking water wells in fenamiphos use areas during the early and mid 1990s, but did not detect fenamiphos (another round of sampling is currently underway). Hawaii, Michigan and North Carolina report that fenamiphos was not detected in a total of fewer than 100 drinking water or monitoring wells, and fenamiphos is not included among analytes in the NAWQA program.

Therefore, while fenamiphos has been detected in vulnerable to very vulnerable soils in Florida and California, sufficient data is not available which could allow a more detailed monitoring assessment for other areas of the country.

i. Sources of Recent Ground-Water Monitoring Data

The Agency contacted **pesticide lead agencies and other agencies in all 50 States** to inquire whether OPs were included in surface-water or ground-water monitoring (either ambient or drinking water) programs over the last decade. OPP requested recent data since 1) earlier data are more likely to be included in the aggregate assessments of individual OPs, 2) recent data are more likely to reflect current use rates and use areas, and 3) such data are more likely to be in electronic format, accessible either over the Internet or as an e-mail attachment. Government scientists in nearly all States offered to describe or provide summaries of current monitoring programs, or directed the Agency to data which are available online.

As a result of the relative non-persistence of most OPs in soil and the limits on funding for monitoring in State and Federal programs, few OPs are included in ground-water monitoring programs conducted over the last decade. Chlorpyrifos, diazinon and malathion are the OPs most commonly included as analytes in State ground-water monitoring programs. In some States, multiple OPs are included as part of a general screen under EPA methods 507 or 525.5. In such cases, the levels of detection are often higher than in more chemical-specific analyses.

The voluntary cancellation of non-agricultural uses of chlorpyrifos and diazinon affects the ground water assessment for these chemicals. While many of the agricultural uses remain, the Agency believes that most of the ground water monitoring detections of these chemicals are associated with uses that have been cancelled. The termiticide use of chlorpyrifos, which is currently being phased out, represents the use that has led to the highest known concentrations of any OP in ground water. The concentrations of chlorpyrifos measured in wells affected by the termiticide use ranged as high as 2090 μg/l, significantly higher than concentrations found in agricultural areas, which generally are below 1 μg/l.

The **USGS NAWQA program** is the other major source of ground-water data for the OPs. While the NAWQA program has provided a very valuable ground-water data set, it has several important limitations with respect to the cumulative OP drinking water assessment:

- Only nine OPs included in this cumulative assessment are included.

- Many NAWQA ground-water studies included only a single sample of each well in the network. Even if wells were located in OP use areas, the monitoring was not timed to correspond specifically to account for pest pressure and OP application for that particular year.

- A number of land-use studies in the program were focused on urban areas. The phase-out of homeowner uses of chlorpyrifos and diazinon renders such data less useful for our assessment.

Finally, the design of the ground-water studies differs between each study unit, reflecting the local aspect of ground-water quality that was being investigated in each monitoring program. For instance, monitoring in the Eastern Iowa Basins study unit included 65 domestic wells in order to assess the water-quality of the most heavily used aquifers in the study unit. By contrast, one of the ground-water studies in the Ozark Plateaus study unit was designed to evaluate water-quality in domestic wells in cattle and poultry-producing regions. One of the studies in the Southern Florida study unit included wells less than 15 feet deep and located in the drip line of citrus trees, where the depth to the water table was 2 to 4 feet below the land surface. In addition, a study in the Central Arizona Basins study unit included domestic, public supply, and other wells that draw older water (at least pre-1953) from a confined aquifer, which to this point is considered to have had very little hydraulic connection with potentially contaminated shallower ground-water above the confining layer. **The differing design among the different ground-water monitoring studies limits the applicability of statistical methods to the combined NAWQA ground-water dataset for a national OP drinking-water assessment.**

Some OPs are not included in any ground-water monitoring supplied to the Agency, such as phostebupirim, chlorethoxyfos and tribufos. Other OPs have only very limited monitoring data from the 1980s in which a small number of ground-water detections are reported. One example is methamidophos, which was detected in four wells near a Maine potato field in 1986 at concentrations up to 10 ug/l. Such data may not well represent current use or use rates, but may also have underpredicted possible ground-water contamination due to higher analytical detection limits. Older studies which revealed ground-water contamination indicate that exposure to rarely analyzed OPs is possible. However, the lack of extensive, recent ground-water data for some compounds makes it very difficult to quantify the potential risk nationwide.

With few exceptions, ground-water monitoring programs which include OPs are surveys which are not targeted specifically to assess the effects of OP use on ground-water quality. Examples of exceptions include chlorpyrifos termiticide use studies and fenamiphos studies near Florida golf courses. The results of survey studies give some indication of the

possible exposure to populations as a whole. However, since survey studies usually include sampling of wells in areas where OPs are not used, they are less useful for quantifying potential drinking-water exposure in OP use areas.

Few ground-water studies include OP transformation products as analytes. The fenamiphos prospective ground-water studies and the USGS golf-course study mentioned above are rare exceptions. Lack of monitoring for transformation products might be important for other OPs which form sulfoxide and sulfone degradates, such as disulfoton, phorate and terbufos. If these OPs follow the same pattern as fenamiphos, the sulfoxide moieties of these chemicals may be a greater concern for ground-water contamination than the parent compound.

d. Effects of Drinking Water Treatment on OP Pesticides

The weight of evidence from open literature, a registrant-sponsored study, an ORD/EPA laboratory study, and the USGS-EPA reservoir monitoring program show parent OP pesticide residues in water are likely to be transformed during drinking water treatment. The most probable pathway is transformation by oxidation through chlorination and not physical removal. Oxidative transformation products of toxicological concern, such as sulfones, sulfoxides, and oxons, have been detected in finished water samples from water-treatment plants. Although not all oxons were tracked, the USGS-EPA reservoir study suggests that malathion may have been converted to malaoxon as a result of treatment.

Studies have shown oxons to be relatively stable in chlorinated drinking water for at least 48 hours. Although the detection frequencies of oxidative degradation products were low in the reservoir monitoring data, they were more frequently detected in finished water than in raw water. These data suggest oxidative degradation products such as oxons, sulfones, and sulfoxides have a high likelihood of occurrence in finished drinking water.

Appendix III.E.4 provides additional detail on removal and transformation of organophosphorus pesticides and certain degradation products through water treatment. The review extends the OPP water treatment literature review (http://www.epa.gov/scipoly/2000/September/sept-00–sap-dw-0907.pdf). Documents in this report include open literature, registrant-sponsored water treatment data, and the USGS-OPP pilot reservoir monitoring data.

Available information indicates that two common water-treatment methods lead to transformation of some OPs:

- Treatment of water by **chlorine and chlorine compounds for disinfection** can result in transformation of parent OP compounds. The P=S bond of OPs can be oxidized to a P=O bond leading to the formation of oxon transformation products. According to Magara et al (1994), several OPs are transformed to their corresponding oxons in this manner. For instance, diazinon is oxidized to diazoxon, which is relatively stable in chlorinated water for at least 48 hours. In a laboratory study at EPA-ORD's AWBERC facility in Cincinnati, Ohio, about 90% of chlorpyrifos-methyl was removed by chlorine treatment. The removal was most probably due to oxidation of the insecticide to oxons and other products.

- In areas where **water softening treatments** add lime and soda ash to reduce calcium and magnesium levels in water, the pH can increase to about 10 - 11. This high pH can lead to base-catalyzed hydrolysis of the OPs which are susceptible to hydrolysis under alkaline conditions. In the ORD treatment study, more than 99% of malathion was removed during softening treatment. The effects of softening may not be so dramatic for all OPs; although phorate has a 3-day hydrolysis half-life at pH 9, lower removal (20%) of phorate was observed.

A complete review of a registrant-sponsored jar test study on the potential effects of chlorination on six OP pesticides and four oxons (Tierney, et al., 2001) was hindered by incomplete information on the experimental procedures (particularly, water quality data, the impact of sodium thiosulfate on water chemistry, storage stability, and clarification regarding pesticide concentrations above the limit of detection and below the limit of quantification). Despite the lack of information on experimental methods, the data indicate organophosphorus pesticides (acephate, azinphos-methyl, chloropyrifos, diazinon, malathion, and methamidaphos) are transformed in chlorinated drinking water. Chemical oxidation of the organophosphorus compounds led to the formation of oxons for azinphos-methyl, chloropyrifos, diazinon, and malathion. Chloramines were formed during the experiment, and because chloramines have lower oxidizing potential than hypochlorus acid, the extent of degradation and formation of oxidative degradation products (oxons) may be different under conditions of higher free chlorine concentrations.

e. Suitability in Meeting Cumulative Assessment Needs

While the available monitoring studies provide a profile of OP occurrence in water, critical limitations preclude basing the cumulative water exposure assessment solely on monitoring. In particular, the monitoring studies were not designed to characterize daily concentration profiles and are not robust enough to provide daily distributions. Nor have the studies been conducted over a long period of time (typically less than three years) necessary to characterize year-to-year fluctuations due to weather patterns. While the NAWQA study units coincide with a number of high OP-use areas, not all of

the major OP use areas have monitoring data. Lack of monitoring for some compounds make it difficult to completely assess co-occurrence. Finally, monitoring provides a snapshot in time and does not reflect recent mitigation actions, such as lower application rates and fewer applications or cancellation of certain uses or chemicals, initiated for individual chemicals during the risk management phase.

Despite these limitations, water monitoring was used in the cumulative assessment to help identify vulnerable surface water sources, characterize OP residues in ground-water sources, compare relative impacts of OP use on water resources in different locations across the country, and provide a baseline comparison for estimated OP concentrations used in the probabilistic exposure assessment. Appendices III.E.1 and III.E.2 compare estimated OP concentrations with available local monitoring. Significant trends between estimated concentrations and monitoring are highlighted in the regional assessments in Part II.

With the publication of data from the nationwide set of NAWQA study units, more surface-water data for the OPs is available than ever before. However, the cumulative OP drinking-water exposure assessment requires the estimation of simultaneous daily drinking-water exposures to multiple pesticides, which is something that has never been attempted before. Although the available data is extensive, the cumulative drinking-water exposure assessment cannot be solely based on monitoring.

Therefore, the daily drinking water exposure estimates have been generated using the simulation models PRZM and EXAMS. A description of the use of these models for the cumulative OP drinking water exposure assessment follows. The use of models allows estimation of possible concentrations of OPs not included in monitoring programs, or in areas for which monitoring for locally important OPs was not available. As described in the Risk Characterization section, peak values from the modeling are not always as high as some seen in small streams in the NAWQA program. However, the models allow the Agency to estimate a cumulative exposure assessment for **all** OPs used in representative scenarios for each region, even if they do not consistently match all the highest detections for each individual chemical.

3. Drinking Water Assessment Methods

The goal of the cumulative assessment is to aggregate exposure from the organophosphorous (OP) pesticides over multiple routes of exposure (food, drinking water, residential) in a manner that is consistent in time (i.e., those exposure routes that are likely to occur on the same day are combined; those that are not likely to occur on the same day are not combined) and in location (i.e., only those exposures that may potentially occur in the same location are considered together). The Agency needs reasonable approximations of daily

distributions of OP residues (concentrations) in drinking water to combine with food and residential exposures using a probabilistic, calendar-based approach.

This cumulative risk assessment represents the first attempt to quantify possible drinking water exposure to multiple chemicals at the same time. Available surface-water monitoring is not sufficient to allow estimation of potential daily drinking water exposure to the OPs included in this assessment. No currently-available model is specifically designed to simulate the simultaneous application and transport of multiple pesticides in a watershed. Therefore, the Agency looked to available tools to provide these daily exposure estimates for consideration with food and residential exposures.

Because drinking water is local, the national exposure assessment for drinking water must address localized areas of the country where exposure to one or more OPs may occur due to drinking water contamination. The consideration of OP use in specific regions of the country will facilitate the assessment of potential co-occurrence of different OPs in drinking water, leading to a cumulative assessment of OPs in drinking water on a regional basis.

The sections that follow describe the steps OPP has taken to generate regional drinking water exposure assessments as a part of the cumulative OP assessment.

a. Chemicals and Uses Included in the Cumulative Assessment

Table I.E.1 lists the parent OP, transformation product(s) of toxicological concern, and approach for considering the contributions of the transformation products to the cumulative water exposure. Detailed chemical-specific inputs, based on environmental fate studies submitted by the OP registrants, are documented in Appendix III.E.5. These inputs are based on the individual chemical assessments that were published in the REDs.

Table I.E-1. OP Pesticides and Toxic Transformation Products Included in the Cumulative Water Exposure Assessment

Pesticide	Transformation Products of Toxicological Concern	Approach for Including Transformation Product
Acephate	Methamidophos	Conversion from parent to product; max rate based on fate studies
Azinphos Methyl	Oxon	Formed by treatment
Bensulide	Oxon	Formed by treatment
Chlorethoxyfos	Oxon	Formed by treatment
Chlorpyrifos	Oxon	Formed by treatment
Diazinon	Diazoxon, Hydroxy-diazinon	Formed by treatment
Dichlorvos (DDVP)	None	na
Dicrotophos	Monocrotophos	Not in field studies
Dimethoate	Oxon	Formed by treatment
Disulfoton	Sulfone, Sulfoxide	Combined residues
Ethoprop	SME, OME, M1	Not modeled; negligible residues; parent relatively stable
Malathion	Malaoxon	Formed by treatment
Methamidophos	None	na
Methidathion	None	na
Methyl Parathion	Methyl Paraoxon	Formed by treatment
Naled	Dichlorvos (DDVP)	Conversion from parent to product; max rate based on fate studies
ODM	Sulfone	Not modeled; negligible residues
Phorate	Sulfone, Sulfoxide	Combined residues
Phosmet	Phosmet Oxon	Formed by treatment
Phostebupirim (also known as Tebupirimphos)	Oxon	Formed by treatment
Profenofos	None	na
Terbufos	Sulfone, Sulfoxide	Combined residues
Tribufos	None	na

i. Parent Chemicals and Uses

The drinking water exposure assessment includes those OP pesticides with registered outdoor uses that may potentially impact surface- or ground-water sources of drinking water (Table I.E.1). Those pesticides or pesticide uses that are being cancelled and/or phased out as a result of agreements between the Agency and the specific OP registrants, and

those OPs with uses that are unlikely to reach drinking water were not included in the water exposure assessment. Those agreements in place as of May 1, 2002, were considered in this assessment. Revisions since the preliminary assessment in December 2001 include exclusion of fenamiphos and azinphos methyl use on cotton, both of which are being voluntarily cancelled.

ii. Transformation Products

Those OP transformation products identified as being of toxicological concern (Table I.E.1) were included in the cumulative drinking-water risk assessment when environmental fate studies indicate that these products may be formed in the environment or may form as a result of water treatment. Some OP risk assessments did not consider the transformation products quantitatively because no environmental fate data was available, while others assumed that the characteristics of the transformation products were equivalent to that of the parent, or combined limited data with conservative assumptions for a screening assessment.

Sulfoxide and Sulfone Products: The sulfoxide/sulfone products of disulfoton, phorate, and terbufos are often more persistent and mobile than the parent compounds. Full environmental fate profiles are not available for the sulfoxide/sulfone transformation products, requiring some assumptions to be made about their physicochemical properties. The parent OP and two transformation products were modeled as "total toxic residues". Formation and decline curves from aerobic soil-metabolism studies allowed the assessment team to fit a single modeling half-life for the combined residues. However, this required the assumption that all three chemicals were equally toxic, and that the sulfone and sulfoxide had the same soil-water partitioning coefficient as parent.

Oxon Products: Table I.E.1 identifies ten OP pesticides which form oxon transformation products. While the oxons are generally not found at significant levels in the environment, available studies suggest they are formed by water treatment – in particular, through chlorination of the parent OP, as noted earlier. Based on the available studies, OPP assumed that oxons were not formed in the environment and, for the most part, would not be found in signficant levels in untreated drinking water sources. This assumption was supported by the results of the USGS-EPA reservoir monitoring study, in which oxons were detected in the treated water samples but not in samples taken at the drinking water intake.

Transformation To Another Active OP: Acephate transforms to methamidophos and naled transforms to diclorvos (DDVP). For these pesticides, OPP assumed a conversion from one OP to the other based on the maximum percent transformation from available environmental fate studies. Thus, OPP assumed that 25% of applied acephate transformed

into methamidophos and 20% of applied naled transformed into DDVP. The transformed OP as modeled separately, with an application rate that reflected the appropriate percent conversion of the parent OP (with adjustment for differences in molecular weights). The timing of the simulated "application" was off-set by one half-life period. In the case of acephate, this amounted to two days (e.g., the timing of the formation of 25% methamidophos was simulated as occurring 2 days after acephate was applied). Because the half-life for naled was less than 1 day, the 20% DDVP load was assumed to form on the same day as application.

iii. Accounting for Water Treatment By-Products

Limited scientific evidence (section I.E.d) suggests that many parent OP pesticides may be transformed during drinking water treatment, primarily by oxidation through disinfection. The oxidative transformation products of toxicological concern – sulfones, sulfoxides, and oxons – have been detected in treated water. Limited data suggest that these treatment by-products may be stable for sufficient periods of time (for least 24 to 96 hours) to move through the distribution system.

The information is not sufficient to make quantitative adjustments to the cumulative exposure estimates. OPP estimated maximum potential impacts to determine whether additional information is needed by assuming that all OP parents that form oxons, sulfoxides, or sulfones (see Table I.E.1) are completely transformed into those products as a result of oxidation. Where the transformation is less than complete, and where non-toxic products are also formed, the such an assumption will overestimate drinking water exposure. For a preliminary evaluation, OPP did not assume removal of any of the other OP parent pesticides. OP assumed that the sulfoxide and sulfone products are equal in toxicity to the parent and that the oxon products are ten times more toxic than the parent. A comparison of the RPFs for dimethoate (0.32) and omethoate (0.96), the oxon of dimethoate, suggests that this assumption would be protective. The impacts are addressed in the risk characterization (I.G).

b. Regional Approach for the Cumulative Water Exposure Assessment

The Agency used a regional approach as a first step in addressing the impacts of regional and localized variability in site, environmental, and management practices that effect pesticide concentrations in water. The USDA Farm Resource Region map (Heimlich, 2000) provided a framework for focusing the cumulative assessment (see Appendix III.E.10). By providing general groupings according to similarities in key environmental factors affecting runoff and leaching, such as precipitation, irrigation practices, and soil types, these farm resource regions provide a framework for identifying one or more locations which represent an area of the greatest concern for

drinking water exposure in each region. In this way, the Agency chose a set of locations to represent drinking water sources throughout the US.

Within the regions, drinking water exposure will vary locally due to OP use, agricultural practices, nature and vulnerability of drinking water sources, and weather patterns. Thus, the water exposure assessment focused on one or more specific geographic areas within each region in a manner that would be realistically protective of all sites within the region. OPP selected locations where OPs in drinking water sources are likely to be of concern. If OP levels in water from these vulnerable sites are not major contributors to the total regional cumulative OP exposure, then the Agency can reasonably conclude that drinking water exposures will not be a concern in other, less vulnerable, portions of the region. If drinking water exposure from one or more of these vulnerable sites is a significant contributor to the total cumulative exposure, then additional assessments are necessary to characterize the extent of the potential exposure.

Based on results of the preliminary cumulative risk assessment, OPP has condensed the twelve farm regions into seven regions (Figure I.E-3). Table I.E-2 compares the combined regions with the original regions.

Table I.E-2. New and Old Regions and Representative Vulnerable Sites Used in the Cumulative Water Exposure Assessment

New Region	Old Region	Representative Vulnerable Site
A - Florida	Fruitful Rim, SE (12)	West Palm Beach Co (FL) *
B - Northwest	Fruitful Rim, NW (10)	Willamette Valley (OR) *
C - Arid/Semiarid West	Fruitful Rim, SW (7)	Central Valley (CA) counties of (a) Merced, San Joaquin, Stanislaus * (b) Fresno, Tulare, King, Kern
	Basin & Range (8)	none (Red R. Valley surrogate)
D - Northeast/ Northcentral	Northern Great Plains (3)	Red River Valley (ND/MN) *
	Heartland (1)	Central IL
	Northern Crescent (2)	Southcentral PA
E - Humid Southeast	Southern Seaboard (6), east	Coastal Plain, northern NC *
	Eastern Uplands (5), east section	Western NC
F - Lower Midwest	Prairie Gateway (4)	Central TX Hills *
	Fruitful Rim, TX (11)	Central TX Hills (surrogate)
G - Midsouth	Mississippi Portal (9)	Northeast LA, west-central MS *
	west sections of E. Uplands, S. Seaboard	none

* Scenario used to represent new region in revised OP cumulative risk assessment.

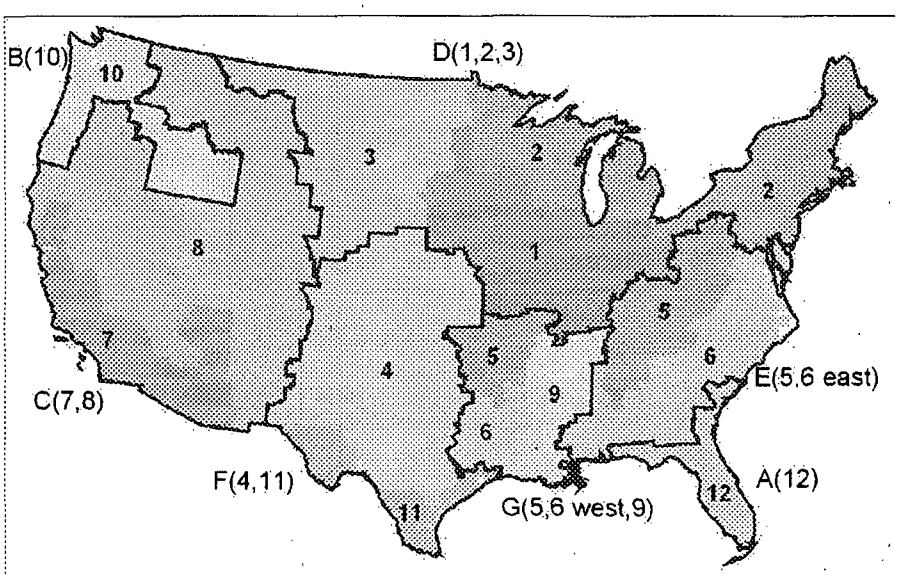


Figure I.E-3. Regions used in OP Cumulative Risk Assessment, based on USDA Farm Resource Regions

c. Selection of Regional Water Exposure Assessment Locations

The selection of a specific location for regional drinking water assessments involves several steps. First, OPP identified the high OP usage areas and high agricultural intensities within each region; these are shown on a national scale in Figure I.E-4. Next, in each high usage area within the region, OPP determined the types and locations of drinking water sources. The final step in choosing a location is to assess the vulnerability of drinking water sources within the high usage area within the region. OPP adapted vulnerability schemes proposed by Kellogg and others at USDA for this purpose. Locations of surface drinking water intakes overlain on runoff vulnerability maps (Figure I.E-5) were compared with the OP use areas to determine whether potentially vulnerable surface water sources of drinking water coincided with high use areas. For ground water, OPP compared OP use areas with a pesticide leaching vulnerability map (Figure I.E-6).

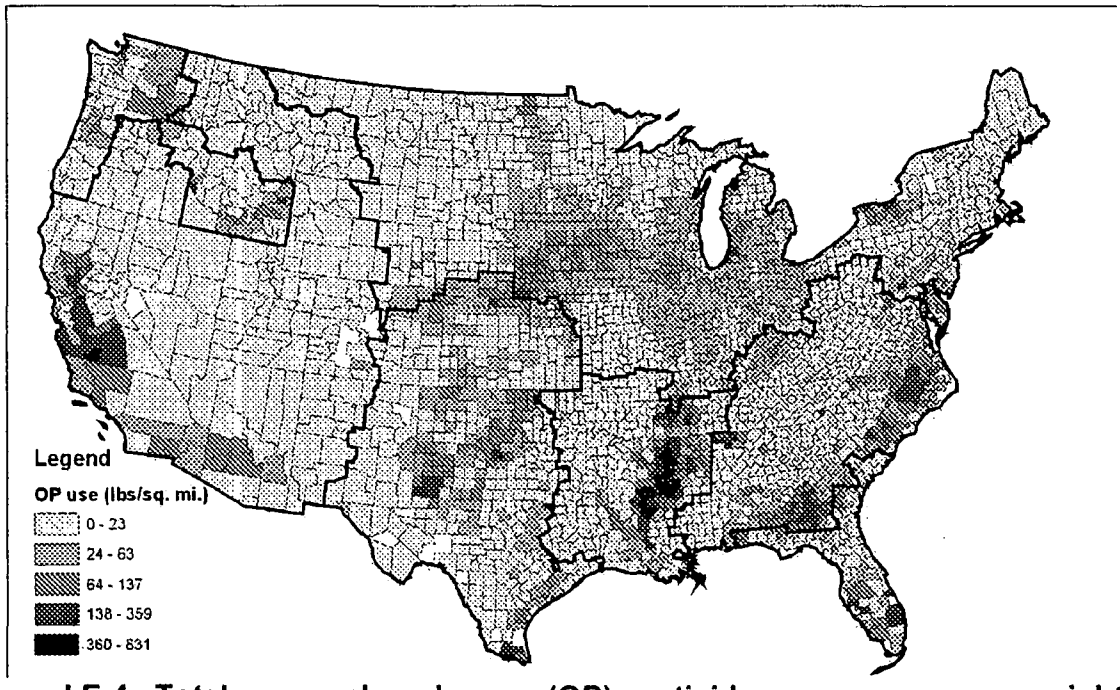


Figure I.E-4. Total organophosphorous (OP) pesticide usage on an area-weighted basis, showing high-use areas in each region.

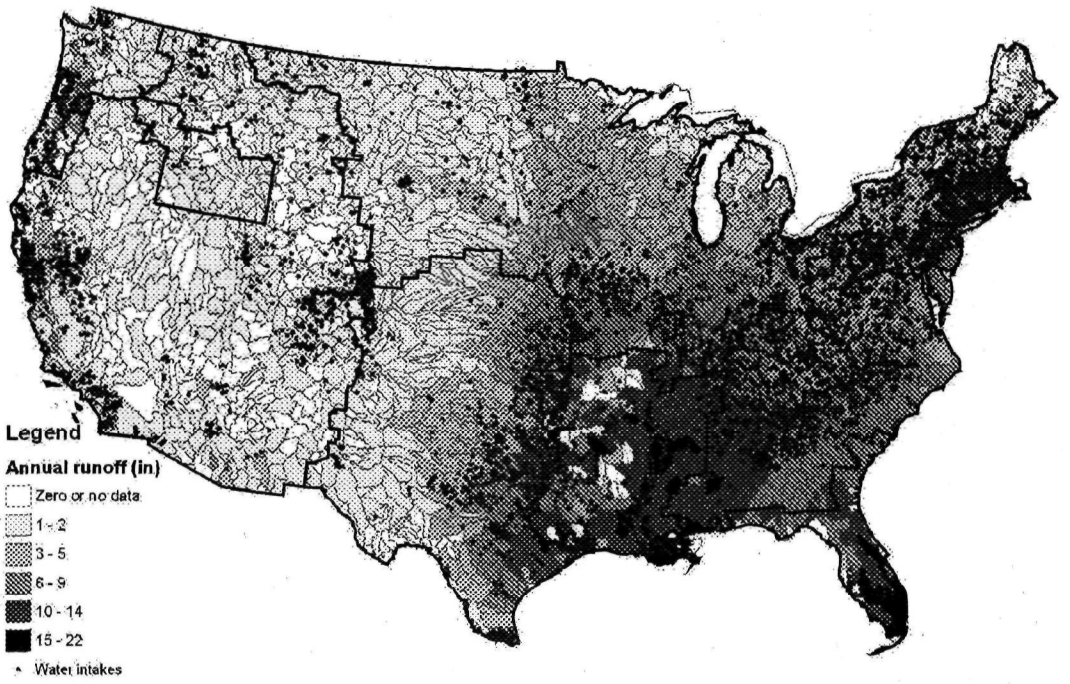


Figure I.E-5. Runoff vulnerability (in/year), adapted from USDA (Kellog, 1998)

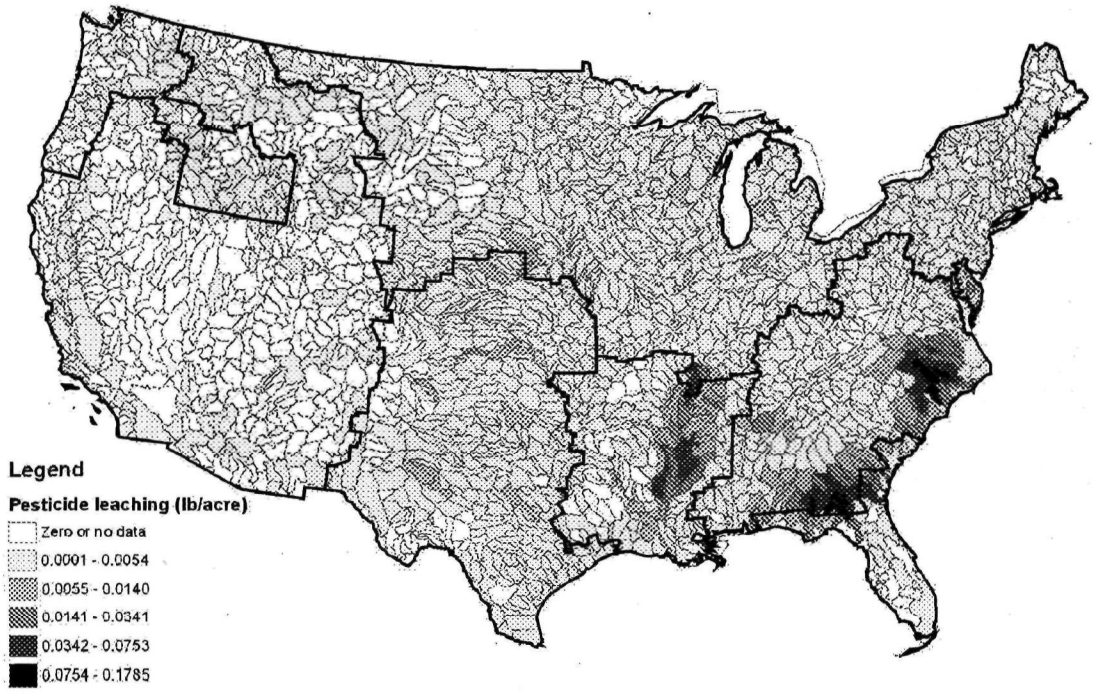


Figure I.E-6. Pesticide leaching vulnerability, adapted from USDA (Kellogg, 1998)

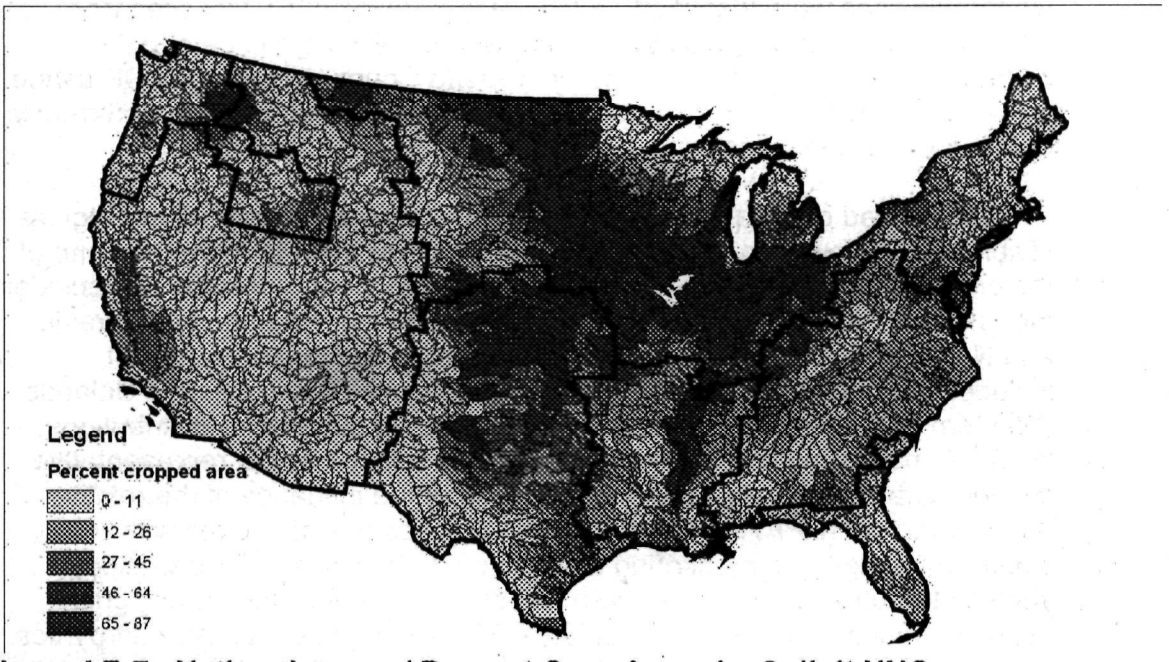


Figure I.E-7. National map w/ Percent Crop Areas by 8-digit HUC

Details of this process are provided in each regional assessment. The Northwest region (Region A) illustrates this process. Three OP-use areas stand out in the region (Figure I-E-4): Yakima County and eastern Washington are the highest OP use area (predominantly on orchards) and highest percent crop area (Figure I-E-7). The Snake River Valley in Southeast Idaho is the second highest use area (predominantly on potatoes, sugar beets). The Willamette Valley, Oregon, is the third high-use area, with a mix of OP uses. Ground water is the predominant source 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 Willamette Valley will be more vulnerable to OP contamination with a higher potential for co-occurrence of multiple pesticides.

OPP based its surface water assessment for the Northwest Fruitful region in the Willamette Valley in Oregon. We also looked at potential impacts of OP pesticides on ground water resources in eastern Washington and southeast Idaho, relying largely on ground-water monitoring available through the USGS NAWQA program and state monitoring programs.

In the preliminary cumulative risk assessment, OPP selected eleven vulnerable drinking water sources for the drinking water exposure assessment (Table I.E.2). Each of the 12 USDA regions had a representative vulnerable site except for the Prairie Gateway and Texas Fruitful Rim, which shared the same Central TX Hills site, and the Basin and Range, where no

vulnerable sites were identified. In the Central Valley (CA), two sites were identified: (a) Fresno County and south, where OP usage is among the highest in the country, and (b) north of Fresno County, where total OP usage is lower, but surface water sources are more vulnerable to runoff, particularly during the dormant season.

This revised cumulative risk assessment combines several of the regions (Table I.E.2). However, only two combined regions include more than one of the original vulnerable sites. The Northeast/ Northcentral Region (D) includes the original Northern Great Plains (Red River Valley), Heartland (Central IL), and Northern Crescent (Southcentral PA) sites. The Humid Southeast includes the original Southern Seaboard (Eastern NC) and Eastern Uplands (Western NC) sites. OPP compared the estimated cumulative distributions, NAWQA monitoring results, and OP usage to select a single representative site for each of these new regions. Because of the influence of the relative potency factors (RPF) in the cumulative OP loads in water, sites with significant usage and monitoring detections of the higher-RPF pesticides, such as terbufos and phorate, were selected over sites which had higher uses and monitoring detections of lower-RPF pesticides such as chlorpyrifos, diazinon, and malathion. These comparisons are discussed in the regional assessments in Part II.

d. Estimate of Pesticide Concentrations in Drinking Water Sources Within Each Region

After considering several predictive tools, the Agency adapted its paired PRZM and EXAMS models for the Index Reservoir (PRZM-EXAMS IR) to estimate a distribution of daily drinking water concentrations that could be used for multiple chemicals over several years of predictions across the country. PRZM-EXAMS IR has been modified to calculate concentrations in a small drinking water reservoir in a primarily agricultural watershed. PRZM-EXAMS has the capability of predicting water concentrations over a number of years based on collected historical weather data for the sites which are being modeled.

The PRZM component of the model is designed to predict the pesticide concentration dissolved in runoff waters and carried on entrained sediments from the field where a pesticide has been applied into 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, surface roughness, field geometry), pesticide application parameters (application rate, frequency, spray drift, application depth, application efficiency, application methods), agricultural management practices (tillage practices, irrigation, crop rotation sequences), and pesticide environmental fate and transport properties (aerobic soil metabolism half-life, soil:water partitioning coefficients, foliar degradation and dissipation, and volatilization). OPP selects a combination

of these different properties to represent a site-specific scenario for a particular pesticide-crop regime.

The EXAMS component of the model is used to simulate environmental fate and transport processes of pesticides in surface water, including: abiotic and biotic degradation, sediment:water partitioning, and volatilization. Currently, OPP is using an index reservoir as the benchmark surface water body for drinking water exposure assessments.

For each component, the values used are derived from real world data. Pesticide environmental fate properties used in the modeling come from registrant-submitted data used for pesticide registration or reregistration. The values used for soil properties and site characteristics are chosen from real world databases appropriate for the sites on which the pesticide may be used. For example, if the pesticide is approved for use on cotton, OPP uses data reflecting the soil types in the Cotton Belt. The index reservoir being modeled is based on and represents an actual, small flow-though reservoir used for drinking water. Finally, the weather inputs for the model are taken from regional specific weather data, based on the USDA Major Land Resource Areas. PRZM modeling is generally simulated for 20 to 36 years in order to calculate a return frequency of concentration in surface water body. Further information on how the Index Reservoir model is used for screening-level drinking water assessments of individual pesticides can be found in the EPA Environmental Fate and Effects Division's pesticide science policy paper, "Guidance for Use of the Index Reservoir Guidance for Use of the Index Reservoir in Drinking Water Exposure in Drinking Water Exposure Assessments."

Running the assessment with historical data for several years provides more confidence that variations due to weather have been considered in the assessment. Having the historical weather data, pertinent site information and reported use histories allows the Agency to factor regional variations into the assessment. With this method, multiple chemicals which have varying uses and application factors are assessed and co-occurrence is realistically accounted. Since the day by day component is retained, this distribution can easily be paired with residues resulting from residential applications.

The PRZM-EXAMS/IR tool has been used in many of the individual assessments to predict a reasonable high end screening concentration to factor into the aggregate assessment. However, the cumulative assessment focuses on the probability or likelihood a person will be concurrently exposed to multiple pesticides from food, water, and residential use. The method which was used in the aggregate assessments has been modified in several ways to focus on the probability of co-occurrence from the various routes.

The most significant change in terms of predicted exposure is that the entire range of PRZM-EXAMS/IR output is used for the probabilistic distribution. In other words, instead of choosing a single value at the upper end of the distribution to represent the exposure, all daily concentration values are used in the CALENDEX runs.

The cumulative assessment modeling used "typical" application rates with typical numbers of applications instead of labeled maximum rates and maximum numbers of applications which were used in the individual chemical assessments. While this is reflective of the "typical" condition, it does not reflect potential concentrations that may occur when the pesticide is used at maximum rates because of pest pressure.

The drinking water assessments for cumulative are regional in nature. This allows EPA to make informed judgements about when compounds co-occur and when they compete. Overall, the assessment is much more realistic on a regional basis. Scenarios chosen for regional assessments are reflective of regional differences in cropping and pesticide use as well as differences in run-off and leaching vulnerability.

i. Cumulative Adjustment Factors for Crop Area and OP Use

PRZM is a field-scale model, while the OP cumulative water assessment focuses on watershed-scale impacts (i.e., the contributions of multiple OP uses on multiple crops occurring in multiple fields in a watershed). In individual chemical assessments, PRZM is used to simulate a watershed. In the OP cumulative assessment, the Agency used PRZM to model multiple fields in a watershed. While this approach provides a more realistic depiction of multiple chemical usage in a watershed, it still has limitations. PRZM can simulate multiple fields, but provides no spatial context for those fields. It also assumes that the runoff from each of those fields goes into the reservoir. In other words, each field is assumed to be uniformly distributed in the watershed, with no distinction made between those fields located in the upper reaches of the watershed and those near the reservoir.

To adapt PRZM for this watershed approach, OPP must adjust the estimated pesticide concentrations to account for the portion of the watershed that is treated by a particular OP. This was done using a Cumulative Adjustment Factor (CAF), which accounts for the percentage of the watershed that is planted to a particular crop and the fraction of those acres which receive OP applications.

The CAF accounts for the percent of the location area planted to crops and treated with the corresponding OP pesticides. The CAF is based on several different data sources. The Agency used the USGS 8-digit Hydrologic Unit Codes (HUCs) to delineate watersheds, and the National

Agricultural Census for 1997, reported on a county basis, to identify areas planted to agriculture. This procedure was presented to OPP Science Advisory Panel (available through the Agency web site at http://www.epa.gov/scipoly/sap/1999/may/pca_sap.pdf) and is described in an OPP science policy paper (available through the Agency web site at http://www.epa.gov/oppfead1/trac/science/reservoir.pdf). Percent crop area values were calculated for each region. To determine the total acres planted for each crop within the selected location, the Agency used the most recent county level production statistics, generally taken from USDA publications. And finally, to calculate the area treated by the various OPs, the most recent percent of crop treated estimates, generally taken from USDA\NASS publications were applied.

In addition to primary USDA publications, various other data sources (California Department of Pesticide Regulation, Pesticide Use Reporting Data, academia publications) were used to obtain acres planted and acres treated estimates.

The following example (Table I.E-3) illustrates how CAFs are calculated and applied. Suppose, that after reviewing the various data (drinking water source, vulnerability, crop production, pesticide use, and monitoring data), a location (one or several counties) is identified around which the drinking water assessment is conducted. The total area for this location is 800,000 acres; agricultural cropland accounts for 600,000 acres of this total area, and 320,000 acres of the agricultural cropland are planted to four crops (corn, alfalfa, beans and apples) that are treated with OP pesticides:

Table I.E-3. Cumulative Adjustment Factor Illustration: Deriving Cumulative OP Percent Crop Area

		Acres	Percent of area	PCA
Total Area		800,000		
Crop Area, All Agricultural Uses:		600,000		75%
OP Uses in Region:	Corn	200,000	25%	
	Alfalfa	80,000	10%	
	Beans/legumes	16,000	2%	
	Apples/pome fruit	24,000	3%	
Total OP Use Area		320,000		40%

Further, suppose that 4 different pesticides are used on each of the 4 crops (some pesticides are used on more than one crop). Acres treated represent the total number of acres of the crop that were treated with each pesticide (may represent more than one application). Following the numerical example above, if 60,000 acres of field corn were treated with pesticide A, then the CAF for this particular use (field corn-pesticide A) is 0.075, or:

$$CAF_{Corn\text{-}OP(A)} = (Total\ Acres\ Planted_{All\ OP\ Crops} / Total\ Acres) \times (Acres\ Treated_{Corn\text{-}OP(A)} / Acres\ Planted_{All\ OP\ Crops})$$
$$= (320{,}000 / 800{,}000) \times (60{,}000 / 320{,}000) = 0.075$$

Table I.E-4. Cumulative Adjustment Factor Illustration: Individual Crop-Pesticide Factors Used for Conversions.

Crop	Pesticide	Acres Treated	Cumulative Adjustment Factor
Corn	A	60,000	.075
Corn	B	1,000	.00125
Corn	C	500	.000625
Corn	D	40,000	.05
Alfalfa	A	16,000	.02
Alfalfa	B	4,000	.005
Alfalfa	E	10,000	.0125
Alfalfa	F	8,000	.01
Apples	A	10,000	.0125
Apples	F	15,000	.01875
Apples	G	6,000	.0075
Apples	H	6,000	.0075
Beans	B	16,000	.02
Beans	E	1,000	.00125
Beans	I	16,000	.02
Beans	J	2,000	.0025

Again, these CAF are applied to the model is run for a particular chemical:crop combination. In this manner, since the use statistics come from reported data, competing and compatible uses are accounted for by summing the appropriate distributions across days after the RPFs are applied.

ii. Relative Potency and Safety Factor Adjustments

The resulting CAF-adjusted concentrations for each OP-crop combination must be converted to a concentration equivalent for an index chemical. Once this is done, the concentrations can be combined into a single set of daily distributions (spanning multiple years) for each region. The concentrations were normalized to methamidophos equivalents using the relative potency factor (RPF) and safety factor. This normalized output for each chemical:crop combination was summed day by day to give a single distribution of potential combined water residues for the region.

Factors to convert from individual to cumulative distributions:

$$Cv_{(OPx,CROPz)} = C_{(OPx,CROPz)} \times CAF_{(OPx,CROPz)} \times RPF_{(OPx)} \times SF_{(OPx)}$$

where

$Cv_{(OPx,CROPz)}$ is the converted concentration for OPx on CROPz
$C_{(OPx,CROPz)}$ is the raw PRZM/EXAM daily concentration
$CAF_{(OPx,CROPz)}$ is the cumulative adjustment factor
RPF is the Relative Potency Factor
SF is the FQPA Safety Factor

e. Pesticide Usage Information

The estimated OP cumulative distributions in each region are based on typical application rates and numbers of applications (taken as the average of rates reported in pesticide usage summaries). The timing of pesticide applications was based on label specifications (e.g., apply at plant, at harvest, at blossom) and locally-derived windows of use based on crop profiles.

USDA National Agricultural Statistics Service (NASS) and other published survey instruments provided the bases for the OP usage patterns described for all regional surface location examined. These state-level snapshots of pesticide practice are, of necessity, limited in time and scope. Usage patterns change continually to reflect OP label amendments and the availability of alternatives which include other, non-OP classes of pesticides and cultural, non-pesticidal control options. Moreover, state survey data is at a level of refinement somewhere between maximum label rates and frequencies and actual agronomic practice in specific location. And, of course, surveys are only as good as the number and quality of responses that educate the derived estimates. With these reservations in mind, this

approach was undertaken to provide transparent modeling scenarios using the best currently available data.

i. Typical Pesticide Use (Rate and Frequency)

For regions exclusive of the Arid/Semiarid West, the primary sources of information for percent crop treated, number of applications, and amount of active ingredient applied are NASS Agricultural Chemical Usage summaries. These documents provide data for selected crops in selected states; they are published annually for field crops and biennially for vegetables and for fruits and nuts. Vegetable chemical usage summaries are reported for even years; fruit and nut chemical summaries are reported for odd years. The years 1997-2000 were reviewed for field crops, 1998 and 2000 for vegetables, and 1997 and 1999 for fruits/nuts. The most recent summary data is cited for state/crop combinations appearing in the cumulative surface water assessments. Citations follow the format: "NASS, 2000 Vegetable Summary."

In a given NASS summary, specific OP pesticides may be noted, by use of an asterisk, as being applied to a crop but no usage data is provided. This situation arises where the number of individuals reporting use of the specific OP is so small (i.e., fewer than five) that respondent confidentiality could be compromised through data disclosure. In such instances, an earlier summary has been consulted.

NASS data were not available for all specific chemical/state/crop combinations examined. In some cases, additional survey instruments were consulted. All usage data sources are documented at their occurrence in the regional summaries.

OPP used the average application rate reported in the NASS summaries to represent the typical application rate for each OP-crop combination in a region. Likewise, OPP used the average number of applications to determine how many times the OP pesticide would be applied to the crop in a particular year. These rates were frequently less than the maximum allowable application rates and frequencies specified on the label. A comparison of OP cumulative distributions estimated by typical and maximum label rates in three regions found that use of all maximum rates generates concentrations that are one to four times greater than those estimated using typical rates (see I.G. and Appendix III.E.11 for detailed analysis). In reality, it is unlikely that all OP pesticides would be used on all crops at maximum rates in the same year. Thus, the difference between OP cumulative loads in a "typical" year and in a year when intense pest pressure requires maximum label rates for one or more OP pesticide on one or more crops is likely to be less than the one- to four-times estimated.

ii. Timing of Pesticide Application(s)

An application window has been established for each of the OP pesticide crop uses reported in each region. This window represents an approximate beginning and ending date for the use of the pesticide on a particular crop. Delineation of these windows was based on review of crop profiles and other relevant crop production publications; surveys such as the Doane Marketing Research, Inc. Agrotrak[tm] reports on agronomic, row and specialty crops; and on consultations with field experts. Unless otherwise noted, the default planting and harvesting dates for crops were taken from the following USDA documents:

- United States Department of Agriculture, Crop Reporting Board, Statistical reporting Service. 1977. Usual Planting and Harvesting Dates for Fresh Market and Processing Vegetables. Agriculture Handbook No. 507.

- United States Department of Agriculture, National Agricultural Statistics Service. 1997. Usual Planting and Harvesting Dates for U.S. Field Crops. Agricultural Handbook No. 628.

These 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. A case in point is the data input for terbufos on corn in North Carolina:

Pesticide	Stage	Application Date	Range	Most Active
Terbufos	Planting	April 17	April 1 - May 20	April 10 - April 25

When most active periods are not provided, the single application date for a pesticide is set at the beginning of the crop stage window. Multiple applications, such as OP cover sprays for tree fruits, are placed at the beginning and equidistant within the application window. The following example is for three cover sprays of phosmet on apples in the Northeast (Pennsylvania):

Pesticide	Stage	Application Dates	Range
Phosmet	Foliar	May 1 June 18 August 5	May 1 - Sep 21 May 1 - Sep 21 May 1 - Sep 21

Because the application dates are held constant through a series of years of weather patterns, variations in the selected date may affect the estimated peak concentrations. Relatively high pulse loads from runoff may occur if application events are closely followed by runoff-producing

rains. However, a comparison of OP cumulative distributions resulting from varying the application dates found that notable differences only occur at the very highest concentrations that distributions at the 99th percentile only vary by a factor of 2 or less (see I.G. and Appendix III.E.11 for discussion).

OPP assumed that the entire application of a given pesticide on a given crop occurred on the same day. Except in Region C, where detailed pesticide use reports from California Department of Pesticide Regulations were available, sufficient usage information was not available to split applications. While this is likely to result in conservative (health-protective) estimates, the assumption is not unreasonable in the smaller, more vulnerable watersheds represented by the index reservoir. A comparison of estimated OP cumulative distributions using split- and single-applications in Region C found a difference of less than a factor of two across the distribution profile (see I.G and Appendix III.E.11 for discussion).

A most likely, or predominant, application method is also designated for each pesticide. The choice is simply "air" or "ground." Review of NASS and proprietary data bases, crop production profiles, as well as consultation with field experts, informed these application method determinations.

iii. Use of CDPR Use Information in Region C

For the Central Valley (CA), used in Region C, the California Department of Pesticide Regulation, Pesticide Use Reporting (PUR) data was used to determine both the acres treated and the application dates. The PUR contains detailed information on every commercial pesticide application made within the State of California. Since the two locations identified and assessed in this region were located in the State of California, the Agency used the PUR data base to calculate the total area treated by each pesticide, on each crop for each date. For some uses, growers reporting making applications on numerous dates (>50 days) throughout the Calendar year. For data management purposes, five application dates were selected for each crop-OP use to be used in the assessment; each application date represents 20% of the total acre treatments made for that particular use.

Evaluations of CDPR and NASS usage information in California found no routine under- or over-estimation of pesticide usage from the survey methods used by NASS. A comparison of OP cumulative distributions generated using both data sources found that the distributions generated with the more complete CDPR information were greater than those generated with the NASS survey data by a factor of 3 (see Appendix III.E.11 for comparison).

f. Incorporate the Drinking Water Exposure Estimate into the Cumulative Assessment

In summary, within each region, a residue file was generated by PRZM-EXAMS/IR for each pesticide:crop combination which was reported in the county or counties selected for assessment. This day-by-day residue file was modified by the CAF specific to that pesticide:crop combination and the relative potency factor for that pesticide. Then, the modified residue files for all pesticide:crop combinations for that location were summed across days to give a distribution of combined daily residues in drinking water.

This distribution of combined daily residues can then be used as an input file for the CALENDEX model which is discussed elsewhere in this document. CALENDEX allows the Agency to combine OP concentrations from water and residential exposures which are time and location dependent with food exposures which are not time and location dependent.

The distribution of daily residues can also be compared to any water monitoring data available for the chemicals and region being examined. Plots of the daily distributions can be analyzed to ascertain which uses may be expected to contribute significant exposures. The comparison of monitoring data and the understanding of which uses contribute to exposure are important aspects of risk characterization of the water portion of the OP cumulative risk assessment.

For each vulnerable site, OPP developed a site-specific scenario for each crop group with reported OP usage (see Appendix III.E.7a and b for a description of scenario development and documentation). Thus, the site and soil characteristics are representative of those that actually occur in the region and support that particular crop growth.

I. Revised OP Cumulative Risk Assessment

F. Cumulative Assessment

1. Introduction

The previous four sections of this document have described the development of the major components of the risk assessment. They describe a highly complex process of combining multiple data sets to develop a description of the possible risks from OP pesticides by each of the pathways described. OPP has had to develop new methods for each component of the assessment in order to produce an assessment which presents as realistically as possible the potential exposure to OP pesticides. The purpose of this section is to explain the concepts used to accumulate risk from each pathway into a total risk estimate, and to provide a basis for understanding the presentations that are provided in Section III for each of the regional assessments.

2. Basic Concepts

The definition of cumulative risk developed as a result of the passage of FQPA requires OPP to conduct a risk assessment for a group of pesticides with a common mechanism of toxicity that is multi-pathway, multi-route, and multi-chemical in scope. As described in section I.B above, the RPF method was used to address the issue of combining toxic responses from OPs with varying propensities to inhibit acetylcholinesterase. Exposure to each OP was normalized to equivalent exposure to the index compound, methamidophos. The toxicity data currently available for conducting this analysis are estimates of response by route-specific dosing, and do not support estimating delivered dose to the target tissue. OPP decided to address this problem by comparing route-specific exposures to route-specific points of departure to produce unitless margins of exposure for each route. In this case, the POD was a BMD_{10}. MOEs were combined by taking the inverse for each route, adding them together, and then taking the inverse of that sum. This process was used to produce a distribution of daily estimates for the subpopulation of concern that reflects regional and seasonal variation in the patterns of exposure that are likely to occur throughout the US across the year. OPP used a probabilistic assessment to capture the full range of exposure possibilities from all sources analyzed. The intent was to produce an estimated range of risk that is as realistic as possible. The OP cumulative risk assessment is not a high end risk assessment. It attempts to reflect the full range of likely exposures for consideration in a regulatory context. However, at the same time it is designed to avoid developing extreme exposure estimates based upon the combination of exposure scenarios and assumptions that are not reasonable.

3. Framing the Population-Based Assessment

OPP focuses its risk assessment on exposure and resulting risk to the population, not to risk to an individual. This distinction is an important one with regard to defining how the components of the assessment will be combined. The current assessment focuses on highlighting inter-individual patterns of exposure instead of attempting to define intra-individual patterns of exposure. OPP made this choice because of the lack of acceptable longitudinal data defining intra-individual behavior for any component of the risk assessment. This issue has been repeatedly discussed at SAP meetings reviewing the conduct of dietary risk assessment methodology. Longitudinal data permitting modeling of the consumption of food and water by the US population is not available. The data describing the use of pesticides in a residential setting is even more uncertain. Although ranges of use parameters are available and have been used in this assessment, they are only adequate to define the behavior of the population across time, and cannot accurately reflect the day to day variability in behavior of an individual. Therefore, OPP decided to develop a series of daily exposure distributions and array them as a distribution across time.

The distribution of daily exposures and resulting MOEs are developed such that the exposures from OPs in foods, drinking water, and from residential uses are all calculated simultaneously for each hypothetical individual in the subpopulation. OPP uses the Calendex software to develop the distributions and resulting MOEs. Calendex permits incorporation of time course information with regard to residential uses of pesticides, but does not permit specific allowance for regional variability. OPP addressed this issue by running separate risk assessments for each of seven regions of the US. The regions correspond to agronomic cropping areas and reflect climatic and soil conditions that are likely to affect pest pressure and resulting pesticide use. Regional differences in pesticide use are major considerations in appropriately estimating exposure from pesticides in drinking water and residential uses.

To generate a daily distribution of exposure, consumption records are selected from the CSFII for each individual in the survey. Calendex uses this consumption record to estimate OP exposure from food by randomly assigning a residue value for each food reported consumed by that individual. After multiplying each amount of food consumed by its selected residue value, the total exposure from food for this individual is calculated by summing the exposures from the individual foods which were reported consumed. At the same time, all appropriate residential scenarios that may be encountered for the calendar day 1 (January 1) are reviewed. A probability-based decision is made as to whether or not that scenario will be encountered (e.g., a lawn treatment would probably not occur in January in the Northeast/North Central region). If the scenario is assigned a "yes" answer (i.e., treatment does occur), then the appropriate values defining the exposure are selected from the many distributions of input parameters for residential exposure scenarios. The exposures for the dermal, oral and inhalation pathways are calculated for all

selected residential scenarios. A drinking water value taken from the PRZM/EXAMS output for January 1 is selected and paired with the water consumption reported in the CSFII consumption record. These values are used to calculated exposure from drinking water for that date. All of the exposures are converted to route-specific MOEs to define the total exposure to the hypothetical individual on January 1. The process is repeated for each consumption record for the age group in the CSFII ten times (i.e., ten iterations) to build a distribution of exposures for January 1. This process is repeated for January 2, January 3 and so forth across the year.

The 365 daily exposure distributions are arrayed together in order to provide a profile of possible exposures by each route and in total as MOEs. An example of such a distribution of distributions is presented in Figure I.F.1. In this figure, each daily distribution is arrayed on the yz plane of the plot. Day 365 can be clearly seen on the right side of the plot. This distribution of total risk is expressed as a cumulative distribution function of MOEs versus percentile of exposure. Percentile of exposure refers to that portion of the population output distribution that has less than or equal exposure. For example, at the 80th percentile of exposure, 20% of the output distribution has an MOE lower than the one at the 80th percentile point on the distribution.

The distribution of daily distributions is used to estimate the potential risk, with accompanying distributions generated for each pathway and route. OPP acknowledges that this approach does not describe intra-individual risk. In all likelihood, the variability in an individual exposure would be much greater than in a population-based approach because of the limited likelihood of repetitive events such as residential pesticide applications. However, the population at large will experience some degree of exposure each day. This factor is a likely source of conservatism in the current assessment.

4. Interpreting the Outputs

The results of the final assessment are presented in tabular (Calendex output) form in the appendices. The reflect year-long slices across the 3-dimensional plot in Figure I.F.1. In that plot, dark lines can be seen across the total MOE surface. For instance, the top line in the 3-dimensional plot represents the 99.9th percentile of exposure for the population. A slice through the surface parallel to the xy plane at the 99.9th percentile would look like the plot presented in Figure I.F.2. This plot presents the potential total MOE for the exposure scenarios included in this assessment. In addition, the contributions from various pathways and routes of exposure are arrayed separately to assist the risk manager in identifying contributors to risk for further evaluation. Other age groups (or percentiles) of exposure may also be of interest. For example, Figure I.F.3 presents the results of the 99.9 percentile assessment for the age group Adults, 20-49.

5. The Rolling Time Frame Approach

One important aspect of the revised cumulative risk assessment for the organophosphate pesticides (OPs) is the manner in which estimated exposure is compared with toxicity endpoints. The above paragraphs detail and describe one "mode" or option of analysis (termed the *single consecutive day* option) in which separate, independent estimates are made for each day of the year (January 1, January 2, etc.). As discussed above, these can be arrayed into an exposure timeline for any selected percentile (and graphed, if desired). That is, for example, the estimated 99.9th (or any other percentile) percentile exposure value is calculated by DEEM/Calendex for each day of the year from January 1 through December 31. These represent independent daily estimates of the 99th percentile exposures on each day of the year and do not necessarily represent the same individual on consecutive days[1]. Thus, it is NOT possible (with this mode of analysis) to interpret an extended period (or series) of elevated exposures over time as necessarily representing extended exposures to the *same* individual, and comparison of any estimated exposure to multi-day endpoints (e.g., a multi-day BMD_{10} would be expected to provide a very conservative estimate of risk to the extent that exposures on consecutive days at any given percentile are unlikely to be the same individual.

[1] For example, biomonitoring data from CDC and others indicate that a sizeable percentage of the U. S. population has measurable levels of OP metabolites in their urine or blood.

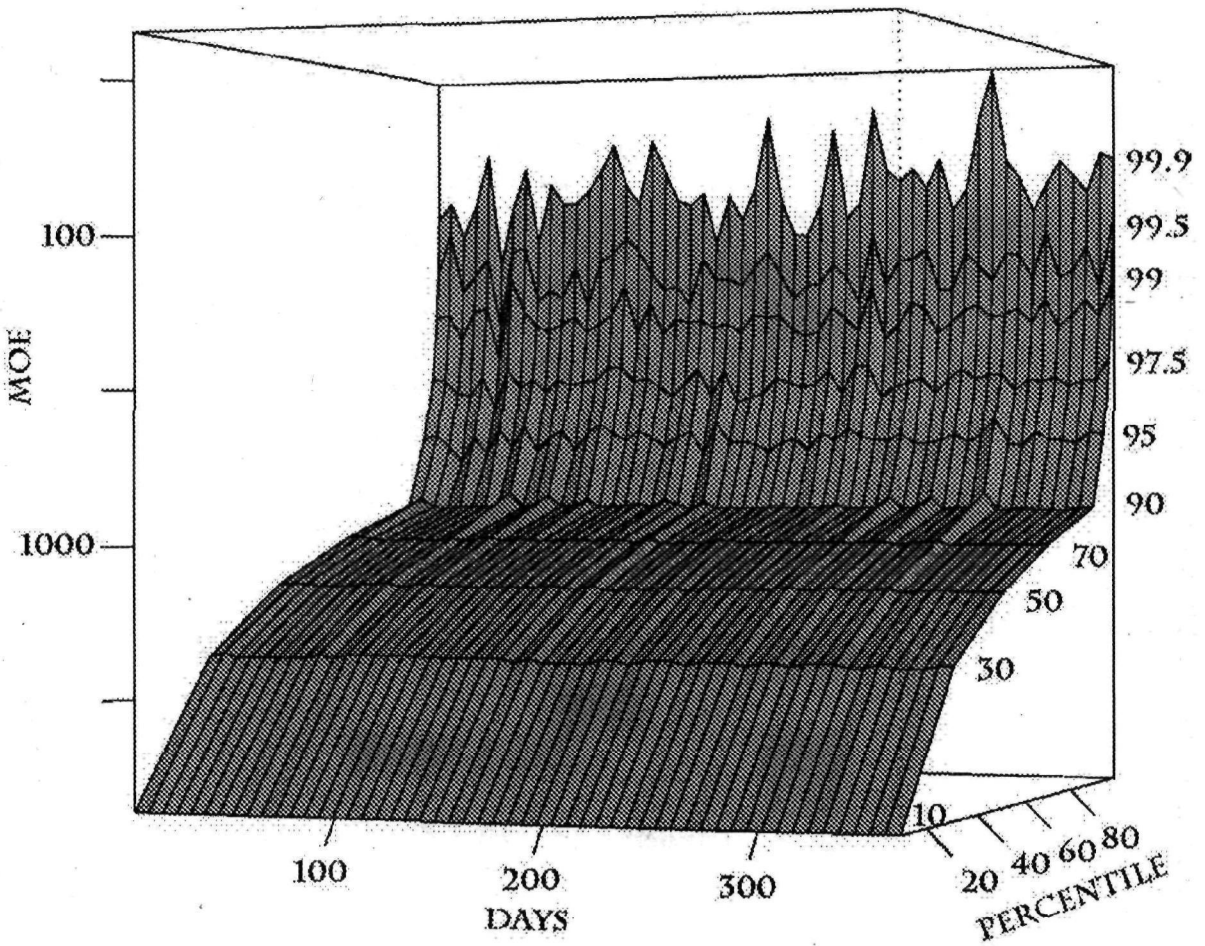


Figure I.F-1. Three-dimensional plot of the total MOE by day of the year and percentile of exposure

Figure I.F-2. Cumulative Assessment - 99.9th Percentile Estimate for Children Ages 1-2 Years for All Routes and Pathways

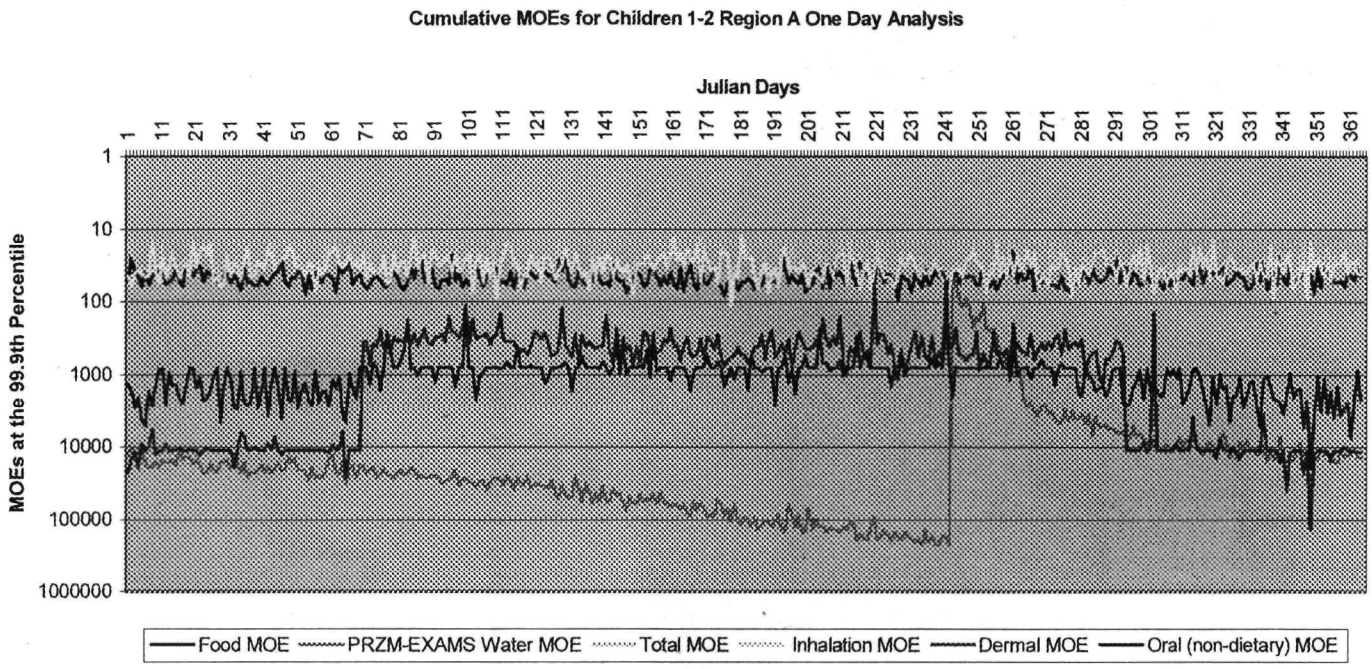
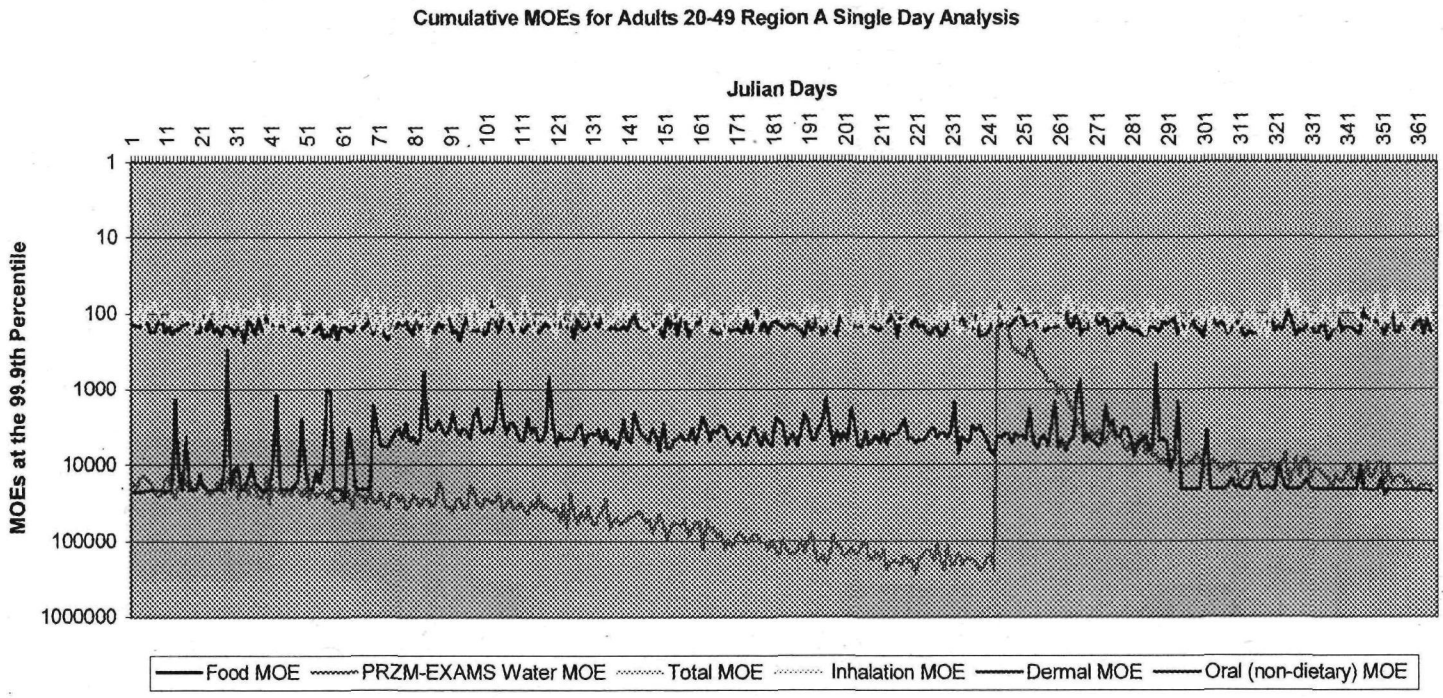


Figure I.F-3. Cumulative Assessment - 99.9th Percentile Estimate for Adults 20-49 Years for All Routes and Pathways



The DEEM/Calendex program can perform analyses under a second option. Under this second option (termed the *multiple sequential day option*), a rolling (or sliding) time frame is used and multi-day average exposures are calculated for each individual (e.g, average exposures for each individual for January 1 through January 7, January 2 through January 8, etc.). Under this mode, average exposures over multiple consecutive days (e.g., January 1 through 7, January 2 through 8, etc.) are assessed for the same individual. It is then this distribution of multi-day average exposures at any given percentile which serves as a basis of comparison with the (multi-day) BMD_{10}. An example graph of this is presented in Figure I.F-4 which shows a seven day rolling average exposure profile for Children 1-2.

In the Preliminary Cumulative Risk Assessment, exposures were estimated on a single-day basis (the first option) and a comparison made of each independent DEEM-estimated single-day exposure with the steady-state (21 day) equilibrium BMD_{10} value That is, separate exposure estimates were made for January 1, January 2, etc. for each individual in the CSFII survey *for each (single) day of the year* with exposure at a given percentile (e.g., 99^{th}) calculated and compared to a multi-day BMD_{10}. In viewing these results, and despite their one-day exposure basis, OPP is NOT concerned with exposure spikes lasting only one or perhaps a few days since the MOE's associated with these "spikes" are based on multi-day toxicity endpoints. Rather, OPP is interested in extended periods of high exposure (or, equivalently, low MOEs) which indicate not that an *individual* is being exposed to high levels of OP pesticides over a multi-day time period, but instead that the overall level of exposure to the sub-population in the tails of the distribution has increased. This is an important distinction which brings up two issues:

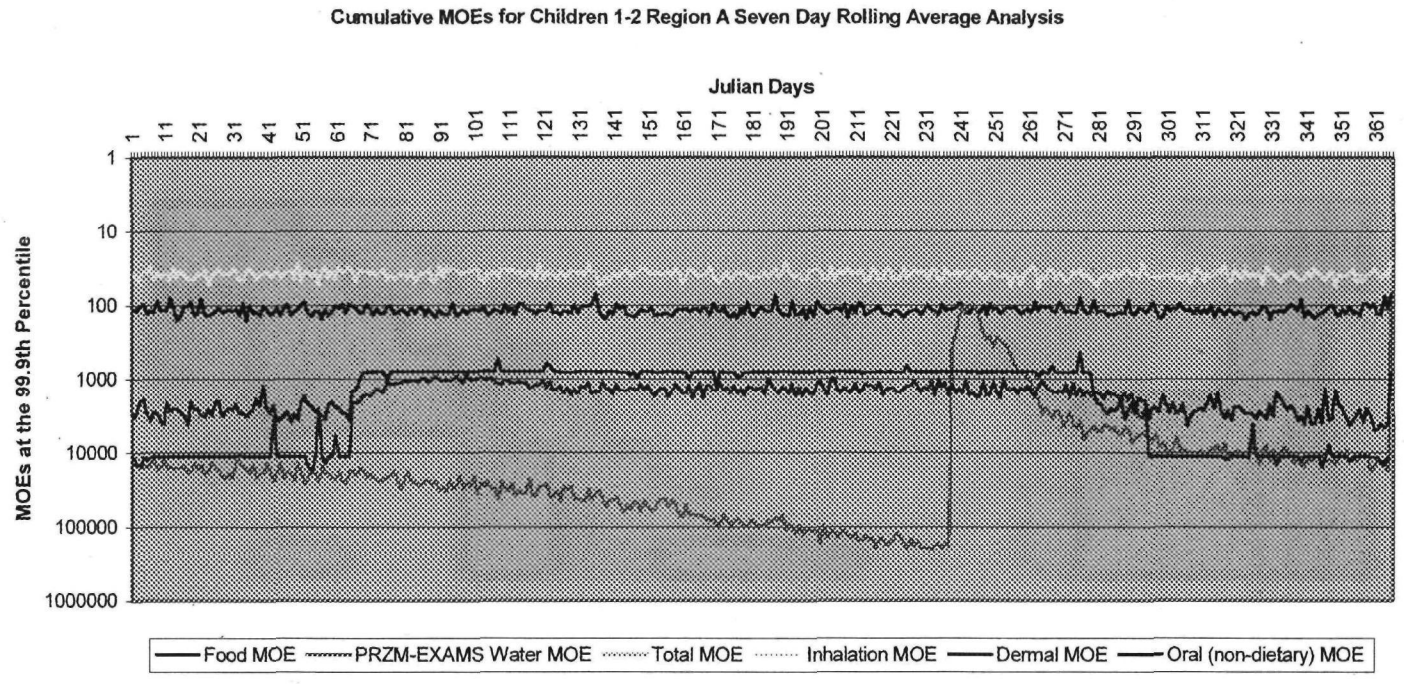
- comparing a series of elevated single-day exposures to multi-day endpoint may have less relevance than comparing a multi-day average exposure (at any given percentile) to a multi-day endpoint.

- Consecutive single-day estimates of exposure are likely to significantly overestimate multi-day exposures to an individual (at higher percentiles) e.g., the 99.9th percentile individuals are unlikely to be the same individual on consecutive days.

An alternative option – which was explored and incorporated into this revised CRA and supplements the *single consecutive day option* – is to estimate multi-day rolling average exposures in which average exposures over multiple consecutive days (e.g., January 1 through 7, January 2 through 8, etc.) are assessed for the same individual. It is this multi-day average exposure which then serves as a basis of comparison with the (multi-day) BMD_{10}. There are a number of advantages to this alternative. In addition to providing a means of estimating exposure which is more directly comparable to a multi-day endpoint, the multiple sequential day mode of analysis better incorporates variability in exposure for an individual across multiple days and is likely to provide a more

realistic estimate of exposures for individuals across multiple days. It is also flexible with respect to matching time-frame associated with BMD10 in that multi-day averages can be calculated over 7, 14, 21, or 28 days. However, as discussed in the February 2002 Scientific Advisory Panel meeting associated cholinesterase inhibition level will be underestimated if one fails to allow for the residual (or lingering) cholinesterase inhibition effect from those previous days in cases where a day's exposure is preceded by nonnegligible exposures on previous days.

Figure I.F-4. Cumulative Assessment - Seven Day Rolling Average 99.9th Percentile Estimate for Children Ages 1-2 Years for All Routes and Pathways



I. Revised OP Cumulative Risk Assessment

G. FQPA Safety Factor

1. Introduction

There is currently a significant focus on the potential susceptibility and increased sensitivity of infants and children to toxic effects of chemicals (see National Resource Council's 1993 report, *Pesticides in the Diets of Infants and Children*). The Food Quality Protection Act of 1996 (FQPA) instructs the U.S. Environmental Protection Agency (EPA or the Agency), in making its "reasonable certainty of no harm" finding, that in "the case of threshold effects, . . . **an additional tenfold margin of safety** for the pesticide chemical residue and other sources of exposure shall be applied for infants and children to take into account **potential pre- and postnatal toxicity and completeness of data with respect to exposure and toxicity to infants and children**." Section 408 (b)(2)(C) further states that "the Administrator may use a different margin of safety for the pesticide chemical residue only if, on the basis of reliable data, such margin will be safe for infants and children."

a. Guidance Used for Consideration of the FQPA Safety Factor

EPA's Office of Pesticide Programs (OPP) has recently released revised guidance addressing application of the FQPA safety factor provision in risk assessments for individual pesticide chemicals (USEPA, 2002a). Additionally, OPP has prepared a separate guidance document addressing the application of the FQPA safety factor provision in the context of cumulative risk assessments for two or more pesticides sharing a common mechanism of toxicity (USEPA, 2002b; released February 28, 2002 for a 60-day comment period). Both FQPA safety factor guidance documents (USEPA, 2002a,b) were used to provide general guidance on applying traditional uncertainty factors and on implementing the FQPA safety factor provision for the cumulative risk assessment of organophosphorus (OP) pesticides. In implementing the FQPA safety factor provision, key considerations in a cumulative risk assessment are:

- Determining the completeness of the data with respect to effects that may occur in the young due to the common mechanism of toxicity;
- Evaluating the degree of concern regarding the potential for pre- and postnatal effects associated with the common mechanism of toxicity and determining the residual uncertainties not addressed by application of traditional uncertainty factors to account for deficiencies in the toxicity data; and
- Determining the completeness of the exposure database for all pertinent pathways of exposure to OP pesticides.

b. Scope of Analysis on Sensitivity and Susceptibility

Single-chemical risk assessments should generally be conducted for each member of a common mechanism group before a cumulative assessment is attempted. Thus, previous determinations have been made whether to retain or replace the FQPA 10X safety factor for the individual pesticide members of the OP cumulative risk assessment group. These FQPA safety factor decisions should be revisited, however, in the cumulative risk assessment process because they are based on broader considerations of potential toxic effects in the young (*e.g.*, teratogenicity, carcinogenic effects) that may not relate to the common mechanism of toxicity. A cumulative risk assessment differs from the single-chemical risk assessment both in focus and purpose. The cumulative risk assessment of the OP pesticides is based on their ability to target and inhibit the enzyme acetylcholinesterase (AChE) in nerve tissue, in other words, the common mechanism of toxicity for which these pesticides are grouped. Thus, decisions on the FQPA safety factor for the cumulative assessment group (CAG) reflect considerations that pertain to the common effect and the common mechanism of toxicity.

Several years ago, the International Life Sciences Institute/Risk Sciences Institute (RSI) convened an expert panel to address whether the OP pesticides act by a common mechanism of toxicity (Mileson *et al.*, 1998). Although some OP pesticides may act by several different neurotoxic mechanisms through interaction with other esterases and nonesterase targets (for review see Pope and Liu, 2001), there are insufficient data to support subgrouping of the OP pesticides based on other actions operating instead of, or in addition to, the inhibition of AChE. It should be pointed out that these other mechanisms are considered in the individual risk assessments of the OP pesticides when there is sufficient available information. For example, in evaluating the susceptibility of the young to chlorpyrifos, OPP considered data that showed effects on the developing rat brain such as structural defects and changes in macromolecular synthesis, neurotransmitter levels, and cell signaling. Although these other neurodevelopmental mechanisms are considered in the single chemical assessment, they will only be considered in the cumulative analysis as they relate to AChE inhibition. Because AChE inhibition is the mechanism of toxicity and precursor event to toxicity, functional effects in the young that result from the inhibition of AChE activity should not occur at doses lower than those causing AChE inhibition.

2. Hazard Assessment: Sensitivity and Susceptibility[1]

The hazard assessment, below, considers the potential pre- and postnatal developmental effects that may be associated with the inhibition of AChE, the comparative AChE inhibition between adults versus the immature animal, and the completeness of toxicity data on AChE inhibition in young animals.

a. Role of Acetylcholinesterase in Neurodevelopment

AChE is the enzyme that hydrolyzes the neurotransmitter acetylcholine at cholinergic synapses and neuromuscular junctions. The inhibition of AChE leads to accumulation of synaptic acetylcholine, overstimulation of postsynaptic cholinergic receptors and consequent signs of neurotoxicity or cholinergic toxicity. It has been suspected, however, for more than 25 years that AChE may have an extrasynaptic, noncholinergic role during development (*e.g.*, Karczmar *et al.*, 1973; Drews, 1975). Recent research indicates that the roles of AChE during development center around neurogenesis, cell adhesion and possibly stress response (*e.g.*, Layer and Willbold, 1995; Grisaru *et al.*, 1999; Bigbee *et al.*, 1999; Brimijoin and Koenigsberger, 1999). Moreover, the widespread expression of AChE is often mirrored by the expression of acetylcholine, which is involved with basic developmental processes such as mitosis, cell-to-cell contact, cell adhesion, cell differentiation, and organization of the cytoskeleton (reviewed in Wessler *et al.*, 1999; Lauder and Schambra, 1999).

Both AChE and acetylcholine are highly conserved molecules which have multiple roles in the developing nervous system as well as extraneuronal functions. Because AChE controls acetylcholine levels in neuronal as well as extraneuronal tissues and blood (*e.g.*, Wessler *et al.*, 1998; Fujii and Kawashima, 2001; Kirkpatrick *et al.*, 2001) and because AChE activity is more commonly measured as compared to acetylcholine levels, most of the work reviewed below concentrates on changes in AChE activity rather than acetylcholine levels. One may assume, however, that as mentioned above, a decrease in AChE activity should also increase acetylcholine concentration. Changes in the structure, activity or level of these neuromodulators, AChE or acetylcholine, may elicit novel effects on the developing brain. It is not known to what extent neuronal AChE needs to be altered to have adverse effects on the developing brain, nor is it known what adverse effects on neurodevelopment may result from AChE inhibition. Nevertheless, because of the potential developmental role of AChE, it is reasonable to consider the evidence for whether inhibition of AChE in the developing nervous system may affect neural development.

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[1]The term susceptibility is used qualitatively to indicate unique effects (*e.g.*, a different pattern of effects of concern) in the young. The term sensitivity is used to refer to quantitative susceptibility, or to quantitatively indicate effects of a type similar to those seen in adults, but which occur at doses lower than those causing effects in adults.

In vitro work has shown that some OP compounds can inhibit neurite outgrowth, but enzyme inhibition does not appear to correlate completely with inhibition of outgrowth (Dupree and Bigbee, 1994; Layer *et al.*, 1993, Bigbee *et al.*, 1999). Inhibition of neurite outgrowth is compound-specific, as some compounds inhibit AChE activity but do not inhibit neurite outgrowth. It is now accepted that the cell adhesive function of AChE is mediated by a peripheral anionic site located at the rim of the 20 Å gorge, a site distinct from the catalytic site located at the bottom of that gorge (Johnson and Moore, 1999; Sternfeld *et al.*, 1998). OP inhibitors bind to the catalytic site; little is known about prerequisites for binding to the peripheral anionic site mediating cell adhesiveness. Perhaps some OPs bind specifically to that site or perhaps some OPs can perturb the function of that site when bound to the catalytic site (*e.g.*, Bigbee *et al.*, 1999).

In any event, AChE inhibition does not necessarily predict perturbations of neuronal differentiation. It is possible to create fruit flies (Greenspan *et al.*, 1980) or mice (Xie *et al.*, 2000) that do not produce AChE because they have no gene for AChE. In fruit flies, this is a lethal mutation, but in mice the absence of AChE is only lethal to approximately 25% of the homozygous fetuses *in utero*. At birth, the surviving homozygous animals appear overtly normal, but fail to develop normally and usually die by day 21 unless care is taken to provide their nutritional needs, in which case they may live to adulthood. The authors speculate that the animals survive because butyrylcholinesterase assumes many of the biochemical functions of the absent AChE. As with any study with knockout mice, the phenotype must be interpreted with caution as compensation may occur during development that would not mimic AChE inhibition during development.

Is there evidence that exposure to OP pesticides pre- or postnatally perturbs neurodevelopment? Some animal studies using prenatal exposures show effects on neurodevelopment, while other studies do not show any effect. In general, the literature shows that high levels of dosing of an OP during gestation (*e.g.*, affecting maternal weight gain) will tend to be embryotoxic (*i.e.*, lethal). More subtle effects may be noted at lower doses if other neurodevelopmental specific tests are employed. For example, the offspring of mice receiving diazinon during gestation showed developmental delays and abnormal endurance and coordination at doses of 0.18 or 9 mg/kg/day (Spyker and Avery, 1977). Malathion or dicrotophos showed dose and age-related abnormalities (assessed histologically) of nervous and extranervous system development in one-, two-, and three-day-old chick embryos (Wyttenbach and Thompson, 1985; Garrison and Wyttenbach, 1985) An *in vivo* study of malathion, however, showed no teratological effects in rabbits dosed from day 7 to day 12 of gestation (100 mg/kg; Machin and McBride, 1989); note that this study did not include any detailed assessment of nervous system tissues. Fetal brains of rats given chlorpyrifos repeatedly during late gestation show abnormalities in neuronal migration and other biochemical endpoints (Lassiter *et al.*, 2002; Qiao *et al.*, 2002).

Gestational exposure (day 6 to day 15) to tribufos, oxydemeton-methyl, azinphos-methyl, fenamiphos, isofenphos or fenthion at doses that produced 20-50% maternal brain cholinesterase (ChE) (ChE is used when there was no distinction between butyryl- or acetyl-cholinesterase in the experimental procedure) inhibition showed no embryotoxicity or teratogenicity; neurodevelopment was not assessed (Astroff and Young, 1998). Although the authors conclude that gestational dosing with these compounds caused "no effect on fetal ChE," this activity was not assessed until five days after the last dose, a time that is not optimal for assessing AChE inhibition in fetal tissues (Lassiter *et al.*, 1998; Michalek *et al.*, 1985).

Rats given OP pesticides postnatally may show abnormal nervous system development. In a series of papers exploring the neurotoxicity of postnatally administered chlorpyrifos, many changes were noted (*e.g.*, RNA levels, transcription factor expression, disruption of catecholaminergic and cholinergic pathways) (Johnson *et al.*, 1998; Crumpton *et al.*, 2000; Dam *et al.*, 1999), resulting in persistent biochemical and behavioral changes long after the dosing ceased (Dam *et al.*, 2000; Slotkin *et al.*, 2001a,b; Levin *et al.*, 2001; Slotkin *et al.*, 2002). Other studies in which chlorpyrifos was administered to the dam so that the pups received their dosage only through the milk were largely negative (Breslin *et al.*, 1996; Deacon *et al.*, 1980; Maurissen *et al.*, 2000), although the endpoints examined were not as targeted and discriminating as those used by the Slotkin laboratory. The relationship of these neurodevelopmental changes to ChE inhibition is unclear because many studies are lacking correlative ChE activity, thus making it difficult to draw firm conclusions. In the few prenatal studies where ChE activity was assessed, however, few of these effects occur at dose levels that do not inhibit ChE activity in the fetal brain, and probably none of these effects occur in the absence of ChE inhibition in maternal tissues. In both the studies assessing prenatal effects of chlorpyrifos, effects on brain development were noted at dosages (1 mg/kg/day) that did not inhibit fetal brain ChE (Lassiter *et al.*, 2002; Qiao *et al.*, 2002), but would be predicted to show inhibition of maternal blood and brain ChE activity (Maurissen *et al.*, 2000). In postnatal studies, there are no reports of effects in the absence of ChE inhibition. In some cases, this assertion is made by the authors, but the authors fail to ascertain that the ChE measurements were taken at the time of peak effect. Often the measurements are taken 24 hours after the last dose, rather than assessing ChE activity during the entire dosing period. Thus, it is reasonable to assume that adverse neurodevelopmental outcomes that are a result of the inhibition of ChE should not occur at doses that do not inhibit ChE. Because, however, the cumulative risk assessment is based on adult brain ChE data, it is important to address the age-related sensitivity of ChE inhibition in the adult versus the young animal. The available studies are reviewed below.

b. Differential Sensitivity of the Young Compared to the Adult

Although reports of increased sensitivity of the young following exposure to OP pesticides date back over two decades, it is the work that has emerged recently that provides a better basis for understanding the issues concerning the sensitivity of the young to ChE inhibition. This understanding comes from recently generated chemical-specific data in young animals on ChE activity, as well as generic human and animal studies on the biological and biochemical parameters involved in age-dependent sensitivity. The current state of the knowledge is summarized and discussed below.

i. Human Incident Information

There are reports of symptoms associated with cholinergic toxicity due to accidental acute exposures. A 1999 review based on pesticide-related exposures (excluding cases of exposure to multiple products, attempted suicides, malicious intent, and confirmed non-exposure) examined Poison Control Centers Data from 1993 through 1996 (USEPA, 1999). Of the exposures that occurred in a residential setting 16% were due to OP pesticides. The review of the residential pesticide exposure concluded:

Organophosphate pesticides pose a greater hazard from accidental acute exposure than do other pesticides, especially for children under six years-of-age. Children were three times more likely to be hospitalized, five times more likely to be admitted for critical care, and four times more likely to have experienced a major medical outcome or death than if exposed to some other pesticide.

In this review of residential exposures, there were 24,889 exposures reported in children under the age of six, 5,080 exposures among children six to 19 years-old, and 32,087 exposures among adults. Of those cases with medical outcomes determined, children under age six were 22% more likely to experience a life-threatening or fatal outcome as a result of their exposure than adults or children six to 19 years-old. Additionally, based on the Centers for Disease Control mortality data (see http://wonder.cdc.gov/mortsqu.shtml), the ratio for death in young children exposed to OP pesticides was 3.3 times higher than in adults.

These data show that there is more potential for harmful exposures in young children than in older age groups, but they do not necessarily demonstrate an increase in the sensitivity of young children. There is a possibility that young children may be exposed to higher doses on a body weight basis compared to adults (from spills, ingestion, inhalation) because they are ignorant of the hazard, and not because of differences in sensitivity based on age to the effects of these pesticides. Furthermore, the human data on children come from accidental exposures to these pesticides that are associated with acute poisoning

resulting in significantly higher blood, tissue, and urine concentrations of these chemicals compared to exposures that humans would normally encounter in food or the environment.

Because of the reasons stated above, it is difficult to draw conclusions from human incident data on the sensitivity of the young compared to adults. The animal literature below allows for evaluations of age-dependent sensitivity.

ii. Laboratory Animal Studies

Some studies are available in the open literature that have evaluated ChE inhibition following *in utero* or lactational exposures to OP pesticides, as well as dosing of young animals. EPA issued a Data Call-In (DCI) on September 10, 1999 for adult and developmental neurotoxicity (DNT) studies on the OP pesticides, and as part of the DNT protocol, measures of brain, red blood cell (RBC), and plasma ChE activity in dams and pups were required to characterize comparative levels of inhibition at the time of peak effect. However, very few DNT rat studies have been submitted to the Agency.[2] In addition to studies on OP pesticides that allows a comparison of the differential in response to ChE inhibition between adult and immature rats, several recent published studies provide an important perspective on the underlying basis for observed increased sensitivity. The analyses below will focus on differences in ChE inhibition between fetal, neonates, and juvenile rats compared to adults.

Differential Sensitivity Following Gestational/Lactational Exposure

Fenamiphos, tribufos, trichlorfon, and oxydemeton-methyl were evaluated for ChE inhibition in a rat multigeneration reproductive feeding study (Astroff *et al.*, 1998; discussed in Sheets, 2000). Dams were treated with these OP pesticides via the diet during gestation and continuing throughout the lactation period. Pups are assumed to be exposed due to consumption of feed at about 14-21 days-old.

Plasma and RBC ChE activity were measured in the adults during the premating phases of both generations following eight weeks of exposure to each of the OP pesticides, and again at termination when

[2]Out of the 30 OP pesticides included in the December 2001 preliminary cumulative assessment, DNT studies have only been submitted for chlorpyrifos, dimethoate, malathion, methyl parathion, methamidophos, and tribufos. The DNT studies submitted for dimethoate, malathion, and methyl parathion also included comparative ChE activity. These studies investigated ChE activity in adult and immature rats following either acute or repeated dosing. A review of the chlorpyrifos DNT study was completed in 1999, and reviews of the dimethoate and malathion DNT studies have recently been completed. The DNT studies for tribufos, methamidophos, and methyl parathion are currently under review, although a review has been completed on the ChE data for malathion and methyl parathion. It should be pointed out that the DNT studies on methamidophos and tribufos are feeding studies in which the pups were not directly dosed, and thus the pups were presumed to be exposed only *in utero* and during lactation; no comparative ChE data have been submitted for methamidophos and tribufos.

brain ChE activities were measured. Separate contingents of postnatal rats were evaluated for plasma, RBC, and brain ChE activity on lactation day (LD) 4 and on LD21. The effects found on LD4 could be due to gestational and lactational exposure, whereas the results on LD21 may reflect exposure through the milk and some exposure through the diet as pups begin consuming feed in the late lactational period, in other words, postnatal days (PND)14-21. Each study consisted of a control and three dose groups. The highest dose level was selected based on parental toxicity.

Toxicity (reduced body weights or viability) in the young was not apparent until there were significant maternal effects (decreased body weights and food consumption) and substantial ChE inhibition in the blood and brain of the parental animals. In fact, the adult animals were more affected than the young in this study. Although young rats, when exposed to these OPs *in utero* and via lactation, do not appear to exhibit more ChE inhibition than is found in maternal tissues, the dose that may be absorbed by the fetus and adult is unknown. Thus, conclusions can not be reached about the relative sensitivity of fetuses versus dams to ChE inhibition.

Maternal and fetal ChE inhibition were evaluated following maternal exposure to **azinphos-methyl, fenamiphos, fenthion, isofenphos, tribufos, and oxydemeton-methyl** in a prenatal developmental toxicity study in rats (Astroff and Young, 1998). These pesticides were administered to the dams by gavage on gestation days (GD) 6-15. Maternal ChE activity (brain, RBC, plasma) was measured onGD16 and 20, and fetal brain ChE activity was measured on GD20. The dose levels for these studies were selected such that maternal ChE inhibition at the highest dose tested was greater than 20%. At the highest dose tested on GD16 (in plasma [except for azinphos-methyl], RBC [except for fenamiphos], and brain [except for fenamiphos], and on GD20 (in plasma [only for fenthion], RBC [except for aniphos methyl], and brain [except for fenamiphos]), maternal ChE was significantly inhibited. However, no remarkable brain ChE inhibition was observed in fetuses at any dose on GD20.

The effect of treatment with **chlorpyrifos** on ChE activity was compared in dams and fetuses by Mattsson *et al.* (1998; 2000). Pregnant Sprague-Dawley rats were administered chlorpyrifos by gavage at doses of 0, 0.3, 1.0, or 5.0 mg/kg/day on GD6-20. The magnitude of brain, plasma, and RBC ChE inhibition in the fetus on GD20 was found to be less than or equal to that observed in dams. At 5.0 mg/kg/day, ChE activity in fore- and hindbrain of the dams on GD20 was inhibited by 76.0 and 86.7%, respectively, and by 58.8% in fetuses. At 1.0 mg/kg/day, brain ChE activity in fore- and hindbrain was inhibited in dams by 7.8 and 8.0% (statistically significant at

$p \leq 0.05$ or 0.01), respectively; there was no statistically significant depression of brain ChE activity in fetuses. In another study of the comparative ChE inhibition between dam and fetus with chlorpyrifos, Lassiter *et al.* (1998) concluded that the fetal brain ChE inhibition was less than the maternal brain ChE inhibition during repeated dosing primarily because the fetal brain tended to recover more completely between doses than the maternal brain ChE. When dams were given a single dose, both maternal and fetal brain ChE appeared to be depressed to the same degree, but when subjected to a repeated dosing regimen, the fetal brain showed less inhibition probably because of the higher rates of new synthesis or more rapid turnover of inhibited molecules of ChE in the fetuses compared to the adult. In two different studies which compared the tissue burden of chlorpyrifos and metabolites in dam and fetus, one group (Mattsson *et al.*, 1998, MRID 44648102, Mattsson *et al.*, 2000) found lower blood concentrations of chlorpyrifos in the fetus as compared to the dam, whereas another group (Hunter *et al.*, 1999) found three times more trichloropyridinol (a metabolite of chlorpyrifos) in the fetal brain as compared to the maternal brain. Trichloropyridinol (TCP) can either be produced as a by-product of a toxic action (*i.e.*, TCP is the leaving group wh chlorpyrofos-oxon binds to ChE) or as a detoxification action (*e.g.*, TCP can be produced when chlorpyrifos-oxon is catalyzed by PON1).

Results of a recently submitted DNT study with **dimethoate** indicated that treatment by gavage of dams with the pesticide induces equal or less inhibition of ChE in the fetus compared with the dams (Meyers, 2001; MRID 45529702). Treatment of dams with 0.5 mg/kg/day of dimethoate during GD6-20 induced statistically significant but marginal ChE inhibition (10%) in brain tissue of both adult and fetal rats. The responses at 3 mg/kg/day (the highest dose tested) indicated less brain and RBC ChE inhibition in fetuses (33% and 31%, respectively) compared with dams (60% and 58%, respectively). Measurements of ChE inhibition were also conducted on four-day-old pups that were exposed to dimethoate *in utero* from GD6 to GD20, but not directly exposed postnatally. At 3.0 mg/kg/day, brain and RBC ChE activity was inhibited by 13% and 17% in the PND4 pups.

A DNT study performed with **malathion** (Fulcher, 2001; MRID 45566201) also showed that there was less effect on ChE activity (measured at GD20) in fetuses than in dams that had been treated by gavage with the pesticide during GD6-GD20. At the highest dose examined (150 mg/kg/day), RBC ChE was inhibited by 19% in fetuses and by 51% in the dams. No effects on brain ChE activity were observed in either the fetuses or dams at that dosage. At PND4, at which time the only exposure to malathion could be through milk, ChE activities in treated pups were comparable to controls.

ChE data that were recently submitted to the Agency (Beyrouty, 2002b; MRID 45656501), supplemental to a DNT study on **methyl parathion**, demonstrated that treatment of dams by gavage from GD6-20 induced more ChE inhibition in the brain of dams than in the fetuses. Analyses of brain tissue at GD20 showed that ChE activity was inhibited by 31% in dams at a dose of 0.60 mg/kg/day (the highest dose tested), while there was no brain ChE inhibition in their fetuses. At the same dose, RBC ChE inhibition was 58% in dams and 22% and 18% in male and female fetuses, respectively. In PND4 pups, ChE was not inhibited in any compartment.

In summary, results of studies with fenamiphos, tribufos, trichlorfon, oxydemeton-methyl, chlorpyrifos, methyl parathion, dimethoate, malathion, and azinphos-methyl show that treatment of pregnant dams with an OP pesticide during gestation induces more ChE inhibition in the dams than in the fetus. Data from these studies also show that the newborn (one- to four-day-old pups), when only exposed *in utero* or possibly through the milk, also has less inhibition of ChE than the maternal, adult rat. The lack of similar levels of ChE inhibition in fetuses or neonates relative to adults may be due to the fetuses receiving a lower dose of these OP pesticides compared to their dams because of pharmacokinetic differences, such as a lower dose being transferred to the fetus through the placenta or to the neonate through the milk than is received by the dam directly in the diet. A lower response in the immature animal may also be due to the increased synthesis or more rapid turnover of inhibited molecules of ChE in the fetal brain compared to the adult (Lassiter *et al.*, 1998; Mortensen *et al.*, 1998).

Differential Sensitivity Following Direct Postnatal Exposures

Neonatal, juvenile, and adult rats show differential sensitivity to ChE inhibition following an acute gavage treatment with **chlorpyrifos** (Pope, 2001a). When rats from each age group were administered chlorpyrifos at 0.5 times the LD_{10} (7.5 mg/kg, neonates; 23.5 mg/kg, juveniles; 68 mg/kg, adults), peak ChE inhibition in the cortex (estimated from Figure 11 of the report) was 70% (neonates), 65% (juveniles), and 68% (adults). Thus, based on similar magnitudes of peak ChE inhibition at 0.5 of a LD_{10} dose and considering the differentials in the 0.5 LD_{10} doses, neonates were shown to be about threefold more sensitive than juveniles and about ninefold more sensitive than adults. In another study by Moser *et al.* (1998) a single gavage dose of 20 mg/kg produced 89% and 91% (males and females) brain ChE inhibition in PND17 pups, compared to 39% and 36% (males and females) inhibition in adults (*i.e.*, about a twofold difference in relative sensitivity).

Chlorpyrifos produces a minimal difference in ChE inhibition in neonatal rats compared to adult rats following repeated dosing (14 treatments by gavage during PND7 to PND21). Based on ED_{50} levels (adults, 3.3 mg/kg/day and neonates, 2.2 mg/kg/day), the difference in the response of neonates to brain ChE inhibition compared to adult males is a 1.5-fold increase (Zheng *et al.*, 2000).

Similar results were reported in a recent study in which neonatal and adult rats were administered chlorpyrifos by subcutaneous injection (Liu *et al.*, 1999). Neonatal (seven-day-old) pups and adults were administered 0, 5, or 10 mg/kg/day for seven or 14 days and sacrificed for ChE measurements one day after the final dose. At seven days, inhibition of ChE activity in the cortex and striatum of the neonates was 62 and 65%, respectively, compared with 50 and 55% in adult animals. Following 14 days of treatment, ChE inhibition in the cortex and striatum of neonates was 60 and 65%, respectively and 65% in both of these tissues from adult animals.

Diazinon. A recent abstract by Moser and coworkers (Padilla *et al.*, 2002) reported an increased sensitivity to ChE inhibition for diazinon when PND17 pups were given a single oral dose (via gavage) of 75 mg/kg (75% brain ChE inhibition) compared to adult rats (38% brain ChE inhibition). This observation was correlated with detoxification by carboxylesterases and A-esterases (as discussed later in Section II.C.). There are no data available on the effects on ChE activity following repeated dosing of neonates or young adults with diazinon.

Dimethoate. In a recent DNT study (Meyers, 2001; MRID 45529702), dimethoate was evaluated for ChE activity in plasma, RBC, and brain following acute exposures and repeated dosing (subacute exposures) to 0.1, 0.5, and 3 mg/kg/day of dimethoate. Dimethoate was given by gavage to pregnant rats GD6 through LD10 (LD10; equivalent to PND10); their pups were treated by gavage from PND11 through PND21. Plasma, RBC, and brain ChE was measured at GD20 (dams and fetuses), PND4 (pups only), and PND21 (pups only). ChE activity was also measured following an acute dose of dimethoate to additional groups of young adult and PND11 rats. In general, there was no striking difference in sensitivity to dimethoate-induced brain or plasma ChE inhibition between males and females of either adults or pups following acute or repeated treatment.

Acute (single dose) treatment with dimethoate of adult male and female rats and 11-day-old offspring with 3 mg/kg/day induced statistically significant, treatment related ChE inhibition in brain or RBC. At that dose, brain ChE inhibition in adult male and female rats was 12% and 14%, respectively, and in day 11 male and female

offspring 17% and 18%, respectively. At 3 mg/kg/day, RBC ChE inhibition was greater in adult females than in adult males (26% versus 17%) and there was no statistically significant depression of RBC ChE activity in PND11 offspring.

Repeated dosing (11 doses) with 0.5 mg/kg/day dimethoate induced statistically significant but marginal brain ChE inhibition (10-13%) in both sexes of adult and 21-day-old rats. The response is likely due to treatment with the chemical because of the positive finding in both sexes of both age groups and because data from GD20 dams also showed an effect at 0.5 mg/kg/day. At the 3 mg/kg/day dose level, brain ChE inhibition was substantial in both adults (up to 58%) and 21-day-old offspring (up to 45%). In the repeated dosing study, a small, but statistically significant, difference in brain ChE inhibition was found at the low dose (0.1 mg/kg) between adults and pups (GD20, PND4 and PND21). As the dose was increased, this differential was not found at the high dose 3.0 mg/kg (see Table 1).

Because dimethoate does not show age-dependent sensitivity (discussed above), it is reasonable to assume that its oxon–omethoate–will also not show a differential toxicity in adults versus pups. Unlike acephate (discussed later), the parent compound–dimethoate–has been characterized for ChE inhibition in the young animals compared to adults.

Malathion. Recently submitted ChE data (supplemental to a DNT study) (Fulcher, 2001; MRID 45566201) clearly demonstrate a differential sensitivity to inhibition of the ChE enzyme in immature animals compared to adult rats treated with acute or repeated exposure to malathion. In this study, pregnant rats were administered malathion by gavage from GD6 through LD10; gavage dosing of their pups was then continued from PND11 through 21. Plasma, RBC, and brain ChE was measured at GD20 (dams and fetuses), PND4 (pups only), and PND21 (pups only). ChE activity was also measured in additional groups of young adult and immature (PND11) rats that had been administered a single (acute) dose of malathion. The dose levels were 5, 50, 150 mg/kg/day in the repeated dosing studies, and 5, 50, 150, and 450 mg/kg in the acute studies.

Following an acute dose of malathion, brain ChE was inhibited in PND11 pups at 150 mg/kg (44% in males and 48% in females) and at 450 mg/kg (84% in males and 81% in females), while brain ChE was not affected in young adults at either of those doses. At 450 mg/kg, however, RBC ChE was inhibited in both young adults (25% in males and 17% in females) and PND11 pups (72% in males and 61% in females).

Repeated dosing of malathion at 150 mg/kg/day from PND11 through PND21 (11 days of treatment) produced a marked inhibition of plasma (24-32%), RBC (67-68%), and brain (16%) ChE compared to controls. For dams, 14 days of treatment at 150 mg/kg/day resulted in RBC ChE inhibition (51%), but no inhibition of plasma or brain ChE. Similarly, for young adult rats that were treated for 11 days with 150 mg/kg/day malathion, RBC ChE was inhibited 43% in males and 48% in females, while plasma and brain ChE were not affected. At 50 mg/kg/day, plasma (19%) and RBC (34-39%), but not brain, ChE activity was inhibited in the PND21 offspring, while in dams and young adults, only RBC ChE (19-20%) was inhibited. No effects on ChE activity were seen at 5 mg/kg/day for dams or young adults. In PND21 offspring, however, RBC but not plasma or brain ChE was inhibited (17% in males, 15% in females).

Methamidophos was evaluated for age-related differences in ChE inhibition by Moser (1999). Comparisons for brain and blood ChE activity were made between PND17 and adult rats following acute oral doses of 1, 4, or 8 mg/kg. The dose response curves for ChE inhibition were quite similar between pups and adult rats. ED_{50} values for brain ChE inhibition in PND17 and adult rats were approximately 3.3 and 3.0 mg/kg/day, respectively. The ED_{50} values for blood ChE inhibition were 2.5 (PND17) and 2.2 (adults) mg/kg/day.

Although acephate is metabolized to methamidiphos, it is not possible to determine, based on available data, whether acephate would show comparable responses in adult and young rats. This is because acephate, the parent compound, has not been evaluated for comparative ChE activity in young versus adult animals. In rats, only a small portion of acephate is metabolized to methamidiphos (5%) (Warnock, 1973; MRID 00014219). Furthermore, it is unknown to what extent the parent chemical may induce ChE inhibition or to what extent the parent chemical may alter the effects of methamidiphos on ChE activity in the adult or young rat.

Treatment of neonatal, juvenile, and adult rats with a single gavage dose of **methyl parathion** induces a differential response among the age groups in ChE inhibition in the brain (cortex) (Pope, 2001a). Treatment with methyl parathion at doses of 1.0 mg/kg (neonates), 2.05 mg/kg (juveniles), or 7.3 mg/kg (adults) induced similar magnitudes of peak ChE inhibition (60%-70%, estimated from Figure 14 of the report). Based on a comparison of the doses that induced similar levels of ChE inhibition, neonates are 2.5-fold more sensitive than juvenile rats and about sevenfold more sensitive than adult rats to methyl parathion induced ChE inhibition.

Methyl parathion was investigated by Liu *et al.*, (1999) for ChE activity and other neurochemical effects after repeated dosing in postnatal and adult male rats. Adult and postnatal rats (eight-day-old) were treated with methyl parathion subcutaneously at 1.5 mg/kg/day or 3.0 mg/kg/day for either seven or 14 consecutive days. Brain ChE activity was measured in the cortex and in the striatum one day after seven days of dosing or eight days after 14 days of dosing. Brain ChE activity was more reduced in postnatal pups compared to adults. Following seven days of dosing at 1.5 mg/kg/day, neonates showed 62 and 75% ChE inhibition in the cortex and striatum, respectively, compared to 25 and 30% in the adult male rats. In neonates treated subcutaneously with methyl parathion for 14 days, ChE activity was inhibited in the cortex by 65% and in the striatum by 80%. ChE activity was inhibited in adult rats by 40% (cortex) and by 50% (striatum).

A recently submitted DNT study on methyl parathion with supplemental ChE data (Beyrouty, 2002b; MRID 45656501) demonstrated a differential sensitivity of immature versus adult rats to ChE inhibition following acute or repeated exposure. The protocol for this study was similar to that used for the DNT ChE studies conducted for dimethoate and malathion. Methyl parathion was administered by gavage to pregnant rats from GD6 through LD10 at doses of 0.03, 0.11, 0.3, and 0.6 mg/kg/day. Pups from these litters were then administered methyl parathion by gavage from PND11-21. Plasma, RBC, and brain ChE was measured at GD20 (dams and fetuses), PND4 (pups only), and PND21 (pups only). Additional groups of young adult and PND11 rats were dosed acutely with methyl parathion (at doses of 0.03, 0.11, 0.3, and 0.6 for adults and doses of 0.03, 0.11, 0.3, and 1.0 for pups), and ChE activity was measured. Following acute exposures of 0.3 mg/kg, ChE was inhibited in brain (15-18%), RBC (20-31%), and plasma (25%) in PND11 pups; no inhibition was observed in any compartment for adults.

Repeated dosing of PND11 to PND21 pups (which had also been exposed *in utero* and via lactation) also showed an increased sensitivity of neonates compared with adult rats to treatment with methyl parathion. At 0.3 mg/kg/day, ChE activity was inhibited in PND21 pups (brain 26-29%, RBC 62-65%, and plasma 24-31%). In dams treated with the same dosage from GD6 to GD20 (*i.e.*, 14 days of treatment), ChE inhibition was seen in brain (9%) and RBC (35%), but plasma ChE was not affected. In adult rats treated with 11 repeated doses of 0.3 mg/kg/day methyl parathion, ChE inhibition was seen in RBC (30% in males and 35% in females) and plasma (25% in males), but there was no inhibition of brain ChE. At 0.6 mg/kg/day, brain ChE was inhibited 60-62% in PND21 pups, 31% in GD20 dams, and 6-13% in adults; RBC ChE was inhibited 85-86% in PND21 pups, 58% in GD20 dams, and 40-58% in adults; and plasma ChE was

inhibited 56-61% in PND21 pups, 29% in GD20 dams, and 28-34% in adults.

Summary of Differential Sensitivity

Table 1 shows results of ChE measurements performed in acute and repeat dosing studies with OP pesticides using neonatal, juvenile, or adult rats. The information provided in Table 1 is confined to data that could be used to estimate the relative sensitivities of different age groups based on the amount of ChE inhibition reported following treatment with an OP pesticide. Estimates of relative sensitivities (4th column) were derived by either: (1) the ratio of the response *(i.e.*, percent ChE inhibition) for adults: pups at the same dose of chemical, or (2) the ratio of doses in adults: pups that induce a comparable amount of ChE inhibition. The different approaches to estimating the relative sensitivities to a ChE-inhibiting chemical were necessary because of the differences in study designs and results among the studies evaluated. For example, some studies used single doses such as a proportion of an LD whereas other studies used multiple doses that allowed calculations of an ED_{50}. It should be noted that estimates of relative sensitivities are a function of the doses or percentages of ChE reported in studies and that, depending on dose-response characteristics of ChE inhibition among different age groups, actual sensitivities may be different at doses other than those used in Table I.G-1.

[Since this section was written, preliminary BMD_{10}'s were derived for the dose-response ChE data from repeated dosing studies on pups and adults in RBC and brain for malathion (Fulcher 2001), methyl parathion (Beyrouty 2002)and chlorpyrifos (Zheng et al., 2000). These data were modeled using the EPA Benchmark Dose Software version 1.3.1 - Hill model (available at website: http://cfpub.epa.gov/ncea/cfm/bmds.cfm?ActType=default). The modeling confirmed that there was less than two-fold difference in response between adults and pups following repeated dosing with chlorypyrifos. For malathion, a difference between adults and pups up to approximately 3-fold was found for RBC ChE inhibition based on the BMD10s. For brain ChE , there was 16% inhibition in pups at the highest dose tested (150 mg/kg/day) but no inhibition in adults. Thus, relative sensitivity could be determined because of the lack of comparable dose response data in pups and adults. Although Table 1 reports a differential in brain ChE inhibition for methyl parathion up to 3.-fold (comparing percent inhibition), modeling the Beyrouty data showed differences up to approximately 4-fold based on BMD10s.]

Table I.G-1. Summary of Sensitivity to ChE Inhibition in Neonatal or Juvenile Rats Treated with Organophosphorus Pesticides

Pesticide & Reference	Treatment Groups; Doses (mg/kg/day); Route of Administration	Results	Relative Sensitivity (Fold Difference)
Chlorpyrifos			
(Pope, 2001a)	Neonates, juveniles, and adults 7.5 neonates, 23.5 juveniles, 68 adults single gavage dose	**Neonates:** 70% ChEI in cortex at 7.5 mg/kg **Juveniles:** 65% ChEI in cortex at 23.5 mg/kg **Adults:** 60% ChEI in cortex at 68 mg/kg	**ACUTE** **Juveniles/neonates:** 23.5 mg/kg/ 7.5 mg/kg = 3.1 **Adults/neonates:** 68 mg/kg/ 7.5 mg/kg = 9.1
Moser *et al.*, (1998)	Adults and PND17 pups 20 mg/kg single gavage oral doses	**Pups Brain ChEI:** 89% (♂) and 91% (♀) **Adults Brain ChEI:** 39% (♂) and 66% (♀) inhibition in adults	**ACUTE** **Pups/Adults:** 89 % ChEI/39% ChEI=2.3; 91% ChEI/36% ChEI=2.3
(Zheng *et al.*, 2000)	Repeated gavage doses of 0.15, 0.45, 0.75, 1.50, 4.50, 7.50, or 15.0	**Pups:** ED_{50} for ChEI in cortex, 2.2 mg/kg/day **Adults:** ED_{50} for ChEI in cortex, 3.3 mg/kg/day **Pups:** 54.9% RBC ChEI, 1.5 mg/kg/day **Adult:** 91% RBC ChEI, 1.5 mg/kg/day	**REPEATED** **Adults/pups:** 3.3 mg/kg/day/2.2 mg/kg/day = 1.5 (no difference) **Adult/pups:** 54.9% ChEI/91% ChEI = 0.6 (no difference)
Diazinon			
(Padilla *et al.*, 2002)	Adults and PND17 pups single gavage dose of 75	**Pups:** 75% brain ChEI **Adults:** 35% brain ChEI	**ACUTE** **Pups/Adults:** 75% ChEI/35%ChEI = 2.1
Dimethoate			
(Myers, 2001; MRID 45529702, unpublished)	Adults and PND11 pups single gavage doses of 0.1, 0.5, or 3.0	**Pups:** 18% brain ChEI at 3.0 mg/kg; 26% RBC ChEI at 3.0 mg/kg **Adults:** 14% brain ChEI at 3.0 mg/kg; 27% RBC ChEI at 3.0 mg/kg	**ACUTE** **Pups/Adults:** At 3 mg/kg 18% ChEI/14%ChEI=1.3 26% ChEI/27% ChEI=1 (no difference)

Table I.G-1. Summary of Sensitivity to ChE Inhibition in Neonatal or Juvenile Rats Treated with Organophosphorus Pesticides

Pesticide & Reference	Treatment Groups, Doses (mg/kg/day), Route of Administration	Results	Relative Sensitivity (Fold Difference)
	Adults and PND11-21 repeated gavage doses of 0.1, 0.5, or 3.0	**Pups:** 45% brain ChEI at 3.0 mg/kg/day; 13% ChEI at 0.5 mg/kg/day; 65% RBC ChEI at 3.0 mg/kg/day; no RBC ChEI at 0.5 mg/kg/day **Adults:** 60% brain ChEI at 3.0 mg/kg/day; 13% brain ChEI at 0.5 mg/kg/day; 63% RBC ChEI at 3.0 mg/kg/day; no RBC ChEI at 0.5 mg/kg/day	**REPEATED** **Pups/Adults:** At 3 mg/kg/day 45% ChEI/60% ChEI=0.8 (no difference) At 0.5 mg/kg/day 13% ChEI/13% ChEI=1 (no difference) At 3 mg/kg/day 65% ChEI/63% ChEI=1 (no difference)
Malathion			
Fulcher, 2001, MRID 45566201, unpublished)	Adults and PND11 pups single gavage doses of 5, 50, 150, or 450	**Pups:** 84% brain ChEI at 450 mg/kg; 48% brain ChEI at 150 mg/kg; 72% RBC ChEI at 450 mg/kg; 55% RBC ChEI at 150 mg/kg **Adults:** No brain ChEI at 150 or 450 mg/kg; 25% RBC ChEI at 450 mg/kg; no RBC ChEI at 150 mg/kg	**ACUTE** **Pups/Adults:** 84% brain ChEI/no brain ChEI at 450 mg/kg; fold difference uncertain **Pups/Adults:** 72% RBC ChEI/25% ChEI at 450 mg/kg = 2.9
	Adults and PND11-21 pups repeated gavage doses of 5, 50, or 150	**Pups:** 16% brain ChEI at 150 mg/kg/day; no brain ChEI at 50 mg/kg/day; 68% RBC ChEI at 150 mg/kg/day; 39% RBC at 50 mg/kg/day 17% RBC ChEI at 5 mg/kg/day **Adults:** No brain ChEI and 51% RBC ChEI at 150 mg/kg/day; 20% RBC ChEI at 50 mg/kg/day	**REPEATED** **Pups/Adults:** 16% brain CHEI/no CHEI at 150 mg/kg/day and no brain at 50 mg/kg/day in pups or adults; fold difference uncertain **Pups/Adults:** 68% RBC ChEI/51% RBC ChEI at 150 mg/kg/day =1.3; 39% RBC ChEI/20% RBC ChEI at 50 mg/kg/day =2.0
Methamidophos			
(Moser, 1999)	Adults and PND17 pups single gavage dose of 1, 4, or 8	**Pups:** ED_{50} for brain ChEI 3.0 mg/kg; ED_{50} for blood ChEI 2.3 mg/kg **Adults:** ED_{50} for brain ChEI 3.0 mg/kg; ED_{50} for blood ChEI 2.0 mg/kg	**ACUTE** **Pups/Adults:** 3 mg/kg/3 mg/kg=1 (no difference); 2.3 mg/kg/2 mg/kg=1.2 (no difference)
Methyl Parathion			

Table I.G-1. Summary of Sensitivity to ChE Inhibition in Neonatal or Juvenile Rats Treated with Organophosphorus Pesticides

Pesticide & Reference	Treatment Groups; Doses (mg/kg/day); Route of Administration	Results	Relative Sensitivity (Fold Difference)
(Pope, 2001a)	Neonates, juveniles, and adults treated with a single gavage dose neonates 1.0, juveniles 2.05, adults 7.3	**Neonates:** 60% ChEI in cortex at 1.0 mg/kg **Juveniles:** 60% ChEI in cortex at 2.05 mg/kg **Adults:** 70% ChEI in cortex at 7.3 mg/kg	**ACUTE** **Juvenile/neonate:** 2.05 mg/kg/ 1.0 mg/kg = 2.05 **Adult/neonate:** 7.3 mg/kg/1.0 mg/kg = 7.3
(Beyrouty, 2002a; MRID 45656501, unpublished)	Adults and PND11 pups single gavage doses of 0.03, 0.11, 0.3, or 1.0 pups; 0.03, 0.11, 0.3, or 0.6 adults	**Pups:** 18% brain ChEI at 0.3 mg/kg; 31% RBC ChEI at 0.3 mg/kg **Adults:** No brain or RBC ChEI at 0.3 mg/kg	**ACUTE** **Pups/Adults:** 18% brain ChEI/no brain ChEI at 0.3 mg/kg; fold difference uncertain 31% RBC ChEI/no RBC ChEI at 0.3 mg/kg; fold difference uncertain
	Adults and PND11-21 pups repeated gavage doses of 0.03, 0.11, 0.3, or 0.6	**Pups:** 62% brain ChEI at 0.6 mg/kg/day; 29% brain ChEI at 0.3 mg/kg/day; 86% RBC ChEI at 0.6 mg/kg/day; 65% RBC ChEI at 0.3 mg/kg/day **Adults:** 31% brain ChEI at 0.6 mg/kg/day; 9% brain ChEI at 0.3 mg/kg/day; 58% RBC ChEI at 0.6 mg/kg/day; 35% RBC ChEI at 0.3 mg/kg/day	**REPEATED** **Pups/Adults:** 62% brain ChEI/31% brain ChEI at 0.6 = 2.0 29% brain ChEI/9% brain ChEI at 0.3 =3.2; 86% RBC ChEI /58% RBC ChEI at 0.6=1.5; 65% RBC ChEI/35% RBC ChEI at 0.3 =1.9

iii. Recovery from ChE Inhibition in Young Rats Treated with Organophosphorus Pesticides

Studies that included analyses of recovery from ChE inhibition in young rats have been performed on chlorpyrifos, methamidiphos, methyl parathion, and parathion.

PND17 pups were reported to recover from ChE inhibition in one week after cessation of dosing with a single maximum tolerated dose (MTD) of **chlorpyrifos** of 15 mg/kg compared with a greater than two-week recovery period in adults administered a MTD dose of 80 mg/kg/day (Moser and Padilla, 1998). Pope *et al.* (1991) also reported a faster recovery in ChE activity in neonates compared to adults when treated with a MTD of chlorpyrifos. Adults treated with an acute, subcutaneous, dose of 279 mg/kg chlorpyrifos showed about a 90% inhibition of brain ChE activity seven days after dosing compared to approximately 40% inhibition in the brains of seven-day-old neonates treated with 45 mg/kg chlorpyrifos.

One day following oral treatment every other day with three doses of 3 mg/kg/day and eight doses of 6 mg/kg/day from PND1-21, brain ChE activity was inhibited by 57% (Tang *et al.*, 1999). Following a 19-day recovery period, brain ChE activity (about 20% inhibition relative to controls) was still depressed. Thus, although ChE levels in juvenile rats return to control levels after an acute treatment with chlorpyrifos, repeated treatments can lead to prolonged ChE inhibition.

PND17 and adult rats orally administered 8 mg/kg **methamidiphos** each showed about 80-85% brain ChE inhibition 1.5 hours after dosing (Moser, 1999). Twenty-four hours after dosing, more recovery was noted in the pups than adults (30-35% brain ChEI in pups versus 55% in adults). At 72 hours post dosing, ChE activity in pups had returned to normal but there was still brain ChE inhibition in adults (10-15%)

Neonatal (seven-day-old) pups and adults were found to have similar brain ChE activities (about 20% activity compared to controls) when administered a MTD of **methyl parathion** (7.8 mg/kg: neonates; 18 mg/kg: adults) but a more rapid recovery was reported for the neonates (Pope *et al.*, 1991). By seven days after treatment, neonatal ChE activity was almost completely recovered (about 90%) whereas brain ChE activity in adults was about 50% relative to controls.

Repeated treatments with methyl parathion of PND7 or 14 neonates and adults showed more inhibition initially but a faster recovery in the young rats (Liu *et al.*, 1999). On day 8, one day after seven days of subcutaneous treatment of neonates and adults, inhibition in the cortex of neonates administered 1.5 mg/kg/day was 73% (neonate) and 32% (adults). At a dose of 3.0 mg/kg/day, more inhibition was found in striatal than cortex tissues: Striatal inhibition at that dose was reported as 86% (neonate) and 64% (adult) one day following seven days treatment; seven days after cessation of dosing, brain ChE inhibition was about 45% in both age groups, indicating that more recovery had occurred in neonates (41%) than in adults (only 19%).

Liu *et al.* (1999) also investigated the effects on ChE inhibition in neonatal rats and adults following administration of MTD doses of **parathion**. As with methyl parathion, maximum brain ChE inhibition was similar (>85% on the day of dosing in neonates and 90% in adults four days after dosing), but recovery in the neonates was more rapid. Seven days after cessation of dosing, brain ChE activity had essentially returned to normal in neonates but brain ChE was inhibited by 80% in the adults.

c. Mechanisms Underlying the Differential Age-Related Sensitivity For ChE Inhibition

Age-related differences in sensitivity to pesticides can occur for a number of reasons (Pope, 2001b). Exposures to pesticides are age-related (discussed in Section D) where children may be more exposed than adults based on their diet and behaviors. Toxicodynamic and toxicokinetic differences may also contribute to the young being at a different risk to pesticide exposure. As summarized below, there are several reports in the literature investigating the basis underlying the differential sensitivity found for certain OP pesticides.

Toxicodynamic Considerations: There may be different mechanisms underlying age-related sensitivity to ChE inhibition for different OP pesticides. The exact mechanisms are not clearly understood in laboratory animals. For obvious reasons, no data are available in humans. There are studies, however, in laboratory animals that provide such information. Intrinsic differences in neuronal AChE (*i.e.*, differential inhibition of the target enzyme itself) do not appear to account for the observed age-related sensitivity found in young animals as suggested by *in vitro* studies (Benke and Murphy, 1975; Chanda *et al.*, 1995; Mortensen *et al.*, 1996; Atterberry *et al.*, 1997). Another toxicodynamic factor, the ability to restore function following exposure, does not appear to be the basis for age-related sensitivity to the OP pesticides because more rapid recovery of AChE activity in younger animals is found compared to adults (Chakraborti *et al.*, 1993; Moser, 1999; Pope *et al.*, 1991; Pope and Liu, 1997).

Other toxicodynamic differences that could affect age-related sensitivity to AChE inhibition concern the regulation of acetylcholine receptor number as well as acetylcholine release. Inhibition of ChE activity in the nervous system results in the accumulation of acetylcholine in the synapses causing hyperstimulation of the cholinergic receptors on postsynaptic cells. It is this hyperstimulation that leads to cholinergic toxicity. This hyperactivity may also lead to a decrease in the number of muscarinic receptors (*i.e.*, down-regulation). As a measure of toxicodynamic response to OP dosing, some studies have compared the degree of muscarinic down-regulation in adult and young rats. In a study of repeated, subcutaneous dosing with methyl parathion or chlorpyrifos, Liu *et al.* (1999) found that muscarinic receptor number was markedly reduced in pups compared to adult rats following repeated dosing with methyl parathion, suggesting age-dependent differences in mucarinic receptor adaptation. Interestingly, the chlorpyrifos exposure also produced more receptor down-regulation in the pup as compared to the adult, but the effect was not as pronounced as the methyl parathion effects. Moreover, using a different route, the same group showed that repeated oral dosing with chlorpyrifos caused equal down-regulation of muscarinic receptors in neonatal and adult brain (Zheng *et al.*, 2000). The effect on receptor down-regulation appears to be compound-specific, and possibly, route-specific. In the normal cholinergic synapse, it is known that feedback inhibition of acetylcholine release occurs through activation of the muscarinic acetylcholine receptors located on the presynaptic nerve terminals (see Pope, 2001b). Activation of the muscarinic acetylcholine receptors would decrease further acetylcholine release, thereby reducing the excessive stimulation of the postsynaptic receptors following AChE inhibition. A limited ability or adaptability of this presynaptic regulatory process in the young could lead to increased sensitivity to OP pesticides. There are only a few reports exploring age-related differences in muscarinic presynaptic acetylcholine receptor activity: evoked acetylcholine release was lower in brain tissues from newborn animals and aged animals compared to rats aged one to six months (Pedata *et al.*, 1983; Meyer and Crews, 1984). There is no information on the receptor response (either total muscarinic receptor number or feedback inhibition of acetylcholine release) in the developing human brain.

Toxicokinetic Considerations: Toxicokinetic differences among age groups can contribute to age-related differences in response, with the interplay of metabolic activation and detoxification processes being an important major factor, particularly in the first few months after birth (*e.g.*, see Ginsberg *et al.*, 2002). It appears from the literature that toxicokinetic differences play an important role in the differential sensitivity of the young to ChE inhibition following treatment with OP pesticides (*e.g.*, Brodeur and DuBois, 1963; Benke and Murphy, 1975; Scheidt *et al.*,1987, reviewed in Pope, 2001b). In addition to inhibiting AChE, OP pesticides also interact with other esterases, *i.e.*, carboxylesterases and/or A-esterases, an by doing so become inactivated or detoxified. A-esterases (*e.g.*, chlorpyrifos oxonase,

paraoxonase, or PON1) detoxify some OP pesticides by hydrolysis, whereas some OPs bind to carboxylesterases, a reaction which effectively lessens the amount of pesticide available for inhibiting AChE. Many investigators have noted the decreased capability of the young animal to detoxify OP pesticides by A-esterase or carboxylesterase esterases compared to adults (Mortensen *et al.,* 1996; Atterberry *et al.*, 1997; Costa *et al.*, 1990; Padilla *et al.*, 2000; Padilla *et al.,* 2002; Karanth and Pope, 2000).

Laboratory Animal Literature: The importance of A-esterase protection against the toxic effects of the anticholinesterase activity of OP pesticides has been demonstrated in several studies in which exogenous administration of A-esterase can lessen OP toxicity in rodents (Costa *et al.*, 1990; Li *et al.*, 1993; Main, 1956). Studies with an A-esterase knockout mouse reinforced the important role that A-esterases play in the detoxication of OP pesticides: knockout mice were much more sensitive to chlorpyrifos oxon or diazoxon (the active metabolites of chlorpyrifos or diazinon, respectively) than their wildtype litter mates (reviewed in Furlong *et al.*, 2000). In rats, A-esterase activity is virtually nonexistent in the fetus (Lassiter *et al.*, 1998) and increases from birth to reach adult levels around PND21 (Mortensen *et al.*, 1996; Li *et al.*, 1997). The animal data regarding the role of carboxylesterase in mediating OP toxicity are also quite extensive (*e.g.*, Clement, 1984; Fonnum *et al.*, 1985; Maxwell, 1992 a,b), but there are sparse data on the role of carboxylesterase activity mediating age-related toxicity to OP pesticides. Fetal rats possess very little carboxylesterase activity (Lassiter *et al.*, 1998) with increasing activity as the postnatal rat matures, reaching adult values after puberty (50 days-of-age) (Morgan *et al.*, 1994; Moser *et al.*, 1998; Karanth and Pope, 2000).

The temporal pattern of A-esterase activity (and carboxylesterases) correlates reasonably well with studies on OP sensitivity (see summary in Table 2). Several studies have shown an increased sensitivity of newborn rats to OP compounds which are detoxified via the A-esterase and/or carboxylesterase pathways (Gagne and Brodeur, 1972; Benke and Murphy, 1975; Pope *et al.*, 1991; Chambers and Carr, 1993; Padilla *et al.*, 2000; 2002; Karanth and Pope, 2000). For example, Padilla *et al.* (2002) and Karanth and Pope (2000) have correlated age-related sensitivity with the maturational profiles of these esterases. Using an *in vitro* assay, Padilla *et al.* (2000) showed that methamidophos, a pesticide which is not more toxic to the young rat, is not detoxified by A-esterases or carboxylesterases. These observations have been extended in a recent abstract to other OP pesticides using this *in vitro* model which measures the detoxification potential via these esterases in various tissues (*e.g.*, liver, plasma) (Padilla *et al.*, 2002). It was reported that the differential sensitivities of paraoxon (the active metabolite of parathion), malaoxon (the active metabolite of malathion), and diazoxon (the active metabolite of diazinon) were also correlated with the less efficacious detoxification by these esterases in young animals (Table 2). Karanth and Pope (2000) noted that the lower levels of esterases in neonatal and juvenile

rats correlated with the increased *in vivo* sensitivity to ChE inhibition found for chlorpyrifos and parathion.

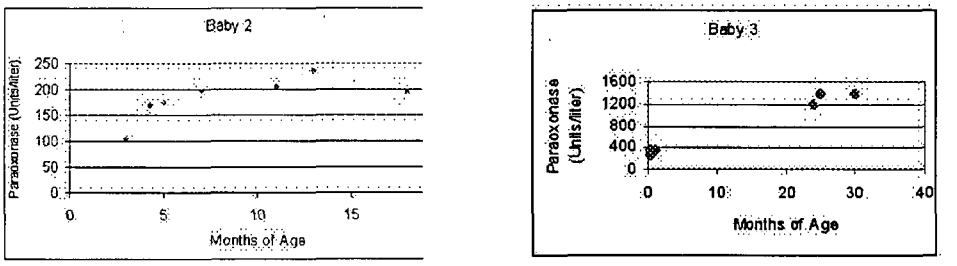
Table I.G-2. Summary of General Results for Age-Related Detoxification and Sensitivity in Rat Studies

Pesticide	Hydrolyzed by A-Esterases?	Bind to Carboxyl-esterases?	Age-Related Detoxification ?	More Sensitive to Young?	Reference
Chlorpyrifos	Yes	Yes	Yes	Yes (acute dose of PND No (repeated dosing of)	Karanth and Pope, 2000;Padilla *et al.*, 2002
Diazinon	Yes	Not Much	Yes	Yes	Padilla *et al.*, 2002
Dimethoate	Not tested	Not tested	Not tested	No	Meyers, 2001
Malathion	No	Hydrolyzed	Yes	Yes	Fulcher, 2001; Padilla *et al.*, 2002
Methamidophos	No	No	Not tested	No	Moser, 1999; Padilla *et al.*, 2000
Methyl Parathion	No	Yes (limited)	Yes	Yes	Pope, 2002a; Chambers and Carr, 1993
Parathion (not included in cumulative assessment)	No	Yes	Yes	Yes	Karanth and Pope, 2000; Padilla *et al.*, 2002

Human Literature: There are only a few studies in the older literature that have assessed A-esterase activity in children. Based on these studies, it appears that serum A-esterase levels are very low in human infants compared to adults (Augustinsson and Barr, 1963; Mueller *et al.*, 1983; Ecobichon and Stephens, 1972). After birth, there is a steady increase of this activity during the first six months to about one year (Augustinsson and Barr, 1963). In a related study of the age-dependence of total serum arylesterase activity (of which a large component is A-esterase activity), adult levels were achieved by two years-of-age (Burlina *et al.*, 1977). Although serum A-esterases are reported to achieve adult levels around six months to one year-of-age, there is uncertainty surrounding those values for the one-year-old due to the variability in the rate of maturation expected as these enzyme systems mature at different rates in a cross-section of one-year-old children. Suggestive evidence of this is the large degree of variability seen in the six-month and one-year age groups in the limited serum esterase data available for children (Augustinsson and Barr, 1983). This source of variability (maturational rate) is unique to children and is in addition to the host of factors that contribute to interindividual variability in the rest of the population and normally considered in noncancer risk assessments. Given the small number of children studied for this parameter, population distributions that reflect the central tendency and lower percentile value for A-esterase function

in one-year-olds relative to adults cannot be discerned from the data (for example see Ecobichon and Stephens, 1972; Figure 1). Moreover, these studies have only examined a few children, and given the high interindividual variability, it is very difficult to discern with confidence the maturation profile for serum A-esterases in young children. In ongoing studies in C. Furlong's laboratory, the same child is being evaluated for the appearance of serum A-esterase over time (*i.e.*, so that the high natural variation does not obscure developmental patterns) to better define the developmental profiles for serum A-esterases (See Figure 1 below). Preliminary results indicate that children reach adult levels of A-esterases around 12 to 15 months-of-age. Note that this age of maturation corresponds reasonably well with the maturation of human serum arylesterases mentioned above (Burlina *et al.*, 1977). It should also be pointed out that there is no information on the maturational profile of A-esterase in the human liver (an organ very important for detoxification), and there appears to be no information about the maturational profile of carboxylesterases in humans.

Figure I.G-1. Maturation Profile of Serum A-Esterase (Paraoxonase) Appearance in Infants and Children (Costa *et al.*, 2002).



Any anticholinesterase pesticide that is a substrate for A-esterase, the lower A-esterase levels in the blood of very young would result in more inhibitor available to reach target neuronal tissues. It should be noted that in addition to age-dependent differences in A-esterase activity, a human and animal genetic polymorphism has been well established (*e.g.*, Mackness *et al.*, 1998). Differences in observed rates of hydrolysis of paraoxon between individuals can vary by at least 20-fold (Furlong *et al.*, 2000). This large difference in A-esterase activity does not necessarily translate into equivalently large differential sensitivities to OP pesticides. There is also some recent evidence in the literature that low A-esterase activity may

predispose adult humans to a greater toxic response (Haley *et al.*, 1999; Cherry *et al.*, 2002) to nerve agents and/or pesticides.

Not only is limited detoxification a factor in increased sensitivity of the young, but another potential factor is the age-dependent ability to activate OP pesticides via oxidation by cytochrome P450s to their oxon form (*i.e.*, the active anticholinesterase metabolite). For example, oxidation by CYP3A4 plays a key role in the oxidation of OP pesticides in humans (Butler and Murray, 1997). Ginsberg *et al.* (2002) using the children's pharmacokinetic data from the therapeutic drug literature showed that compared to adults, oxidation by CYP3A4 tends to be more active in children beginning as early as two to six months-of-age with this difference lasting until at least two years-of-age. While this may increase concern for greater oxidative bioactivation in the young, the CYP-mediated oxidative dearylation pathway, which may also be more active at these ages, is involved in the detoxification of these pesticides. Therefore, it is important to compare the maturation profiles for these two CYP pathways. Based on data from rat liver microsomes (Ma and Chambers, 1994) and as modeled by Timchalk *et al.* (2002) for humans and rats, the activation step is 2.5-fold faster (based upon Vmax/Km ratios) and importantly, the activation step has a 8.4-fold lower Km than the dearylation step. The significance of this is that at relatively low, environmental exposures, OP molecules reaching the liver may be much more likely to be oxidized by the activation pathway than detoxified by the dearylation pathway. This evidence supports the potential concern that greater oxidative capacity in one- to two-year-olds may lead to more OP activation than seen in adults. The enhanced ability of the young to bioactivate OP pesticides to their oxon form, however, has not been correlated with an increased sensitivity to ChE inhibition. Nonetheless, when coupled with the potential limited ability of young children to detoxify these pesticides via the A-esterase and carboxylesterase pathways, this produces a source of uncertainty in the pesticide risk assessment for children.

d. Hazard Characterization Summary

There have been reports of signs and symptoms associated with cholinergic toxicity following high exposures to OP pesticides of adults and of young children. Common signs and symptoms of cholinergic toxicity in humans range from changes in heart rate and blood pressure, miosis, diarrhea, headaches, nausea, muscle weakness to unconsciousness, convulsions, and death. Not only can cholinergic toxicity occur in children following exposure to OP pesticides, but emerging investigations have raised concern about the effects of antiChE activity on neurodevelopment which may be a sensitive process susceptible to adverse perturbations.

As discussed in Section A, there is evidence that ChE and acetylcholine act as important neuromodulators in the developing brain. Because neurogenesis is not limited to the intrauterine period and may continue

throughout childhood, all stages of brain development are considered to be potentially susceptible to disruption by ChE inhibition. During the first few years of life, brain development is a tightly orchestrated process of migration and "pruning," which is under the influence of neuromodulators (ChE, acetylcholine, and other neurotransmitters), genetic controls, and the experiences of the child. Although OP pesticides may influence the migration of cells and the connectivity of the central nervous system (CNS) and result in consequences that could last into adulthood, it is not known how much of a perturbation (*i.e.*, degree of ChE inhibition) is needed, or how long this perturbation must be sustained, to disrupt normal development. The majority of OP pesticides included in the cumulative risk assessment have not been evaluated for neurodevelopmental effects (*e.g.*, functional, behavioral, or neuropathogical effects) or for ChE activity in immature animals.

In light of this uncertainty, it should be assumed that small perturbations resulting from either a single exposure or repeated exposure could potentially disrupt neurodevelopment. Therefore, it is important to insure that the adult brain ChE endpoints used in the cumulative risk assessment for OP pesticides are adequately protective of the young. Thus, a key issue in this assessment is whether ChE inhibition in the young will be caused at lower doses of these pesticides compared to adults or whether the young will show a higher level of ChE inhibition at comparable doses. It is the integration of the chemical-specific information along with the basic biological understanding of sensitivity and susceptibility that informs the need for the application of additional safety or uncertainty factors in the cumulative risk assessment to protect fetuses, infants, and children.

Because in humans, the process of brain development begins during gestation and continues postnatally through adolescence, it is important to identify the developmental windows of age-dependent sensitivity to ChE inhibition. In laboratory animals, ChE inhibition can be found to occur in all developmental stages of the young (*i.e.*, in fetal, neonatal, juvenile, and young adult rat tissues). In general, oral dosing of pregnant rats with OPs causes ChE inhibition in the fetus and/or neonate, but fetuses/neonates that are exposed *in utero* (and via early lactation) generally do not exhibit more ChE inhibition than is found in maternal tissues. These studies need to be interpreted with caution with respect to comparative sensitivity because the absorbed dose to the dam and fetus is typically not known. Also, the fetal rat appears to be less affected from repeated exposures to OP pesticides presumably because of the rapid recovery and resynthesis of the AChE in fetal tissue compared to the dam, making it difficult to compare relative responses in the fetus versus dam. It should be noted that rat fetal tissues and the placenta are deficient in key detoxification systems, including A-esterases and carboxylesterases. Overall, there is limited pharmacokinetic information available in fetal versus maternal tissues for OP pesticides.

Continued treatment following birth is important to ensure that critical periods of sensitivity are evaluated. Direct dosing of the postnatal rat may be necessary, however, because of the possibility of limited exposure through the milk via lactational transfer of OP pesticides. Although direct dosing of the pups (typically via oral gavage) maximizes and allows for quantification of exposure to the pups, it does not necessarily mimic the dietary intake exposure patterns in children. Furthermore, certain stages of brain development in the early postnatal rat are equivalent to the third trimester human fetus, and thus direct dosing of very young postnatal rats would not represent the pharmacokinetics of the chemical in the mother. Nonetheless, direct dosing experiments do provide a better basis to determine the comparative sensitivity of the pups and adult animals. Some direct dosing studies of postnatal rats are available on OP pesticides; however, these few studies have shown that acute postnatal exposures via direct dosing to young rats results in an increased sensitivity to ChE inhibition for certain OP pesticides (*e.g.*, malathion, methyl parathion, chlorpyrifos, diazinon), but not all (*e.g.*, methamidophos, dimethoate and by extension, its metabolite omethoate).

Age-dependent sensitivity to ChE inhibition by OP pesticides can sometimes also be found following repeated dosing studies in laboratory animals. An important issue with repeated dosing is the more rapid recovery (synthesis of new ChE enzyme) in postnatal (and fetal) rat tissues. In most repeated dosing studies comparing the responses of adults to postnatal animals dosed at the same frequency, this faster recovery in the young animals may result in less inhibition as compared to the adults, which is interpreted by some as lower sensitivity of the young. The results of such studies are critically dependent on the time interval between the doses and also the time (in relation to the last dose) at which the ChE inhibition is sampled in both age groups. As acute studies have shown, age-related sensitivity differences in rodents depend on the age at dosing, since the detoxification pathways are rapidly maturing. Therefore, in repeated dose studies, the fact that the animals are probably becoming less sensitive over time by virtue of this changing toxicokinetic pattern is an additional confounding factor. For all these reasons, a smaller differential for ChE inhibition has often been found between the pups and adults following repeated dosing when compared to acute exposure.

Although age-dependent sensitivity is found in some animal experiments, a key question is whether this sensitivity will occur in children. Children may respond to toxicity at lower doses than adults because infants and very young children may be less able than adults to metabolize and excrete toxic substances (Ginsberg *et al.*, 2002). Animal studies have shown a correlation of age-dependent sensitivity to certain OP pesticides with the developmental profiles of the A-esterases and/or carboxylesterases (enzymes that detoxify OP pesticides). As described in Section C, based on limited data, young children may have lower levels of these detoxification pathways. The most

highly exposed age group in the OP cumulative risk assessment was identified as the one- to two-year-olds. Although after birth there is a steady increase of A-esterase activity during the first six months to one year, these maturation profiles may vary among children (due to interindividual variability) and may vary among different tissues. Maturation profiles are not available for the carboxyesterases, and the developmental profile for either A-esterases or carboxylesterase has not been delineated in liver (a major detoxication organ). Furthermore, young children may also have an increased ability to activate OP pesticides to the oxon form as compared to the adult. Therefore, given the uncertainty surrounding the maturation profiles of young children for A-esterases and carboxylesterase, their potential to be more active than adults at bioactivating OP pesticides to their oxon form, as well as their rapidly developing nervous system, infants and very young children (including children in the one- to two-year age group) would potentially be vulnerable to chemical interference due to OP pesticide exposure.

Because some OP pesticides do show age-dependent sensitivity, and there are missing ChE data in young animals for many of the OP pesticides in this cumulative risk assessment, there is a degree of uncertainty regarding the estimation of risk. Under the children's safety factor provision a default safety factor of 10X is required to address this database deficiency unless there are reliable data to support a conclusion that a different safety factor would be safe for infants and children. As the following discussion indicates, OPP has concluded that reliable data do exist to support use of a database uncertainty factor to address this data deficiency. To determine whether a database uncertainty factor could protect infants and children, the degree of difference between the doses needed to cause a certain level of ChE inhibition between the young and adult was evaluated. As shown in Table 1, the differential between adults and immature animals following repeated dosing (typically 11 consecutive days) is at most approximately threefold. A single acute dose is found to cause differences ranging from about twofold up to approximately ninefold.

The relative sensitivities of immature animals found in repeated dosing studies are considered more appropriate than the results of the acute dosing studies for the cumulative risk assessment of OP pesticides for several reasons. Acute dosing studies were done with PND11 pups, which are more like the human newborn with limited detoxification ability. Repeated dosing studies of OP pesticides usually started treatment at PND11 and continued to PND21. As the immature animal ages, it rapidly reaches adult levels of A-esterases around PND21. Thus, evaluation of ChE activity in repeated dosing studies more closely mimics the maturation of A-esterase activity in children around one year-of-age when children are reaching adult levels of A-esterases. Thus, the use of repeated dosing studies better approximates the maturation profile of the age group that is significantly exposed to OP pesticides in the cumulative risk assessment. Children generally do not begin

to consume fresh (uncooked) fruits and vegetables until after six months-of-age or more. The highly exposed group in the cumulative risk assessment is the one- and two-year-olds, not the infants. Repeated dosing studies were also used to determine relative sensitivity because people are exposed every day to an OP pesticide through food, and thus an animal study using repeat exposures is considered appropriate. Also, following exposure to an OP, regeneration of ChEs to preexposure levels does not occur for days or weeks, making the exposed individual potentially more vulnerable to subsequent exposures during that period.

Repeated dosing studies are now available on six of the 22 OPs in the cumulative risk assessment. For three of these OP pesticides, the repeated dosing studies showed no increased sensitivity in the young, whereas increased sensitivity was seen in the other three. The differential sensitivity between adult and immature animals ranged from 1X (*i.e.*, no differential) up to a 3X difference. These studies are considered to provide a reasonable basis on which to establish the size of a database uncertainty factor for the following reasons. Although these six OP pesticides do not represent every structural and pharmacokinetic characteristic of the large class of OP pesticides included in the cumulative risk assessment, they are nonetheless a reasonable subset of different structural and pharmacokinetic characteristics. For example, methamidophos is a phosphoramidothioate of small molecular weight with no ring structure, does not require metabolic activation to generate an oxon form, and is not detoxified by esterases. On the other hand, methyl parathion is a phosphorothioate of larger molecular weight with a ring structure, hepatically bioactivated to its oxon form, and detoxified by esterases. In addition to the observed differential between adult and young animals following repeated dosing, it must also be kept in mind that the differential between the adult and young animal decreases as the animal ages and reaches adult levels of the detoxification enzymes. For these reasons, there are sufficient data to conclude that a 3X database uncertainty factor should be applied, and that the 3X UF_{Db} should be sufficient to account for potential age-dependent sensitivity to ChE inhibition. It should be noted that the application of a 3X UF_{Db} is in addition to the application of the customary intra- and interspecies uncertainty factors, which takes into account variability among the human population.

The question remains as to how such a database uncertainty factor should be incorporated into the cumulative risk assessment. In the cumulative risk assessment process, uncertainty or safety factors can be either applied to estimates of individual member's toxic potencies (*i.e.*, relative potency factors or RPFs) or applied as a group factor on the index chemical's point of departure.[3] Because age-dependent sensitivity to ChE

[3]In the cumulative risk assessment, the RPF approach is used to determine the joint risk of the OP pesticides, which applies dose addition. The RPF approach uses an index chemical as the point of reference for standardizing the common toxicity of the chemical members of the (CAG). Relative

inhibition is not common to all OP pesticides, application of a database uncertainty factor would be more appropriately applied as chemical-specific adjustments to the RPFs to account for ChE inhibition potentially occurring at lower doses in the young than in the adult or resulting in a more potent response at the same dose compared to the adult. These chemical-specific adjustments should be made on the RPFs for those OP pesticides that lack ChE data in the young. There are ChE data for a few OP pesticides that show age-dependent sensitivity. However, RPFs are based on a uniform measure of toxic potency using the same species, sex, endpoint, and age group from studies of comparable methodology. Given that there are too few data in young animals to determine RPFs for the OP Cumulative Assessment Group (CAG), the RPFs for those chemicals showing age-dependent sensitivity should also be adjusted to account for sensitive effects in the young. The RPFs of those OP pesticides that do not cause age-dependent sensitivity after brief periods of repeated exposure (dimethoate and by extension omethoate, methamidophos, chlorpyrifos) should not be adjusted.

In conclusion, the limited animal data on the relative sensitivity of young animals to cholinesterase inhibition (ChEI) caused by OP pesticides has raised uncertainty about the adequacy of the adult RPFs to be protective of the young and should be addressed by application of the traditional database uncertainty factor (UF_{Db}). Application of this UF_{Db} should be protective of potential age-dependent sensitivity to ChE inhibition and of potential adverse neurodevelopmental outcomes that are a result of the inhibition of ChE. Thus, there are reliable data to assign an additional factor (a database uncertainty factor of 3X) other than the default 10X additional safety factory. Further, because the database uncertainty factor addresses potential age-dependent sensitivity there is no a need to retain an additional special FQPA safety factor for potential pre- or postnatal toxicities associated with inhibition of ChE.

3. Cumulative Exposure Assessment

Another important consideration for the FQPA safety factor is the completeness of the exposure database. Whenever appropriate data are available, OPP estimates exposure using reliable empirical data on specific pesticides. In other cases, exposure estimates may be based on models and assumptions (which in themselves are based on other reliable empirical data). This section explains how the safety of the exposure estimates to infants and children were estimated.

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potency factors (*i.e.*, the ratio of the toxic potency of a given chemical to that of the index chemical) are then used to convert exposures of all chemicals in the CAG into exposure equivalents of the index chemical.

EPA identified and included three exposure pathways for the OP Pesticide cumulative risk assessment: food, drinking water, and residential/nonoccupational. Each of these pathways was evaluated separately, and, in doing this step of the analysis, EPA determined which of the OP pesticides were appropriately included for a particular pathway. The cumulative assessment of potential exposure to OP pesticides in food includes: 22 OP pesticides that are currently registered in the U.S. or have import tolerances; residential or nonoccupational pesticide uses included 11 OP pesticides (Note: many residential uses have been canceled as a result of risk mitigation efforts or are not expected to result in any significant exposure); and 24 OP pesticides (as well as several toxic transformation products) were considered in the cumulative water exposure assessment. Calendex™ software was used to determine the distribution of exposures and resulting Margins-of-Exposure (MOEs) from OPs in foods, drinking water and from residential uses.

Up until this time, OPP has performed its risk assessments using several different age groups for children including nursing infants less than one year, non-nursing infants less than one year, children one to six years-old, children seven to 12 years-old, and children 13 to 19 years-old. Because of the availability of more extensive data on children's food consumption, EPA was able to subdivide the children's age group one through six years-of-age into two different age groups: children one through two years-old and children aged three through five years-old. EPA also made some other slight adjustments to the age breaks defining groups for older children. As explained below, EPA analyzed all of the different children's age groups, but did not analyze every age group for every scenario. The children's age groups that were analyzed for all of the exposure scenarios in the revised OP cumulative risk assessment were one through two years-of-age and three through five years-of-age. EPA selected these two age groups because in single chemical risk assessments (including for the individual OPs) they most frequently reflect the highest levels of exposure. Thus, a narrow range of ages were used to capture the finer details associated with major contributors to risk under the premise that they reflect the exposure scenarios most likely to be emphasized in risk management activities.

In addition, EPA produced exposure estimates for all of the other children's age groups (children less than one year, children six through 10 years and children 11 through 19 years) for the Florida region. Florida was selected because it appears to have the highest level of exposure from all sources of pesticides combined. As expected, the exposures estimated for children less than one year-old or six and older were consistently lower than the exposures estimated for one- to two- and three- to five-year-old children. Based on this analysis, EPA concludes that, by focusing on two age groups of children (one- to two-year-olds and three- to five-year-olds), its risk assessment does not underestimate potential exposure to any age group of children.

a. Food Pathway

Exposure to foodborne pesticides is an important factor in evaluating the susceptibility of the young. Young children tend to eat more food in proportion to their body size and they tend to eat more frequently than adults. As discussed below, these characteristics are incorporated in the assessment of exposure to OP pesticides via food.

The food component of the cumulative risk assessment has been highly refined to reduce OPP's Tier 1 default assumptions (all foods contain residues at the maximum amount allowed under tolerance) to more realistic estimates of actual human exposure. It is based on residue monitoring data from U.S. Department of Agriculture (USDA) Pesticide Data Program (PDP), supplemented with information from the U.S. Food and Drug Administration (FDA) Surveillance Monitoring Programs and Total Diet Study. The PDP data provide a very reliable estimate of pesticide residues in the major children's foods. They also provide direct measures of co-occurrence of OP pesticide residues in the same sample, alleviating much of the uncertainty about co-occurrence in foods that are monitored in the program.

Another important aspect of the food exposure assessment is that it is based on actual consumption data from the USDA's Continuing Survey of Food Intakes by Individuals (CSFII). The CSFII provides a detailed representation of the food consumption patterns of the U.S. public across all age groups, during all times of the year, and across the 48 contiguous states. Additionally, OPP used a more recent CSFII in the OP cumulative assessment (the 1994-96 CSFII) that was supplemented in 1998 by the Supplemental Children's Survey. This 1998 survey focused on children from birth to nine years-old and greatly expanded (by several fold) the number of birth to four-year-old children in the survey database. OPP believes that the food consumption information used provides a very realistic estimate of potential risk concerns because it reflects the current eating habits of the U.S. public, including those of children. The use of the newer CSFII and the finer age breakouts should increase the accuracy and utility of the risk assessment overall by making it more descriptive of the anticipated exposures and risks for children.

A large percentage of the foods consumed in children's diet is addressed in this assessment. Only about 3% of the foods consumed by children still remained unaccounted for after using PDP and the FDA Total Diet Study and FDA monitoring data.

OPP is aware that some or all baby food manufacturers have adopted policies that restrict the use of OPs on fruits and vegetables that will be used in their products. As a result, children consuming commercially prepared baby food may not be exposed to OPs in their diet. OPP has investigated the impact of this assumption for children one through two years-of-age, and for

children less than one year-old. The residues in commercially prepared baby foods were assumed in the first case to be equivalent to those found in an adult diet. They were also set to zero to bound the lower limit and determine the extent of the impact on any risk assessment. Setting all residues in commercial baby food to zero had little impact on the magnitude of risk estimated for children one through two years-of-age. This observation is consistent with the very small amounts of baby food consumed by this age group. However, a substantial impact was observed for the age group of children less than one year-of-age because of the relatively large proportion of baby food in their diets. OPP believes that estimating exposure to pesticides from baby food as containing residues comparable to those in adult diets will not impact regulatory decision-making because the overall exposure to children less than one year-of-age is less than exposure to children one through two years-of-age.

Two exposure issues unique to children are not directly addressed in the current assessment. OP exposure from breast milk is not incorporated quantitatively. A review of the literature to identify any potential pesticide transfer from breast milk to children indicated no evidence that this pathway would represent a significant source of exposure (ILSI, 1998). However, further analysis has identified a study that demonstrated the presence of chlorpyrifos and chlorpyrifos-oxon in the milk of rats (Mattsson *et al.*, 1998, 2000). The results of studies generated by the regulated community in support of pesticide registration indicate no significant transfer of OPs to milk. OP pesticides are not found to transfer into cow's milk when cattle are fed a diet containing OPs. This finding is uniform across the entire class of OP pesticides. As a result, OPP believes that breast milk is not likely to be an important contributor of OPs to the diets of infants and children, especially at environmentally relevant levels of exposure. Baby formula is included in the current assessment with its consumption reflected in the FCID (Food Commodity Intake Database) translation of CSFII food consumption survey, and residue data available for all of its components.

OPP's dietary assessment also captures the metabolites of OPs that are known to occur at significant levels in food commodities (*e.g.*, omethoate–metabolite of dimethoate; methamidophos–metabolite of acephate; and, dichlorvos–metabolite of naled and trichlorfon). Although there is not extensive analytical data on other OP metabolites, there is adequate data (*e.g.*, from metabolism studies, FDA monitoring data) to indicate that the food assessment is not missing significant residues in food (such as for malaoxon– metabolite of malathion).

In summary, given the comprehensive data on potential exposure to OP pesticide residues through the food, OPP is confident that exposure to all age groups, including children via the food dietary pathway has been well characterized.

b. Drinking Water Pathway

Daily drinking water exposure estimates were generated using the simulation models PRZM and EXAMS (a description of the use of these models can be found http://www.epa.gov/oppefed1/models/water/index.htm). The use of these models allows estimation of concentrations of OP pesticides. OPP used these models to provide daily distributions of OP pesticide levels in water for incorporation into the probabilistic cumulative exposure assessment. Twelve regional water exposure assessments were conducted that were designed to represent exposures from typical OP usage conditions at one of the more vulnerable surface watersheds in the region. Each regional assessment focused on areas where combined OP pesticide exposure is likely to be among the highest within the region as a result of total OP usage and vulnerability of the drinking water sources. These methods have provided OP pesticide distributions that are, in many cases, reasonably comparable with available monitoring data in the same or nearby locations. There are too little data to quantify OP degradates that may result in drinking water. These metabolites, however, have been qualitatively assessed in the revised cumulative risk assessment by assuming complete oxon conversion with a 10-fold increase in toxicity compared to the parent compound: it was found that this assumption did not have an impact on the upper percentile distributions. In summary, OPP believes that the current cumulative assessment represents a reasonable, health protective estimate of likely exposure to OP pesticides from water to all age groups, including children.

c. Residential or Nonoccupational Exposure Pathway

The residential/nonoccupational exposure analysis includes the exposure from home lawn and garden treatments, pesticides used on golf courses, and applications made by governmental entities for the control of public health pests such as wide area mosquito sprays. The oral, dermal, and inhalation routes are considered. This analysis has incorporated activity patterns of children and the major sources of exposure to young children (*e.g.*, nondietary ingestion and hand-to-mouth behavior as established by video tapes of children). Furthermore, pet uses have been incorporated in the revised assessment. For the first time, the residential analysis used distributions of data and exposure elements instead of point values. In most cases, these data and exposure elements were chemical-specific. The analysis reflects all remaining residential uses of OP pesticides, consideration of both homeowner and professional applications, and postapplication exposures resulting from these applications. The analysis also employed the most recent survey data of residential uses and use information. Exposure due to activity in and around schools and parks is not addressed directly, because there does not appear to be any remaining OP pesticide uses for school structures and grounds. Nonetheless, the possibility of exposures encountered away from the home has been indirectly built into the

assessment by conservatively extending the duration of residential exposure beyond the two hours spent on grass to 3.5 hours spent outdoors.

The calendar-based model (Calendex™) that was used in the preliminary OP cumulative risk assessment allowed for the temporal aspects of the residential use of pesticides in twelve distinct geographic regions to be accounted for; these regions not only represent major crop growing areas and their influence on residues of OP pesticides in surface and ground water, but also present an opportunity to consider the unique climate patterns, pest patterns and potential socioeconomic patterns that influence residential pesticide use and expected exposure to OP insecticides. Furthermore, Calendex™ allows one to delineate the critical timing aspects of seasonal uses of OP insecticides that result in exposure, as well as to identify potential co-occurrences from multiple sources. Again, it cannot be emphasized too strongly that the exposure, monitoring, and residue studies that were used as input parameters in the modeling of residential/nonoccupational exposures represent the best available data on these pesticides (*i.e.*, the input parameters for residue levels and dissipation rates based on actual measurements).

d. Biological Monitoring Studies of Children

Biomarkers can serve as a useful measure of direct exposure aggregated over all sources and pathways by measuring integrated exposure from all routes. Biomarkers can be used to characterize the relative magnitude of exposure within population subgroups. In addition, biomonitoring can be used to verify predictions of exposure models.

Urinary biomarkers of OP pesticides and their metabolites have been used to characterize reference body burden levels for adult and children populations in the U.S. and Europe (Murphy *et al.*, 1983; Kutz *et al.*, 1992; Hill *et al.*,1995; Aprea *et al.*, 1996, 1999, 2000; Macintosh *et al.*, 1999; Fenske *et al.*, 2000; Quackenboss *et al.*, 2000; Adgate *et al.*, 2001; Heudorf and Angerer 2001; Krieger *et al.*, 2001). Most of this research has been designed to determine if children have higher exposures to OP pesticides than adults, and, if so, what are the differences in these exposures and what are the factors that influence these higher exposures.

Several researchers have conducted monitoring studies that have collected environmental and/or biological samples to assess the potential aggregate (inhalation, dermal, ingestion (dietary and indirect)) exposure to OPs by adults in their everyday environments. Hill *et al.* (1995) analyzed single spot urine samples from approximately 1000 adults (20-59 years-of-age) living in the U.S. to establish reference range concentrations for OP pesticide residues. Chlorpyrifos exposure was indicated by TCPY concentrations of 13 µg/L (95^{th} percentile value) and 77 µg/L (maximum value observed). Macintosh *et al.* (1999) reported on the relationship between

short-term and long-term average levels of OP biomarkers for 80 adults living in Maryland. First-morning void urine samples were collected at up to six different time periods equally spaced over a one-year period, with the range of urinary OP metabolite values being similar to the levels reported by Hill *et al.* (1995).

Only a handful of studies have been published in the literature that were specifically focused on biomonitoring of children for OP pesticides and their metabolites. These researchers noted that young children may be more highly exposed and are more susceptible to health risks from exposures to OP pesticides than adults because they are undergoing rapid physiological and behavioral development. Furthermore, in comparison to adults, young children: have a larger surface area to volume ratio; have a relatively large brain size as compared to total body mass; take in more air, food, and water on a per unit body weight; and, absorb, distribute, metabolize, and eliminate pesticides differently than adults (Guzelian *et al.,* 1992). Children also engage in specific activities in which they may more likely come into direct contact with contaminated surfaces and objects (Hubal *et al.,* 2000). These child-type activities include: sitting, playing on the floor; eating while roaming around the house; putting hands, objects, toys into the mouth; licking the furniture, pet, floor; etc.

The Minnesota Children's Pesticide Exposure Study (MNCPES) was the first published study to report multipathway pesticide exposures in a population-based sample children (Quackenboss *et al.,* 2000; Lioy *et al.,* 2000; Adgate *et al.,* 2001). Personal (hand rinse, duplicate diet, time activity diaries and questionnaires, videotape segment), biological (urine), and environmental (indoor/outdoor air, residential surfaces, soil, drinking water) samples were collected to assess children's aggregate pesticide exposure and attempt to identify the critical pathways of exposure. Three first-morning void urine samples were collected on three separate days during the study. The urine samples were then analyzed for metabolites of commonly used OP pesticides (Adgate *et al.*, 2001). Analysis of these urine samples for OP pesticides and their metabolites have shown that children do have a body burden level of OP metabolites (Quackenboss *et al.*, 2000; Lioy *et al.*, 2000; Adgate *et al.*, 2001). While the MNCPES study didn't assess adult exposures, Adgate *et al.* (2001) compared these urinary biomarker levels of OPs for children with the reference levels reported by Hill *et al.* (1995) and found similar ranges for both children and adults.

Fenske *et al.* (2000) collected and analyzed single void urine samples for OP metabolites from 109 children (up to six years-of-age) who lived in an agricultural community in the State of Washington. The children's urine samples were collected at the convenience of the child and parent. From the children's OP pesticide doses derived from this biologic monitoring study, the authors suggested that residents of agricultural communities may be more exposed to pesticides than the general population.

Two studies have compared urinary metabolite levels for all members of a household (Heudorf and Angerer 2001; Krieger *et al.*, 2001). Heudorf and Angerer (2001) examined urinary metabolite concentrations for children and adults living in dwellings that had not been recently treated with OPs (most recent treatment was four years prior). These investigators suggested that urinary OP metabolite concentrations in children and adults were not different. Krieger *et al.* (2001) assessed the extent of exposures for family members (adults and children) residing in homes where pesticides have been used. Chlorpyrifos was applied in this study by three different methods: fogger, broadcast, and crack and crevice. Analysis of the family urine samples for OP metabolites showed no significant difference between children and adult exposures for those family members living in the same households. However, both studies only examined the sample results without considering the factors associated with the physiological and behavioral differences between adults and children, a step needed to better describe and understand the real potential for exposure.

Interpreting the results of these published studies presents several challenges. First, only a few studies have been conducted and the results published in the literature. Secondly, the methodologies employed in each study have varied. Only spot urine samples have been collected, and, more importantly, the sample collection times for these spot urine samples have differed for many of the studies, ranging from first-morning voids to convenience samples collected during the morning hours. In the few studies that have collected both the environmental and biological samples, the levels of the OP pesticides and urinary metabolites have not correlated with any of the OP concentrations in the other environmental samples analyzed (Lioy *et al.*, 2000). Some investigators have tried to compare the children's and adult's OP pesticide and metabolite levels without correcting these data for the differences found in children associated with their differences in metabolic rates, muscle mass, creatinine production, and urinary output.

Although the available biological monitoring studies generally indicate children do have a body burden level of OP pesticides, based on the limited number of published studies and the inconsistencies noted above, it is difficult to make any general statements concerning the study population, much less the general population. Equally important, from these limited sets of published data, it is difficult to assess whether children's exposures to OP pesticides are the same, higher, or lower than corresponding adult exposures.

Several relatively large-scale children's aggregate pesticide exposure studies which include OP pesticides are ongoing or near completion by the U.S. EPA National Exposure Research Laboratory (NERL) scientists and academicians. However, the analyzed and published results of this research will not be available for several years. Without these additional data, questions regarding whether children's exposures to pesticides are higher

than adults or the validity of the cumulative exposure estimates can not be readily answered.

e. Exposure Characterization Summary

The cumulative exposure assessment of OP pesticides represents the first probabilistic assessment of multichemical and multipathway exposures to pesticides. Estimates of residues in food are based on actual monitoring and consumption data that capture the major food groups consumed by children. Several age groups are defined such that they reflect an adequate number of individuals in each age group and are based on real differences in age-related eating patterns. Estimates from food dietary intake are considered to confidently approximate dietary food exposure of children to OP pesticides. There is also confidence that the dietary drinking water exposure assessment for OP pesticides does not understate potential exposure to children (or any age group) given that regional water exposure assessments were conducted that were designed to focus on areas where combined OP exposure is likely to be among the highest within the region as a result of total OP usage and vulnerability of the drinking water sources. Furthermore, the cross check of PRZM and EXAMS predicted estimates with actual drinking water monitoring data gives confidence in the drinking exposure assessment. Finally, the residential and nonoccupational exposure estimates are also considered to provide protective estimates of children's exposures given the quality of the data and the conservative assumptions used. In summary, there is a high degree of confidence in the exposure data and methodologies used when assessing cumulative risk to children, that are considered to be protective of children without understating risk. Thus, for the exposure assessment, reliable data show that it is not necessary to retain the default 10X special FQPA safety factor.

4. Integrative Analysis of Hazard and Exposure

A weight-of-evidence analysis has been conducted to determine the completeness of the toxicity and exposure databases, and the degree of concern for pre- and postnatal toxicity associated with the common mechanism of toxicity, AChE inhibition. It was determined in the hazard assessment that there are reliable data to support application of a 3X database uncertainty factor (which is used to address the FQPA safety factor provision's expressed concern as to the "completeness of the data with respect to... toxicity to infants and children....") to address the limited data on ChE inhibition in immature animals and evidence that supports the potential for OP pesticides to show ChE inhibitory effects at lower doses in young animal compared to adults (*i.e.*, the age group on which the relative potencies values are based). There is no need for an additional special FQPA safety factor to address potential pre- and postnatal toxicity associated with ChE inhibition because application of the database uncertainty factor to the RPFs for the OP accounts for age-dependent sensitivity in the young and potential neurodevelopmental effects associated with ChE inhibition.

The revised cumulative risk assessment for OP pesticides is based upon the most comprehensive and data-specific exposure assessment ever performed by OPP. This statement is true for all aspects of the exposure estimates including pesticide sources from food, drinking water and residential uses. Each aspect of the assessment relied upon the use of the best available data for input parameters. The data were introduced into the assessment in large part in the form of distributions, permitting the assessment to reflect the full range of variability in each input parameter. This approach deviates from the past practice used particularly for drinking water and residential exposure estimates that relied upon high endpoint estimates. In this assessment, drinking water and residential estimates have been refined in much the same manner previously established for food assessments. The comprehensiveness and thoroughness of this exposure assessment allows OPP to conclude that an additional safety factor is not needed to address the completeness of the exposure database.

While the available data and methodologies used by OPP to estimate exposures cannot be used to precisely define an exact exposure for any given percentile of the population, OPP can bracket or otherwise define the range within which exposures are expected to fall. Specifically, OPP believes that the traditional single-day analysis in which individual days are assessed in isolation reflects a likely upper-bound of exposures. OPP also believes that the actual upper-bound of exposure is lower than the high-end estimated by the rolling average exposure (discussed in the Risk Characterization Section of the OP cumulative risk assessment). Additionally, the cumulative assessment was conducted in a way that does not intrinsically bias the analysis toward over estimation or under estimation of exposures, but instead reflects exposures anticipated to be experienced by the public. Accordingly, OPP believes that the analysis captures the highly exposed groups (including children) and represents exposures reasonably likely to occur and that the above-mentioned "bracketing" represents realistic expected upper and lower bounds on the estimated exposure. Final determinations regarding which predicted exposures will be considered in making a regulatory decision will depend on sensitivity analyses of predicted high-end exposures. These determinations could also play a role in a final conclusion about whether OPP remains confident that the analysis adequately captures the upper-bound of estimated exposures and, therefore, whether there is continuing support for the conclusion that an additional FQPA safety factor is not needed to address the completeness of the exposure database.

In summary, given the highly refined nature of estimates for all pathways of exposure, the use of bounding estimates to reflect the potential issues associated with timing and repeated exposures, and the application of the database uncertainty factor of 3X, the presumptive 10X safety factor can be removed.

I. Revised OP Cumulative Risk Assessment

H. Risk Characterization

1. Introduction

Risk characterization is the interpretation phase of the assessment process. Appropriate interpretation of results is particularly important for an assessment as complex as the OP cumulative risk assessment. Many types of data, derived from a variety of sources, have been combined to produce highly detailed estimates of risk from multiple OPs in food, drinking water or from residential use. The outputs of the assessment should be evaluated in a variety of ways. Potential biases in input parameters, the direction of the bias, and the uncertainty surrounding the inputs and the exposure model must be considered with regard to their potential impact on the results of the assessment.

OPP has attempted to reflect the completed risk mitigation measures from the single-chemical assessments. OPP will continue to make risk decisions about individual pesticides over the next months. Changes resulting from risk mitigation measures completed through March 2002 have been included in this assessment. Modifications in OP use patterns made after that date can be incorporated after they occur. The current document presents the estimates of risk associated with exposures to OPs in food, drinking water and from residential uses of OPs. The current assessment has used two modes of analysis (single-day and 7-day)to provide bounding estimates of potential exposures, and also reflects the risk estimates at a variety of percentiles of exposure. In addition, analyses were performed for periods of 14 days and 21 days to demonstrate that extending the averaging time for the risk assessment has little impact on the results obtained. The detailed results of this assessment are presented as a plot of MOEs over a period of 365 days. Contributions from various pathways and routes of exposure are arrayed separately. The results are presented graphically for the seven Regions, for the 1-2 year old and 3-5 year old age groups (Appendix III.J.2 to III.P.2). Data output tables for the 20 to 49 year old and 50+ groups are presented as spreadsheets (Appendix III.J.3) The results presented are based on a one day and seven day rolling average. For Region A the assessment also presents the 14 and 21 day rolling average results for the 1-2 and 3-5 year old groups. **No single value in the assessment should be used to independently arrive at the interpretation of the results.** As discussed below, interpretation of the assessment depends upon the synthesis of a vast body of information about the input data and the processing of that data to determine whether an acceptable risk has been achieved. A number of crop/chemical combinations in the food assessment and one chemical/use combination in the residential risk assessment warrant additional scrutiny in determining any future activities arising from this assessment.

2. Hazard and Dose-Response Assessment

The hazard and dose-response assessment is presented in detail in section I.B. That section outlines the steps in developing the dose-response relationships for each pesticide and its capacity to inhibit acetylcholinesterase in the brain of female rats. It includes a description of all of the data used in the dose-response analyses. Reasons for the selection of methamidophos as the index chemical for the OP cumulative risk assessment are also discussed. Finally, section I.B. describes the exponential dose-response model used to develop the dose response curves that provided the basis for developing the relative potency factors (RPF) for each chemical and the points of departure (POD) for the index chemical for each route of exposure (i.e., oral, dermal, and inhalation).

a. Acetylcholinesterase Inhibition: Data Quality & Common Effect

The first step in deciding that a cumulative risk assessment was needed was the determination that the OPs were toxic by a common mechanism, i.e., cholinesterase inhibition. This determination was made and subjected to peer review by the Scientific Advisory Panel in 1998 (http://www.epa.gov/scipoly/sap/1998/march/comec.htm). Once a common mechanism was identified, the next step in the process was to select an appropriate method for combining the risks from exposures to several pesticides from more than one source/route. A large body of data describing the inhibition of acetylcholinesterase in plasma, red blood cells and brain has been generated for each registered OP. OPP has elected to use the brain acetylcholinesterase data from female rats as the basis for developing RPFs and PODs for use in the assessment. The choice addressed a number of the concerns raised by the SAP and the public. Brain acetylcholinesterase inhibition is the endpoint used because it reflects a response in a target tissue of concern that is relevant to humans. Although RBC and plasma cholinesterase inhibition do reflect exposure to OPs and, therefore, the potential for adverse effects, brain acetylcholinesterase inhibition is an indication of direct effects upon the brain itself. Error due to the extrapolation between the response in a surrogate tissue (i.e., red blood cell and plasma) and a target tissue itself (brain) is eliminated. In addition, the data for the brain compartment have very narrow confidence limits when compared to those from the plasma and RBC compartments, suggesting that there is much less variability in this compartment across the data base.

This assessment uses the Relative Potency Factor (RPF) approach which applies dose addition. Briefly, the RPF approach uses an index chemical as the point of reference for standardizing the common toxicity of the chemical members of the cumulative assessment group (CAG). Relative potency factors (i.e., the ratio of the toxic potency of a given chemical to that of the index chemical) are then used to convert exposures of all chemicals in the CAG into exposure equivalents of the index chemical. The RPF approach

utilizes dose-response information to provide an estimate of each OP's potency for the common toxicity, and thus allows for the quantification of exposure as it relates to the joint risk of the CAG. OPP selected the relative potency factor approach based upon the relatively rich oral toxicity data base on cholinesterase inhibition available for the OPs which permitted consideration of the entire dose-response curve for each pesticide rather than only focusing on NOAELs that are a function of study design. Although a biological or pharmacokinetic modeling approach would have advantages in determining the cumulative risk for these OPs, the input parameters for such an approach are not available. Thus, the pharmacokinetic (PK) characteristics of the OPs could not be incorporated in the dose-response assessment which would allow for a more refined estimate of the combined risk to humans. Therefore, OPP has applied simple dose addition and used an empirical curve fitting model (i.e., the exponential model described below) to determine RPFs and PODs.

b. Exponential Dose-Response Model

OPP, in collaboration with ORD, developed an exponential model to describe the oral dose response curves for each OP that permitted fitting of a combination of cholinesterase (ChE) activity data from different studies. This model has been subjected to public comment and peer review by the SAP (http://www.epa.gov/scipoly/sap/2001/september/finalreport.htm). Although a PK model is the ideal approach, the SAP regarded the exponential model (with their recommended improvements) to be appropriate for the data being analyzed for derivation of relative potency factors and points of departure. OPP has responded to the SAP recommendations on the exponential model by making modifications to address the issues raised. One issue was that the original model did not appropriately reflect cholinesterase inhibition at very low doses. The revised statistical model now incorporates, to the extent supported by the data, a flat region at the low dose portion of the dose response curve. Another issue raised by the SAP concerned the derivation of the factor "B". The B value is the limiting value for the maximum cholinesterase inhibition (called the horizontal asymptote). The SAP raised the issue that the weighting strategy used for calculating the "B" which assumed 100% cholinesterase inhibition (i.e., 0% ChE activity) did not adequately reflect the actual B value for each OP (the B value was often less than 100% inhibition at the asymptote). The revised approach has been modified in order to generate B values for each OP reflective of its dose-response data.

OPP assumed dose additivity by application of a single model to all of the OP's dose-response curves. There is some uncertainty surrounding the assumption of dose additivity given that the B values (horizontal asymptotes) are heterogeneous among the OPs analyzed. This heterogeneity is indicative that the dose-response curves are not parallel and, therefore the application of simple dose addition is only an approximation of joint risk and may not be

precise. Dose additivity assumes that the common mechanism chemicals behave in a similar fashion (i.e., same pharmacokinetics and pharmacodynamics) and that their dose response curves will be parallel (i.e., the ratio of their relative toxic potencies remain the same throughout their dose range). The underlying biological processes that determine the toxic potency of each OP are extremely complex and involve several metabolic systems in different organs as well as re-synthesis rates of the different cholinesterases. The activation and/or deactivation rates differ for some of these OPs. However, because of insufficient data, these pesticides can not be separated into subgroups based on pharmacokinetic and pharmacodynamic characteristics. Thus, current information on OP pharmacokinetics and pharmacodynamics cannot provide a sufficient basis to depart from the assumption of dose additivity. Also, available studies on OP mixture interactions do not provide a sufficient basis for departure from dose additivity.

In summary, OPP believes that the model fitting procedure used in this assessment provides reliable estimates of relative potency and points of departure. The cholinesterase data used for the oral route of exposure was quite extensive and, in general, of good quality for dose-response modeling. The data for the inhalation and dermal routes tended to be less extensive and not as robust for dose response modeling. OPP has refined the dose response modeling for the oral dose by incorporating the SAP recommendations in its dose response assessment of these OPs. OPP has attempted to address uncertainty in extrapolating to lower human exposures by the revised model and by using a low model estimate (BMD10) to develop OP relative potency factors. OPP acknowledges that there is uncertainty that dose addition applies to all of these OPs at human exposure levels. In the absence of data to the contrary, however, dose additivity is assumed. OPP realizes that the assumptions of additivity and the dose response modeling used in this assessment may slightly overestimate response due to the assumption that response will be uniform regardless of the underlying background exposure level.

A BMD10 was selected as the basis for comparison of the dose-response curves for the OPs. OPP's goals in selecting a point of comparison were to choose a point in the observed response range, but low enough on the curve to reduce the impact of any lack of proportionality between response that might result from deviation from the assumption of proportionate dose response between OPs. In addition, OPP was concerned that the magnitude of the response (cholinesterase inhibition) be sufficient to ensure that it was reliably distinguishable from background. A power analysis of the data used in deriving the 21-day steady state determination indicated that there was insufficient power to distinguish the change in cholinesterase inhibition reliably below 10% inhibition. In addition, OPP has used the central estimate of the BMD10 instead of the BMDL generally used for single chemical assessment. This decision reflects the complexity brought to the analysis by the joint

consideration of multiple studies for multiple chemicals. The use of the BMDL has been suggested for those instances in which single studies are modeled to provide an indication of a reasonable lower limit on response. In the OP cumulative risk assessment, the results of several studies were combined, introducing the potential for inappropriately broadening the confidence limits about the BMD10 and making the BMDL a likely underestimate of the POD for each chemical. These considerations strengthened the case for selection of methamidaphos as the index chemical because the BMD10 and the BMDL were very similar suggesting a very good fit of the data to the model.

c. Selecting the Index Chemical

OPP selected methamidophos as the index chemical for the current assessment. Methamidophos has sufficient data for cholinesterase inhibition to support modeling of a BMD10 by all three routes of exposure. The high quality dose response data for methamidophos permits reliable estimates of PODs for all routes without resorting to the use of the less precise NOAELs. Certainty in the PODs was considered to be of great importance in as much as they will impact the outcome of the assessment to a greater extent than any other aspect of the toxicity data base.

d. Use of Steady State

During the data evaluation phase, OPP elected to use only those data points that resulted from exposure of rats for 21 days or longer. This choice was made for a number of reasons. First, because of the many agricultural uses of OPs and the resulting residues that occur in food and water, and also the application of OPs in homes across the US (as reflected in the assessment), the likelihood of encountering an exposure to OPs with no prior recent exposure was considered to be small. Therefore, the use of single-day toxicity data was considered inappropriate. Further, following exposure to an OP, regeneration of cholinesterases to pre-exposure levels occurs in the time scale of days to weeks, not a single day, making the exposed individual potentially more vulnerable to subsequent exposures during that period. Examination of the rat data suggested that for most pesticides, cholinesterase inhibition reached steady state approximately by 21 to 30 days after the start of dosing. After that point, little change occurred in the degree of inhibition resulting from continued administration of the dose for a longer period. OPP selected 21 days as a reasonable time point to assume that steady state had been achieved. For the purposes of this discussion, steady state is defined as the point at which further inhibition of the enzyme is offset by regeneration of the enzyme and equilibrium has been achieved. All of the pesticides considered have very stable, reproducible levels of cholinesterase inhibition in all compartments measured.

The selection of the data set to support the steady state decision hinged upon two determinations about the data available. The first was the

evaluation of rate of change in cholinesterase inhibition as discussed above. The second was the decision that a 10% inhibition of brain cholinesterase was a tolerable level of inhibition that was unlikely to result in an unacceptable adverse outcome for the exposed individual. This decision is the more critical in determining the application of the hazard data to the running time frame approach than the actual selection of the time point of determining the extent of inhibition. The application of a steady state approach is predicated on the assumption that the extent of cholinesterase inhibition on any given day reflects the balance between prior exposures and the extent of recovery experienced. The processes of inhibition and recovery are balanced in the rat data as they are in exposed human populations. The major distinction between the steady state data from the rat studies and the likely inhibition in the exposed population is that the actual dose to the rat on any day and on preceding days is known. In the human population, the prior exposures can not be known with certainty. However, as demonstrated by the current exposure assessment, the prior exposures may be either higher or lower than for the current day. OPP believes that the use of steady state data is consistent with the results of biomonitoring data available in the literature. There is a body of evidence that indicates a sizeable proportion of the US population has a fairly constant background exposure to OPs. This is evident from the results of the NHANES III in which 82% of people who provided urine samples for analysis were found to be positive for trichloropyridinol, a metabolite of the OPs chlorpyrifos and chlorpyrifos-methyl (Hill et al., 1995). Further examination of the NHANES III data indicate that a sizeable proportion of the population have metabolites in their urine that are not compound specific, but are associated with other OPs. Preliminary analyses of data collected under the auspices of NHEXAS also indicate that metabolites from a variety of OPs are found in urine from populations of adults and children sampled around the US.

The use of 21-day steady state data in rats may over- or understate the potential for cholinesterase inhibition based upon exposure in the current day combined with residual effects from the preceding day(s). The extent and direction of the error can not be known, however, data pertaining to prior exposure to OPs such as those cited above reflect a pattern of exposure to humans that is qualitatively different from the repeated daily dosing used in rat feeding studies and therefore there is a possibility that risk is overstated. The use of the 21-day steady state data fixes the estimate of dose relating to a 10% cholinesterase decrement and permits a reasonable estimate of risk from exposure to OPs.

This finding was important in determining the appropriate manner in which to incorporate the available acetylcholinesterase inhibition data into the hazard assessment. In conjunction with the understanding that the period of reversibility for OP-induced cholinesterase inhibition is on the order of several days to weeks, it provides a reasonable basis for the decision to use steady state measures of cholinesterase inhibition as the basis for OPs RPFs and

the PODs for methamidophos. It also supports the need to consider multiple modes of exposure, focusing on both more extreme episodic exposures as well as longer term average exposures. These two modes of analysis when used together acknowledge the potential for continuous exposure over an extended period of time while allowing an evaluation of the potential impact of periods of elevated OP exposure.

In summary, OPP has taken steps to address the most significant methodological issues raised concerning the dose response assessment developed in support of the OP cumulative risk assessment. OPP is confident that the assessment as performed is scientifically and statistically sound and based upon a reliable data set.

3. Use of Calendex and the Mode of Analysis

The use of Calendex in conducting the current assessment is described in section I.F of this document. Calendex permits the simultaneous evaluation of more than one pathway of exposure. It also permits the evaluation of exposure on a calendar basis, considering changes in exposure patterns with season as pest pressures change. In the December 3 Preliminary OP Cumulative Risk Assessment, OPP demonstrated the use of Calendex to develop a distribution of linked single-day exposures. This approach to estimating an annualized distribution of exposures for use in risk assessment received numerous public comments and reviews from the FIFRA Scientific Advisory Panel.

The single day analysis approximates an analysis similar to that performed for acute dietary evaluations in single-chemical assessments. As in the acute dietary analyses, a full range of inputs for dietary residues is paired with the individual consumption records from the CSFII. In addition, a water concentration value is paired with the water consumption value developed as described in section I.E. Finally, an estimate of exposure from residential sources is calculated and combined to develop an estimate of the total MOE. A distribution of total MOEs is generated for each day of the year. A series of percentiles are then selected for each day to evaluate potential risk concern for the combined uses of the OPs. This analysis assumes that the potential exists to experience a high-end exposure on every day of the year. In the current assessment, values are presented for the 99.9th, 99.5th, 99th, and 95th percentiles of exposure.

OPP developed a second assessment considering the potential risk from a series of 7-day rolling averages across the year. This process is described in section I.F. This analysis is an attempt to better match the time frames for the toxicity data with the consumption data which are not directly comparable. The toxicity data used in the assessment are based upon 21 days of exposure to rats in feed. This data reflects steady state measures of cholinesterase inhibition and is readily available for all OPs. Food consumption data are available only on a single-day basis. The 7-day average allows for consideration of the variable

nature of likely exposures to an individual across time. It permits consideration of the impact of varying exposure in the diet and from residential uses of OPs from day to day. OPP also investigated the potential impact of longer averaging times (14 and 21 days) on the results of the risk assessment. The longer averaging times resulted in incrementally small decreases in the estimated risk, with the effect of duration decreasing with increasing time. This behavior is not unexpected in that with longer averaging time, the exposure will approach the mean exposure for the output distribution. However, the longer time frames will further obscure any time-related variability in exposure. The use of the 7-day rolling average provides a more realistic profile of exposure across a series of multi-day exposures while maintaining some sense of anticipated variability.

OPP believes that the results of the single day and 7-day analyses successfully bound the anticipated exposures resulting from residues of multiple OPs in food. The one-day analysis assumes that an individual is exposed to OP exposures from the tail of the distribution every day. This assumption overestimates risk. The seven-day analysis incorporates day-to-day variability in exposure and is more representative of anticipated exposures. The major sources of difference in the results of the two analyses arise from differences in how the data is incorporated into the analyses and the ability to reflect day to day variability. The differences are: the selection process for the two days of CSFII data, the assumption of independence of residue data inherent in the use of the PDP data in the assessment, and the inability of the approaches to allow for carryover cholinesterase inhibition from prior exposures.

a. Use of CSFII Data

In the single day analysis, one diary for each individual in the CSFII is selected to be paired with a randomly selected set of residue values for each food consumed. A set of exposures from OPs in foods is developed and arrayed as a distribution from high to low exposures. This type of assessment assumes that the consumption of foods from one day to another is independent, with no consideration of the potential for eating leftovers or consuming foods purchased in bulk such as juices or potatoes. As a result, the assessment over emphasizes variability in the diet. This factor may bias the exposure assessment up or down depending the food/pesticide combination that is not repeated appropriately. The magnitude of the effect also will vary depending upon the specific food/pesticide combination.

The use of the CSFII data in the 7-day rolling average consists of a random redraw of the two available days of consumption data for each person in the data base. This process is intended to maintain the integrity of the data for individuals, including to the extent possible, any information defining patterns of diet peculiar to them. However, the redraw process results in the implicit assumption that every individual in the CSFII consumes a diet that is limited to the records in the diaries repeated randomly across the year. As a result, the variability likely to occur in the diet is not fully expressed in the

current risk assessment. This factor is expected to reduce the range of exposures to which any particular individual can be exposed by limiting the number of commodities and pesticides possible to those reported in the two daily diaries. This factor is anticipated to introduce a downward bias into the exposure assessment. However, the impact on the assessment is anticipated to be small because all possible combinations of exposures are still available. The shape of the final distribution may be modestly affected by the difference in averaging that occurs due to the reduction in combinations available, but the exposure estimates at the upper percentiles of exposure should not be significantly affected.

b. Use of PDP Data

PDP data are used for most of the pesticide residues in food assessment. These data are introduced into the assessment in a manner that imposes the assumption that all eating days are independent with regard to the source of food consumed. In fact, consumption on any given day may not be independent of preceding days to the extent that individuals consume bulk items such as juice, bunches of grapes, or bags of produce or left-overs that have the same level of residues on multiple days. As a result, exposure from items of these types may be under represented in the single day and 7-day rolling analyses to the extent that a high end residue may be selected on one day, but not resampled on the subsequent days. As result, these assessments may be biased downward with respect to the exposure estimates developed, although the magnitude of the error is not known.

c. Impact of Residual Cholinesterase Inhibition

Cholinesterase inhibition resulting from OP exposure is not immediately reversible. OPs bind covalently to the active site of the enzyme. Recovery is largely due to regeneration of the enzyme rather than dissociation. As a result, the recovery time (time required for cholinesterase levels to return to pre-exposure levels) is extended, requiring on average 1 to 2 weeks in humans. As a result, the cholinesterase inhibition experienced on any given day is the sum of inhibition from that day's exposure combined with residual inhibition due to exposure on the preceding several days. As each day passes, the importance of inhibition from any given preceding day declines until it is fully reversed. The single day analysis does not incorporate an estimate of the phenomenon. This results in a downward bias of unknown magnitude. The magnitude of the bias will be dependent on the likelihood of exposures on previous days. The Calendex model attempts to incorporate some aspect of the prior exposure in the 7-day rolling average approach by allowing for the combined exposure over a 7-day period of time. To this extent, Calendex captures the carryover aspect of **exposure** to pesticides. However, this approach can not account for the biological aspect of declining importance of an exposure with the passage of time. It also de-emphasizes the impact of intermittent high exposures as they are averaged into the

background. To the extent that Calendex can not reflect this aspect of the impact of exposure to OPs, the 7-day rolling average will tend to be biased downward with regard to the estimate of risk from exposure to OPs.

4. Food Assessment

The food component of the OP cumulative risk assessment is based primarily upon two extensive, reliable data sets: 1) USDA's Pesticide Data Program, and 2) USDA's Continuing Survey of Food Intakes by Individuals, 1994 -1996 + 1998 (CSFII). The PDP data provide a very reliable estimate of pesticide residues in the major children's foods. They also provide an indication of the co-occurrence of OPs in the same sample, alleviating much of the uncertainty about co-occurrence in foods that are monitored in the program. The CSFII provides a detailed representation of the food consumption patterns of the US public across all age groups, during all times of the year and across the 48 contiguous states. These two data components provide a firm foundation upon which to assemble other data to develop the OP cumulative risk assessment.

a. Consumption Data

Up until this time, OPP has performed its risk assessments using the 1989-91Continuing Survey of Food Intakes by Individuals (CSFII). This survey was conducted by USDA and was based on responses over three consecutive days. A more recent CSFII was performed (the 1994-96 CSFII) which was supplemented in 1998 by the Supplemental Children's Survey. This 1998 survey focused on children from birth to 9 years old and greatly expanded the number of birth to 4 year old children in the survey data base. Importantly, the Supplemental survey was designed in a manner such that the results from the 1998 CSFII survey could be combined with the 1994-96 survey. OPP believes that the newer survey information provides a more realistic estimate of potential risk concerns because it reflects the current eating habits of the US public. Based in part on past recommendations of the FIFRA Scientific Advisory Panel and other advisory bodies, based in part on OPP analyses of dietary and behavioral patterns, and based in part on a minimum number of individuals needed to provide a good representation of eating patterns, OPP has determined that the following age groupings are appropriate for the cumulative assessment: birth to 1 year of age (i.e., 0 - 11 months); 1 to 2 year of age (i.e., 12 - 36 months); 3 through 5 years of age; 6 through 12 years of age; 13 through19 years of age; 20 through 49 years of age; and 50 years of age and greater.

For this assessment, the following age groups were analyzed for all regions: 1 to 2 years of age; 3 through 5 years of age; 20 through 49 years of age; and 50 years of age and greater. These age groups were selected because the other age groups are rarely the most highly exposed in the single-chemical assessments. For Region A, all subpopulations were evaluated to confirm this assertion. Region A was selected as an appropriate

analysis to demonstrate the impact of a variety of parameters within the assessment because it consistently demonstrates the highest exposures and risks estimated for regions across the US. The change to the more refined age groupings should improve our ability to identify age-related differences in food consumption (especially among young children). The use of the newer CSFII and the finer age breakouts should increase the accuracy and utility of the risk assessment overall by making it more descriptive of the anticipated exposures and risks for each age group.

OPP is confident that the consumption data available from the CSFII permit a reasonable basis for estimating exposure to OPs in foods. The data are used empirically in combination with residue values to estimate exposure. As a result, no issues relating to the appropriateness of curve fitting procedures have been introduced into the assessment. OPP also believes that an adequate number of samples are available to support estimation of exposure. Approximately 4000 consumption days for 2000 individuals are available for each subpopulation. This body of data is sufficient to support simulation well out into the tails of the exposure distribution with little concern for overestimation of consumption. However, as is the case with all sampling protocols, the proportion of samples available declines toward the extremes of the output distribution. As a result, extreme output distribution values are less well represented than those reflecting the central tendency for the output distribution. OPP acknowledges that the use of CSFII in this assessment may not fully reflect the eating habits of high end eaters, introducing some uncertainty with respect to the tails of the distribution of estimated exposures in the assessment.

b. PDP Monitoring Data in the Assessment

The use of PDP as a source of residue data has a number of inherent benefits that preclude the need for the use of conservative assumptions in the assessment. PDP provides a direct measure of the occurrence of more than one OP in any sample analyzed. OPP can use these data as an indication of pesticide co-occurrence likely to be encountered in foods. OPP assumes that co-occurrence mirrors the PDP values; in fact PDP composites contain multiple individual units which may have different profiles of co-occurrence. Therefore, use of PDP data in this manner may overstate potential risk. PDP implicitly reflects the percent of a crop that has been treated with any given OP by measurement of the residues.

Samples with non-detectable residues are assumed to be "zero" values in this assessment. The impact of this assumption was tested in the OP Cumulative Risk Case Study (USEPA, 2000c) that was presented to the SAP in December 2000. In the Case Study, a similar use of PDP data as the residue data source in this assessment was demonstrated for 24 OPs. The resulting data set had characteristics very similar to the one used in the current assessment. The analysis performed demonstrated that the use of

the "zero" values had only negligible impact on the MOEs developed at the upper percentiles of exposure.

Although the result of replacing all non-detectable residues with "zero" values would intuitively suggest an under-estimation bias, OPP has demonstrated through its case study that this change has little impact at all on the portion of the exposure curve likely to be used for regulatory purposes. This result is not surprising for a multiple chemical assessment addressing the number of chemicals under evaluation here. This assessment combines many data elements, with no single chemical or commodity dominating the exposure. The residue data used in this assessment include highly consumed foods, and several of these have large numbers of detects as well as a few high detects of OPs. There are detectable residues of at least one OP on 25% of the samples used in this assessment with a high of 66% on one commodity. Generally, the LODs for PDP data are very low (the average LOD for the entire data base is about 0.01 ppm). Therefore, it seems reasonable that the effect of assumptions related to estimation of values below the LOD would not significantly influence exposures at the highest percentiles of exposure. This result may not be the case for other assessments containing fewer foods or lower levels of detectable residues and should be evaluated for each subsequent case.

c. Data Translation from PDP

Not all foods to which OPs are applied are monitored in PDP. OPP has developed a scheme by which commodities that are measured by PDP serve as surrogate data sources for commodities that are not. This approach is outlined in OPP/HED SOP 99.3 (USEPA, 1999b). It is based upon the concept that families of commodities with similar cultural practices and insect pests are likely to have similar pesticide use patterns. Although this approach is generally sound, it introduces uncertainty with regard to how similar the use patterns for a given pesticide are to those for even closely related commodities.

For example, the same OP may be applied on a similar time schedule. However, the rates of application may differ between the crops treated. The number of treatments may also differ for application to the two crops. This issue is of importance to consider when conducting sensitivity analyses of the results of the risk assessment. When the data are adapted for the use of several chemicals simultaneously, and estimates of co-occurrence are derived from that data, the likelihood of an inappropriately assigned residue becomes greater. Although the commodities may have similar cultural practices, they may differ in the number of OPs registered for these uses. In addition, the translation from one commodity to another implicitly assigns the inherent percent crop treated information from one commodity to another. The direction and magnitude of this error will differ from one commodity to another.

OPP believes that this potential source of error in its assessment will most likely result in over-estimation bias. However, the magnitude of the error is probably not great in that the commodities for which PDP data was translated represent only ~1% of a child's diet.

d. Other Sources of Residue Data

PDP data and surrogate PDP data do not cover all commodities of interest. For meats, seafood and eggs, FDA's Total Diet Study and FDA Monitoring data provided residue estimates. These data suggest that eggs and seafood contain negligible residues. For most meats (beef, pork, sheep and goat), the maximum residue from the Total Diet Study was used. Although the use of the maximum residue as a single data point for meats is an overestimate, OPP has conducted a sensitivity analysis making all residues for meats zero and found that there was no change in the outcome of the risk assessment at the upper percentiles of exposure. This is not surprising in that the highest residue observed is itself very low. Therefore, OPP considers these factors neutral with regard to their impact on the results of the assessment.

Approximately 3% of the foods consumed by children 1 - 2 years of age still remained unaccounted for after using FDA Total Diet Study and FDA Monitoring data. Sugar, molasses and syrups were assigned a residue value of zero. These products are highly processed commodities that are unlikely to retain any significant residues following the processing steps. The limited data from the Total Diet Study found no residues in pancake syrup or sugar. No data are available for field corn or dried beans. However, these commodities are also blended and highly processed before consumption. OPP believes that omission of these foods from the assessment will not result in any change in the results of the assessment.

e. Impact of Regulatory Actions

Inherent in the use of monitoring data to estimate future residues is the concern that any changes in use patterns will not be reflected in the data. The OPs are currently undergoing use changes as a result of the individual chemical decisions. In most cases for which legal agreements have been signed, the uses have been removed from the assessment. For other pesticides, pre-harvest intervals have been extended or rates have already been reduced. These changes are not reflected in the assessment as they are not yet apparent in the monitoring data available. A specific example of this issue is the rate reductions agreed upon for azinphos-methyl on apples in 1999. Although the rate reductions have been implemented, they will not be reflected in monitoring data until the 2002 PDP data become available. This delay reflects the year lag in affecting a new growing season following implementation as well as the long period during which treated apples can remain in the chain of commerce following harvest.

Decisions have not been completed for all OPs included in this assessment. Completion of the regulatory process for these pesticides could result in additional exposure and risk reduction measures. These changes could result in further reductions in exposure in the food portion of the assessment. The magnitude of that change is uncertain.

f. Model Outputs

The single-day food component of the OP cumulative risk assessment was conducted using the DEEM software. This program evaluates the full range of dietary exposures across a single day. It permits a detailed evaluation of the source of exposures with regard to which foods and pesticides are the likely sources of the exposure. This analysis served as the basis for determining which commodity/pesticide combinations warrant further scrutiny in the event that further regulatory action is determined to be needed. The use of the single day assessment was considered to be appropriate because exposure to OPs in foods is uniform nationally, and it has no significant seasonal variations. OPP has extensive experience with the two data bases that confirm this assumption as reasonable. OPP has conducted a large number of seasonal assessments of exposure to individual pesticides in foods. These assessments show virtually no differences in exposures across seasons. This finding is not surprising in light of the widespread distribution of foods across the United States, and the proportion of foods that are imported. Lack of seasonal consumption patterns is also not unexpected given the ability to preserve and store foods for delayed consumption, and the import of seasonal foods to bridge gaps in domestic production periods. Similarly, PDP does not suggest any significant alteration in the types of pesticides encountered or the magnitude of residues across the year. The assumption of nationally uniform distribution of foods does not reflect highly localized consumption events that may be encountered by individuals who obtain foods at road side stands and consume it closer to the time of harvest than the foods available in larger grocery stores. OPP does not have reliable data on either consumption or anticipated pesticide residues to permit evaluation of this type of exposure, however we anticipate that only a small percentage of food consumed would be affected.

The results of the food portion of the revised OP cumulative risk assessment are summarized in Table I.H-1. The results are presented in the form of MOE for children 1 - 2 years of age, 3 - 5, adults 20 - 49, and adults 50+, at the 95th, 99th, 99.5th and 99.9th percentiles of exposure. The percentile of exposure as used in this document indicates the percent of the output distribution that is predicted to experience exposure less than or equal to the exposure at that point on the exposure distribution curve. In other words, at the 95th percentile of exposure, 95% of the output distribution is likely to have the exposure indicated or less. Five percent are likely to be exposed to higher amounts of OPs. The 1 - 2 year age group is consistently the most highly exposed subgroup in the analysis. This is due to a higher consumption

to body weight ratio for this age group. Results are presented for both single-day and 7-day analyses for all regions, with 14-day and 21-day analyses included for Region A. The FQPA Safety Factor was incorporated into the RPFs to permit modification of the assessment on a chemical-specific basis as appropriate based upon our current understanding of age-related sensitivity. The toxicity endpoints for this assessment were developed in consideration of a 10X uncertainty factor to account for interspecies variability and a 10X uncertainty factor to account for intraspecies variability. As discussed fully in section I. G., because some OP pesticides show age-dependent sensitivity and there are missing comparative ChE inhibition data in young animals for many of the OP's, the magnitude of the FQPA Safety Factor was set at 3X for most of the OP pesticides. Age-dependent susceptibility data are available for seven of the OP's. The data for dimethoate, omethoate (a metabolite of dimethoate), chlorpyrifos, and methamidophos support reducing the FQPA Safety Factor to 1X.

MOEs from the 7-day analysis exceeded 100 with all remaining uses (Table I.H-1). The MOE for children 1 - 2 years was 119 at the 99.9th percentile of exposure. As discussed above, OPP believes that this estimate is a reasonable approximation of the risk anticipated from consumption of OPs in foods.

MOEs for the single-day assessment do not reach the target value of 100 at the 99.9th percentile (Table I.H-1). The MOE for children 1 - 2 years was 45 at the 99.9th percentile of exposure. An MOE of 100 was reached at the 99.4th percentile of exposure. OPP believes that the 99.9th percentile of exposure in the single-day assessment is an overestimate of anticipated exposure, especially when considered as occurring over more than one day at a time. In addition, there is an overestimation of exposure resulting from the inability to reflect changes in residues due to recently implemented mitigation activities such as application rate changes and extended pre-harvest intervals increases. This value may be biased toward overstating the risk from OPs in food. However, bias reflected in this particular point estimate is anticipated to diminish at lower percentiles of exposure. OPP can not determine at what point in the exposure distribution the exposure estimate begins to be biased toward understating the exposure anticipated.

The decision as to whether additional mitigation activities are needed can not be made by looking at any single value in the results. Many factors must be weighed in determining the extent to which any particular value over- or understates the need for additional action. OPP believes that the actual exposures to the US public fall somewhere between the results of the two analyses presented. In addition, the application of hazard values results in offsetting issues with regard to the direction of change in the MOEs calculated.

OPP has identified commodity/pesticide combinations that appear at the upper end of the distribution and may warrant further study. These include: acephate on green peppers and succulent beans; azinphos methyl on apples and pears; dimethoate on apples, grapes, green peppers, pears, spinach, succulent beans, and tomatoes,; methamidaphos on potatoes and tomatoes; mevinphos on grapes and spinach; phorate on potatoes; and phosmet on apples, grapes, and pears. Until the individual assessments for DDVP and dimethoate are complete, it is premature to attach significance to these commodity/pesticide combinations. The significance of these commodity/pesticide combinations cannot be fully understood without taking into account all other relevant information, such as the results of the sensitivity analyses.

OPP has evaluated the consumption records occurring in the tail of the distribution to ensure that they reflect reasonable consumption patterns. Analysis of the tail of the distribution (>99th percentile) indicates that no small subset of consumption records dominates the outcome. This observation increases OPP's confidence that the food and water components of the assessment are not unduly influenced by unusual consumption patterns and reflect the consumption habits of the public at large.

Table I.H-1. Summary of the OP Cumulative Food Assessment

Children 1-2 Route: Food*	Percentile	Exposure Period Single Day Analysis MOE**	Exposure Period 7-day Analysis Mean MOE	Exposure Period 14-day Analysis Mean MOE	Exposure Period 21-day Analysis Mean MOE
	95	353	475	517	539
	99	128	249	295	320
	99.5	91	197	239	262
	99.9	45	119	151	166

*The additional FQPA Safety Factor is included as an adjustment to the chemical-specific Relative Potency Factors
**For the single day analysis for food, MOEs were calculated using DEEM software rather than Calendex software and thus no mean is applicable

Children 3-5 Route: Food*	Percentile	Exposure Period Single Day Analysis MOE**	Exposure Period 7-day Analysis Mean MOE	Exposure Period 14-day Analysis Mean MOE	Exposure Period 21-day Analysis Mean MOE
	95	437	570	616	634
	99	158	290	340	364
	99.5	111	225	271	295
	99.9	53	131	165	184

*The additional FQPA Safety Factor is included as an adjustment to the chemical-specific Relative Potency Factors
**For the single day analysis for food, MOEs were calculated using DEEM software rather than Calendex software and thus no mean is applicable

Adults 20-49 Route: Food*	Percentile	Exposure Period Single Day Analysis MOE**	Exposure Period 7-day Analysis Mean MOE
	95	1286	826
	99	439	784
	99.5	304	622
	99.9	146	364

*The additional FQPA Safety Factor is included as an adjustment to the chemical-specific Relative Potency Factors
**For the single day analysis for food, MOEs were calculated using DEEM software rather than Calendex software and thus no mean is applicable

Adults 50+ Route: Food*	Percentile	Exposure Period Single Day Analysis MOE**	Exposure Period 7-day Analysis Mean MOE
	95	1136	824
	99	403	735
	99.5	282	537
	99.9	139	340

*The additional FQPA Safety Factor is included as an adjustment to the chemical-specific Relative Potency Factors
**For the single day analysis for food, MOEs were calculated using DEEM software rather than Calendex software and thus no mean is applicable

5. Residential 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. 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, the timing of the pesticide treatments, frequency and duration of exposure. Use data are also important in identifying geographic regions where the pesticide will be applied. In the current assessment, use data are specific to the region under evaluation and vary according to the specific aspects of that region. Pesticide residue dissipation data address the fate of the pesticides once applied to an environment (e.g., lawns). Exposure contact data are exposure-specific metrics that relate human exposure to pesticide residues. Humans come in contact with the residues by contacting the product directly or by contacting the residues left after the pesticide applications are made. Distributions of human exposure factors, such as breathing rates, body weight and surface areas used in this assessment come from the Agency Exposure Factors Handbook. These will not be discussed in the risk characterization of the document because the values are established and used throughout the Agency.

OPP has used all of the known available data to assess the significant residential uses of the OP pesticides. The residential uses not covered by this assessment are pet collars (DDVP and tetrachlorvinphos), crack and crevice uses (DDVP) and pest strips (DDVP) used in attics, basements and other areas with limited human access. Use of DDVP pest strips in closets and cupboards were included. It should be noted that the DDVP pet collars are currently not being marketed. While the tetrachlorvinphos pet collars have not been assessed, the CRA does address the use of tetrachlorvinphos pet shampoos , sponge-on treatments and powders. Exposure from the shampoo, sponge-on and powder treatments is likely to be higher than from pet collar use. This is because greater amounts of active ingredient are applied and larger areas of the pet are being treated. Although tetrachlorvinphos treated pet collars represent the largest usage of the product, the number of people treating pets with the liquid and powder products were adjusted upwards to reflect the collar use in addition to the use of the other products. The usage data was taken from NHGPUS.

Each data set used in the assessment introduces some potential bias in the outcome of the exposure assessment. A summary of these biases, their direction and magnitude, is presented in Table I.H-2.

EPA recently funded a study assessing adult and children's exposure to insecticides in flea collars. Preliminary results show that the use of pet collars does not result in significant exposure to pesticides (Boone et al., 2001). Spot urine analysis of 110 pre-school children in the Seattle Metropolitan area monitored for dialkylphosphate (DAP) metabolites suggested that DAP concentrations were not significantly higher in children whose parents reportedly used pet care products (Lu et al., 2002).

a. Exposure Contact and Pesticide Residue Dissipation Data

Exposure contact data used to assess exposures experienced by the applicator of consumer oriented pesticides are by far the most robust information used in the residential portion of this assessment. In addition, the application of pesticides is one of the more straight-forward activity patterns to measure since it represents easily defined activities. Recent data generated by the Outdoor Residential Exposure Task Force (ORETF) have been used to assess the use of hose-end sprayers (lawn care products), rotary granular spreaders (lawn care products), hand-pump sprayers (home gardens and orchards) and hand held dusters (home vegetable gardens). Another study, submitted by a registrant, was also used to assess residential applicator exposure using granular shaker cans to apply disulfoton. All studies meet or exceed current Agency guideline requirements (in particular regarding the number of replicates) and can be extrapolated to include clothing scenarios ranging from short-sleeved shirts and short pants to long-sleeved shirts and long pants. OPP has high confidence in the use of these data. Exposure contact data used to address the pet scenarios include chemical specific handler exposure

There are two post-application dermal exposure scenarios addressed in this assessment. These are: post application dermal exposure to lawn care products, and post-application exposure to vegetable and home orchard pesticide applications. Like the applicator scenarios, the post application garden and home orchard exposure scenarios are easily defined activities. For harvesting vegetables or weeding, there is a substantial amount of data based on farm worker exposure performing similar activities in crops requiring substantial hand labor. These contact values have the potential to overestimate exposure since they are based on individuals working for profit based largely on their productivity. Such workers are likely to be more efficient and therefore exposed to a larger amount of treated surface than most home gardeners. A uniform distribution of values representing hoeing and harvesting may overestimate early season activities that consist of potential exposure to small plants.

Dermal exposure from post-application contact with the lawn chemicals is equally varied. Contact data, representative of the range of human activities has been difficult to model. Dermal contact exposure values were identified in data described in Vaccaro et al., 1996, for adults who performed scripted

activities and contact values for children performing non scripted activities on lawns treated with a non-toxic substance were described by Black in 1993. Rates of pesticide transfer in the studies with surrogate compounds were similar to those observed in the chemical specific dissipation data available to OPP.

Turf transferable residue data are available for all turf chemicals. For malathion, these studies were conducted at multiple locations. Studies conducted in Missouri, North Carolina and Pennsylvania were used for the eastern regions and the study conducted in California was used for the western regions. Similar regional residue data were available for the use of malathion on home gardens and orchards and were used accordingly in this assessment. These data are of good quality and provide accurate estimates for this parameter.

There are no chemical specific data that measure the influence of wet hands and the mouthing behavior of young children on the efficiency of residue transfer. OPP considered a study performed by Clothier et al. (2000) in which he observed an increase in transfer efficiency (1.5- to 3-fold) when comparing a turf residue collection method to volunteers pressing dry hands or hands wetted with saliva. He observed a higher transfer rate for the compound with the lowest application rate. This may suggest that the hand surface becomes saturated and thus results in a lower transfer rate at higher application rates. The factor of from 1.5- to 3-fold was used in the assessment. The factor may overestimate the transfer of residues at higher application rates.

Estimates of exposure to pet care products were developed using an approach similar to the one taken with the turf care products. For applicator exposure, the Agency used dermal and inhalation unit exposures coupled with important statistics that influence exposure such as animal weights and number of animals treated. The latter two variables were gleaned from proprietary sources and an EPA funded study (Boone et al., 2001). For post application exposure, surrogate dermal exposure data of individuals exposed to treated animals were used to generate transfer coefficients, based on the transfer efficiency of the available dislodgeable residue data for tetrachlorvinphos on fur.

Tetrachlorvinphos specific data addressing exposure of individuals while treating pets and post application pet fur measurements were recently submitted to the Agency. The unit exposures from pet care product applicator data (n-15) were expressed as an empirical distribution. Dog weights (n-176) were expressed as a cumulative distribution. To assess post application dermal exposure, an exposure study of 16 pet groomers, each exposed to 8 dogs treated with carbaryl, was used. Dermal transfer coefficients were generated based on the transfer efficiencies of the tetrachlorvinphos pet fur data and the measured exposure of the groomers. These data were also

treated as an empirical distribution. Duration of exposure was based on video analysis of children (n-3) playing with pets (Freeman et al., 2001). At this time the method OPP is using in this assessment is the best available as it uses chemical specific data (applicator and fur residue), real world contact data (groomers and video analysis of children).

b. Pesticide Use Data

Accurate pesticide use data are key to the residential risk assessment. Useful information include regional site/pest markets, timing of application and the percent of households using their products. In the absence of specific pesticide use information, OPP developed exposure scenarios based on timing aspects found in regional Cooperative Extension Service publications and surveys such as the National Home and Garden Pesticide Use Survey (NHGPUS), the National Garden Survey, and Doane's GolfTrak. The Cooperative Extension Service publications were useful for establishing the timing of various turf chemicals. The survey data were used to establish the number of households that may use a given pesticide. For some regions, these application windows were expanded to account for the differences in length of growing season. This is particularly important when regions consist of several USDA Plant Hardiness Zones (e.g., Region 8). The NHGPUS 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. The use of this survey introduces uncertainty into the analysis because of the age of the survey (1989-90). The data may not reflect reductions in current OP use patterns and therefore overestimate exposure. Doane's GolfTrak was used to identify the percent of golf courses treated with pesticides and is more timely (1998-99). OPP believes this is a robust data source. The National Garden Survey has been tracking percent of households employing lawn care applicators and is considered very robust. In addition, variables such as vegetable garden size are well characterized since these gardens are easy for survey respondents to define.

c. Use of Calendex

OPP believes using a calendar-based model is justified in order to manage the timing of pesticide applications and delineating subsequent exposures in the general population. Models that can employ distributions of the available residue and contact exposure data are needed to capture the inherent variability in the exposed population and can be used to provide justification regarding co-occurrence of pesticide exposure events. This method is preferable to relying solely on point estimates and combining "what if" scenarios which only adds uncertainty, while providing little information to risk managers regarding the potential numbers of exposed individuals and their ranges of exposure. Calendex provides the ability to evaluate route specific pathways which are defined by the model user so that appropriate residue and residue contact data can be used.

d. Non-dietary ingestion

Non-dietary ingestion is an important exposure pathway in the residential assessment in the southern regions. Frequencies of hand to mouth events used in the assessment are based on real world observations of children in homes and day care centers enumerated on video tape. However, a number of issues surround the estimation of the impact of this activity. The number of hand-to-mouth events occurring in a given time frame was developed by observing children's behavior during quiet play. Video tape data are based on children situated indoors and not outdoors. Hand to mouth frequency may be higher when children are engaged in "quiet play" (e.g., listening to stories) than when engaged in active play (running, tag, etc.). Children playing on lawns are likely to be engaged in active play. Therefore, the frequency of hand-to-mouth events used in the current assessment may be an overestimate.

The variety of hand-to-mouth events (such as the hand being near the mouth rather than in it) makes the enumeration of events difficult. Further, video tape values provide no information on rate of transfer from treated surfaces to hands. Transfer estimates in the assessment were based on studies measuring wet hand transfer efficiency with wet hands using surrogate compounds. No chemical specific data are available. For each hand-to-mouth event, the hand is assumed to have residue when data indicates a child may touch other things (e.g., clothing, non-treated surfaces or nothing).

e. Results

The results of the residential portion of the cumulative risk assessment are relatively straight-forward to interpret. The results of the individual regional assessments can be found in section II of this document. Inhalation exposures to DDVP from No-Pest strips are the major contributor to residential exposures. This determination is relatively obvious because this is the only remaining indoor use for OPs. Removal of DDVP from the assessment resulted in MOEs that were essentially the same as those deriving from food alone. Some of the regional assessments from the southern regions also indicate hand-to-mouth activities by children in conjunction with lawn scenarios as an important contributor to exposure. Some uncertainty surrounds the estimate of exposure from hand-to-mouth behaviors in the assessment. Any bias from this uncertainty is anticipated to overestimate exposure. The magnitude of overestimation is uncertain. OPP believes that the current OP cumulative risk assessment represents a reasonable, health protective estimate of likely exposure to OPs from residential uses.

Table I.H-2. Input Parameters Used in the Exposure Models: Bias, Assumptions, Uncertainties, and Strengths

Model	Input Parameter	Bias*	Assumptions, Uncertainties, or Strengths and Other Comments
Exposure Model for Residential Pathway (Rex)	Human Activity Pattern	+ = upward ~ = neutral - = downward	
Lawn Exposure	**Unit Exposure:push-type rotary spreader** (mg exposure per amount of active ingredient applied)	~	**Assumptions/Uncertainties** 1. This unit exposure is based on 30 replicates consisting of individuals using a push-type rotary spreader. A number of clothing scenarios are possible to be generated from these data. In this assessment short-sleeved shirt and short pants were assumed. This may overestimate exposure as large portion of exposure is to the lower legs. Although a surrogate compound was used, exposure is believed to be more influenced by the type of equipment used rather being chemical specific. OPP has high confidence in these data. 2. A lognormal distribution was selected. 3. Assumed gloves are not worn. Survey data do indicate that some residential handlers use gloves. Because consumers are unlikely to use, remove and care for PPE in the manner of professionals, it is unclear what impact this may have on actual use. 4. The surrogate compound (dacthal) used in the exposure study may be dustier than the granular formulations of the OP compounds assessed. This factor increases confidence that this variable will not underestimate exposure.
	Area treated (square feet)	**- to ~**	**Assumptions/Uncertainties** 5. A difficult variable to estimate. However, the assumption is reasonable given the application equipment used. Although, may underestimate areas that have larger lawns (midwest), margins of exposure are large.

Model	Input Parameter	Bias*	Assumptions, Uncertainties, or Strengths and Other Comments
Exposure Model for Residential Pathway (Rex)	Human Activity Pattern	+ = upward ~ = neutral - = downward	
	Dermal Contact Transfer	**~ to +**	6. Adults: activities performed with tank tops and short pants, lognormal distributions may be reflective of study design rather than actual activities (choreographed) 7. Children: Includes above scripted activities and a range of non scripted activities. Non-scripted activities lognormal distribution may be influenced by use of a non-toxic substance (not a pesticide) 8. Assumes all adults and children living in households being treated with lawn care products are exposed (enter treated area).
	Turf Residues: dermal	**~**	9. Chemical specific data reflect a range of high values (e.g., immediately after application) and influenced by watering-in and rainfall.
	Turf Residues: hand-to-mouth	**~ to +**	10. Based on surrogate data. Lone OP in surrogate data had the lowest transfer.
	Frequency of hand-to-mouth events	**~ to +**	11. Based on video-observations of children situated indoors. Active play outdoors may result in lower hand-to-mouth frequencies.
	Duration on lawn	**~ to +**	12. For children, the value is time spent outdoors in addition to time spent on lawns. Does not account for survey responses of individuals that did not play on lawns or go outside.
Public Health	**Drift**	**~**	13. Distribution of aerial and ground equipment values
	Population Exposed	**~ to +**	14. Assumes a large percentage of the population being exposed (based on those having lawns).

Model	Input Parameter	Bias*	Assumptions, Uncertainties, or Strengths and Other Comments
Exposure Model for Residential Pathway (Rex)	Human Activity Pattern	+ = upward ~ = neutral - = downward	
Home Garden	**Applicator: Small Tank Sprayer**	**~ to +**	15. This unit exposure is based on 20 replicates. individuals using a push-type rotary spreader. A number of clothing scenarios are possible to be generated from these data. In this assessment short-sleeved shirt and short pants were assumed. This may overestimate exposure as large portion of exposure is to the lower legs and upper arms. Although a surrogate compound was used, exposure is believed to be more influenced by the type of equipment used rather being chemical specific. OPP has high confidence in these data. 16. A lognormal distribution was selected. 17. Assumed gloves are not worn. Survey data do indicate that some residential handlers use gloves. Because consumers are unlikely to use, remove and care for PPE in the manner of professionals, it is unclear what impact this may have on actual use. confidence in these data
	Applicator: Granular	**~ to +**	18. This unit exposure is based on 15 replicates. Chemical specific data. Used study assessing exposure while treating shrubs which had higher unit exposures than for flowers. 19. A lognormal distribution was selected.
	Area treated: ornamentals	**~ to +**	20. Assumes all plants are treated.
	Area treated: vegetables/fruits	**~**	21. A lognormal distribution of a well studied variable.
	***Postapplication*: vegetables/fruits**	**~ to +**	22. *Contact values represent a wide range of activities.* All plants are assumed to be treated.
	Frequency of applications	**- to +**	23. Based on survey responses to use of insecticides. Not chemical specific.

Model	Input Parameter	Bias*	Assumptions, Uncertainties, or Strengths and Other Comments
Exposure Model for Residential Pathway (Rex)	Human Activity Pattern	+ = upward ~ = neutral - = downward	
	Plant residues	~	24. Regional and chemical specific
Indoor Air	**Residues**	~	25. Chemical specific
	Reduction in air concentration based on presumed use of smaller strips than in above residue study	**- to ~**	26. Proportional reduction is an assumption
	Duration	~	27. Use of CHAD consisting of several time activity surveys.
	Population Exposed	**~ to +**	28. Values based on use of all pest strips, not just those containing specific active ingredient.
Pet Treatments	**Applicator**	~	29. Chemical/formulation specific data. Number of pets and pet weights reasonable based on an "n" of 148 pets.
	Postapplication	~	30. dermal contact value, from studies in which there was substantial contact 31. Chemical specific fur residue data 32. video-analysis of children in contact with pets. However small n (3). 33. Best available at this time
Calendex	**Input parameter are describe above**		34. confidence in these data

6. Regional Water Exposure Assessments

The regional water exposure assessments are designed to represent exposures from typical OP usage conditions at one of the more vulnerable surface watersheds in the region. Regions were selected to reflect the climate and soil conditions causing increased pest pressure and resulting OP use. Each regional assessment focuses on areas where combined OP residues in drinking water is likely to be among the highest within the region as a result of total OP usage and vulnerability of the drinking water sources. In this manner, OPP is confident that if the regional cumulative risk assessment finds that exposure in water is not a significant contributor to the overall OP exposure from a vulnerable area, it will not be a significant contributor in other areas in the region. However, because the assessment is based on typical usage, it is not a high-end estimate of pesticide exposure via drinking water at that vulnerable site. A comparison of the estimated concentrations from individual OPs with available monitoring indicates that this assessment is by no means worst case or unrealistic. In each region, levels of one or more OP pesticides detected in monitoring studies exist that are greater than that estimated by the cumulative water assessment; in some cases, the estimates are off 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 (see Appendices III.E.1 and III.E.3, as well as the regional assessments in II.A through II.G, for detailed comparisons). Although the potential exists that peak water concentrations for one or more OP pesticides may not be captured in this approach, the impact on the contribution from water to the overall risk assessment is anticipated to be small.

The discussion that follows characterizes the results of the regional water exposure distributions, and identifies assumptions and approaches to the assessment that might impact the level of certainty in the results.

a. What Each Regional Assessment Represents

Each region in the assessment is represented by a geographic area with the highest apparent potential for cumulative exposure to OPs in drinking water. The vulnerable drinking water source in each geographic area represents an area with relatively high usage of multiple OP pesticides in relation to other parts of the region and coincides with surface water sources of drinking water that are vulnerable to potential contamination by these OPs. The focus on surface water sources of drinking water is a likely source of overestimation bias inasmuch as ground water sources generally have lower OP residues than are found in surface water.

Because OP usage varies within the region, the initial evaluation focused on the areas of highest use, based upon the crops grown, which OP(s) are used on these crops, how much OP pesticides are applied and when they are used. Because the relative potency factors (RPF) have a large impact on the

overall OP cumulative distribution, site selection tended to favor high-RPF OPs such as disulfoton, dicrotophos, and terbufos. 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. Since OP use may vary from year to year and cropping and usage patterns may change, some areas in other parts of the region may have greater water exposure in a given year.

Because OPP considers both total OP usage and vulnerability of the drinking water sources, the site selected may not necessarily coincide with the highest OP use area in the region or the area where runoff alone is greatest. For instance, the highest OP use areas in the Northwest region (Region B) are in Yakima County and eastern Washington and in southeast Idaho. However, because of low rainfall, few surface-water intakes, and irrigation-dominated agriculture, OP use in this area did not necessarily pose the greatest risk to drinking water sources. Instead, the surface-water sources of drinking water in the Willamette Valley were potentially more vulnerable, despite lower OP usage.

Comparisons of the estimated pesticide concentrations with available monitoring in each region indicate that, in almost every region, a few known detections of one or more OP pesticides occur at higher levels than are being predicted for the cumulative assessment. As noted, because the estimate focuses on the cumulative impact from multiple OP pesticides, it doesn't necessarily focus on the conditions that lead to the highest concentration of one particular OP. In addition, some of the monitoring data may come from water bodies that are not representative of drinking water sources. In some instances, the higher monitoring levels may reflect uses that are being cancelled, such as the residential uses of chlorpyrifos and diazinon. In the case of azinphos methyl, in which upper percentile regional distributions were consistently one to three orders of magnitude less than monitoring detections, the underestimates may be due to inadequate or missing data on pesticide fate and transport properties or usage.

b. What PRZM-EXAMS and the Index Reservoir Represent

OPP adapted available tools to provide daily distributions of OP levels in water for incorporation into the probabilistic cumulative exposure assessment. While these tools have provided OP distributions that are, in many cases, comparable with available monitoring data in the same or nearby locations, assumptions regarding the nature of the drinking water source and watershed influence the estimated distributions.

i. Nature of the Drinking Water Source

The Index Reservoir is based on the specific geometry (watershed and reservoir size) of an actual reservoir (Shipman City) in the midwest. As such, it may best represent potential transport to similar drinking-water sources in high rainfall areas such as the eastern US. It may not so well represent reservoirs in drier parts of the west, where inflow and outflow are artificially managed. In addition, while the Index Reservoir scenario will not necessarily reflect short pulses of higher concentrations found in flowing rivers and streams, long-term average concentrations in a reservoir may be greater than in streams because of differences in the residence time for water in these water bodies.

The Index Reservoir is adapted to the runoff and stream inflow calculated from local soil and weather data. OPP used the PRZM runoff data for the cropping scenario that generated the lowest total runoff volume in the region to derive the inflow and outflow of the Index Reservoir. This introduces a small additional error into the concentrations calculated for the other chemical-crop simulations in each region.

ii. Nature of the Watershed

PRZM is not a basin-scale model, but a field-scale model which provides an edge-of-field estimate of pesticide loads in runoff to the 5.3-hectare reservoir simulated by EXAMS from a 172.8-hectare watershed. PRZM does not explicitly account for the relative contributions of each field to the Index Reservoir. OPP used a cumulative adjustment factor (a combination of the regional percentage of the total watershed area in crops with OP uses and the percentage of acres treated by each OP on each crop) to adjust the resulting reservoir concentrations calculated by EXAMS. Further information on the assumptions involved in applying Percent Crop Area (PCA) factors for drinking water assessments of individual pesticides can be found in the science policy paper, "Applying a Percent Crop Area Adjustment to Tier 2 Surface Water Model Estimates for Pesticide Drinking Water Exposure Estimates" (USEPA, 2000e).

PRZM does not account for location in the watershed: all fields are assumed to be uniformly distributed within the watershed, with runoff going directly into the reservoir. The simulation of multiple chemicals to multiple crops grown in different soils represents a significant adaptation of PRZM-EXAMS. Ideally, the cumulative drinking-water exposure assessment for a region would allow separating the different crop-soil regions within a watershed, and could simulate the different path lengths through runoff and stream-flow to the Index Reservoir. However, since PRZM is an edge-of-field model, runoff from fields representing the application of each OP to a different crop follows the same path length in the treated field and empties directly to the reservoir. In other words, this

simulation assumes that the treated fields with their individual soils are uniformly distributed throughout the watershed and essentially ring the index reservoir for direct deposition of the edge-of-field load.

Each crop use simulated in PRZM assumes that the entire area of the watershed planted in the crop consists of a single soil. In each of the regions, OPP used actual soil data from local soils on which the crops are grown. When possible, the soil selected for each scenario was a benchmark soil that was prone to runoff (classified as hydrologic group "C" or "D" soils). While OPP attempted to simulate soils that might be prone to runoff, the emphasis in developing the scenarios was to choose important local soils for which sufficient data are available, and which are known to be used to grow the crops of interest. These soils may not represent those most prone to runoff, but afford reasonable certainty that the simulation represents local soil conditions. While an assessment using a single soil assumes that each part of the watershed will be equally vulnerable to runoff, areas of higher and lower runoff vulnerability will exist in an actual watershed.

iii. Multiple Years of Local Weather Data

Because the application rates, frequencies, and timing are held constant, the PRZM/ EXAMS Index Reservoir simulations 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 and EXAMS can account for OP runoff from a wide range of weather patterns not otherwise possible with monitoring studies that span relatively few years. The age of the data (collected through 1983) limits OPP's ability to compare of the modeling output to more recent monitoring data.

Weather data files for PRZM are available for weather stations across the country. The weather station nearest to the county or counties used for the simulations was chosen for the cumulative assessment. To the extent that precipitation in these counties over the period of record might have been greater or less than that recorded at the nearest weather station, runoff for that area may have been over- or underestimated by PRZM.

Additional uncertainty in the modeling results is associated with application of OPs to irrigated crops. PRZM has a relatively simple irrigation subroutine, applying a user-specified amount of irrigation to the simulated field when the moisture content of the top soil layer drops to some fraction of field capacity. Actual irrigation in the field follows a more complicated formula, with irrigation timing dependent on the grower's professional judgement of crop needs. In addition, PRZM has a limited ability to distinguish between various irrigation methods.

c. What the Usage, Cropping Areas, and Acre Treatments Represent

Typical application rates and frequencies for each OP pesticide on each crop were generated by taking the average reported in the USDA NASS (National Agricultural Statistics Service) Agricultural Chemical Usage summaries. This 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. Thus, using these typical application rates and frequencies may underestimate water concentrations in years when pest pressure is higher than in our reported years and may overestimate in years when lower amounts of pesticide is used. The usage data was generally not sufficient to conduct a probabilistic assessment over a distribution of actual application rates.

In some instances, the typical and maximum label application rates were identical. For instance, the typical rate for phorate application on sugarcane in Florida was at the maximum label rate. In many cases the maximum label rates were one to eight times greater than the typical rates (see Appendix III.E.11). The extent to which the differences in rates would be reflected in the OP cumulative distribution depends on a number of factors, including timing of application relative to runoff events and relative potency of the pesticide. As a result, the net difference in estimated cumulative distributions between all typical and all maximum rates ranges from no difference in all but the lowest percentiles in Region A to a factor of 2 to 4 times greater at the higher percentiles (95^{th} and above) in Regions E and G (Appendix III.E.11).

Those comparisons reflect the maximum potential difference between typical and maximum application rates by assuming that all OP pesticides would be applied at the maximum rates to all crops. In reality, given the range in crops and pests treated by OP pesticides, it is more likely that only some of the OP pesticides might be applied at maximum rates in a given year and, thus, the difference would be less than that found in the comparison.

The regional percent crop area (PCA) factors are based on a large area: the size of the hydrologic units (average > 1000 square miles) used 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. However, cropping intensity is variable and smaller watersheds, including those capable of supporting drinking water supplies, may have a much different (higher or lower) 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%.

The regional assessment areas coincided with the area with the highest PCA in all of the regions except the Northwest. In the Northwest, the regional assessment focused in the Willamette River Valley, a generally lower-intensity agricultural area which was otherwise more vulnerable because of OP usage and/or the nature of the drinking water source. However, as already noted, portions of the Willamette Valley had higher percentages in agriculture than reflected by the PCAs generated using the larger hydrologic units.

The typical application rates and percent acres treated are derived from state-level data (or NASS reporting districts) and assume uniform use practices across the state. Indeed, an uneven distribution of application rates and percent acres treated is expected in response to differing pest pressures. 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. In the Red River Valley (Northeast/North Central region), differences in percent acres treated and application rates between the Minnesota counties and the North Dakota counties located within the Red River Valley are more likely due to differences in the state-level data than in actual differences between the adjacent counties.

d. Timing of Application

OPP used crop profiles and other relative crop production publications to establish a time frame for making the applications of the pesticide on a particular crop (application window). The length of the window doesn't necessarily reflect the range over which a pesticide will be applied in a particular year, but the year-to-year variation in the application dates over time. Thus, in any given year, the timing of application may be clustered within a shorter time-frame than suggested by the application window. However, because of weather and other environmental factors, the timing of intensive pest pressure and/or OP application may vary across the window.

The date of application can have an effect on the predicted concentrations generated by PRZM/EXAMS, depending on how close the pesticide application coincides with rainfall events in any given year. To evaluate how this may impact on the OP cumulative distribution, where multiple pesticides are applied at different dates, OPP varied dates of application across the active window for each OP-crop combination in Regions A and D (see Appendix III.E.11 for details). The impact of varying dates of application was most evident at the extremes in the distributions. The ratio in maximum concentrations between the lowest and highest estimates was a factor of 5 to 6. For 99th and lower percentiles of exposure to OPs, the differences were not as dramatic, with the ratio between lowest and highest values generally two or less. This analysis only looked at the cumulative OP distribution and did not evaluate variations in individual chemical distributions. In both regions, the cumulative distribution generated at the beginning of the

application window and used for the regional assessment was less than the maximum estimated distribution. The ratio between the highest estimated concentration distributions and that used for the regional assessment was between 2 to 4 for the maximum estimated concentrations, but less than 2 for 99th and lower distributions.

In the absence of data to show otherwise, OPP assumed that all of the pesticide applied on a particular crop is done on the same date. While this may be an unreasonable assumption for a large watershed, it is not unrealistic for the size of the watershed used in this assessment. This assumption may result in higher peaks, but similar overall average concentrations than if applications are spread out over time. The resulting estimate of exposure may result in a small overestimation bias in the results that will be greater in large than in small watersheds.

In California (Region C - Arid/Semiarid West), OPP used California Department of Pesticide Regulations (CDPR) census data for its regional assessment. This information provided a distribution of applications by actual date of application. For that regional assessment, OPP split the total application into 5 applications, with each application representing 20% of the total amount applied on that particular chemical. The absence of information on application dates in NASS precludes OPP from taking a similar approach in other regions. OPP also generated an estimated cumulative OP distribution by using a single application at the beginning of the application window, as was done in other regions. The cumulative OP concentration distribution estimated using a single application was greater than that estimated using 5 split applications by a factor of two or less (see Appendix III.E.11 for details). While splitting the application over multiple days is expected to result in lower peaks than a single application, the degree to which a difference is seen depends on a number of factors, including the mobility and persistence of the pesticide and the timing of applications in relation to runoff-producing rainfalls.

e. Water Treatment Effects

Although not extensive, scientific evidence suggests that many of the parent OP pesticide residues in water are likely to be transformation by oxidation during water treatment, through chlorination or similar disinfection treatments. These oxidative transformation products, such as sulfones, sulfoxides, and oxons, are still of toxicological concern, have been detected in treated water from water treatment plants. Limited data suggest that these treatment by-products may be stable for sufficient periods of time (for least 24 to 96 hours) to move through the distribution system.

The information is not sufficient to make quantitative adjustments to the cumulative exposure estimates. To estimate potential impacts and to determine whether additional information is needed, OPP assumed that any transformation due to chlorination results in the conversion to a product of toxicological concern. Thus, all OP parents that form oxons, sulfoxides, or sulfones (see Table I.E-1) were assumed to be transformed into those products as a result of oxidation. Where the transformation is less than complete, and where non-toxic products are also formed, the such an assumption will overestimate the ultimate drinking water exposure. While limited information suggests that the other OP parent would be transformed and removed from treated drinking water, sufficient information is not available to quantify this for all OP pesticides. Thus, OPP did not assume that any of the other OP parent pesticides would be removed. OPP assumed that the sulfoxide and sulfone products are equal in toxicity to the parent and that the oxon products are ten times more toxic than the parent. A comparison of the RPFs for dimethoate (0.32) and omethoate (0.96), the oxon of dimethoate, suggests that this assumption would be protective.

Table I.H-3 compares the cumulative OP distribution used in the risk assessment (labeled "No treatment effects") with an estimated distribution using the assumptions of treatment impacts described above (labeled "oxon conversion w/ 10X increase in RPF"). In each region, the main cumulative OP "pulse" in any given year is dominated by an OP which transforms into sulfoxide and sulfone products (terbufos, phorate, or disulfoton). Since the estimated distributions for those OP pesticides reflect the combined parent plus sulfoxide/sulfone residues, any potential treatment effects from oxidation of these chemicals is covered in the assessment. Conversion of OP parents to oxons would not add significantly to the cumulative OP load in these regions because (a) those OP pesticides which form oxons are not contributing significantly to the cumulative "pulse" for the region, and/or (b) those oxon-forming OP pesticides that are frequently detected in water (chlorpyrifos, diazinon, malathion) have very low RPFs in comparison to other OP pesticides (such as dicrotophos, terbufos, and phorate).

Table I.H-3. Comparison of OP cumulative distribution (ppm, methamidophos equivalents) assuming no drinking water treatment effects to distribution assuming oxon conversion with increase in toxicity

	Cumulative OP Distribution, ppm		Ratio no treat: 10X oxon	Cumulative OP Distribution, ppm		Ratio no treat: 10X oxon	Cumulative OP Distribution, ppm		Ratio no treat: 10X oxon
	No treatment effects	Convert to oxon w/ 10X increase in RPF		No treatment effects	Convert to oxon w/ 10X increase in RPF		No treatment effects	Convert to oxon w/ 10X increase in RPF	
Region	**A (Florida)**			**B (Northwest)**			**C (Arid/Semiarid West)**		
Max	1.4E-02	1.4E-02	1.0	1.4E-04	2.6E-04	1.8	7.6E-04	9.9E-04	1.3
99th	9.0E-04	9.0E-04	1.0	1.2E-04	1.4E-04	1.1	2.2E-04	2.7E-04	1.2
95th	7.8E-05	1.0E-04	1.3	9.2E-05	1.0E-04	1.1	1.6E-04	2.0E-04	1.2
90th	3.6E-05	5.8E-05	1.6	7.5E-05	8.1E-05	1.1	1.4E-04	1.7E-04	1.2
80th	2.0E-05	3.5E-05	1.7	5.1E-05	5.7E-05	1.1	1.2E-04	1.4E-04	1.2
75th	1.7E-05	2.9E-05	1.7	4.6E-05	5.3E-05	1.1	1.1E-04	1.3E-04	1.2
50th	8.1E-06	1.6E-05	2.0	3.0E-05	3.6E-05	1.2	7.6E-05	1.1E-04	1.4
25th	3.4E-06	8.3E-06	2.4	2.0E-05	2.6E-05	1.3	4.6E-05	7.8E-05	1.7
10th	1.5E-06	4.5E-06	3.1	1.5E-05	2.0E-05	1.3	3.0E-05	5.4E-05	1.8
Min	4.1E-07	1.1E-06	2.6	8.3E-06	9.5E-06	1.1	1.7E-05	2.4E-05	1.4
Mean	4.6E-05	5.5E-05	1.2	3.7E-05	4.4E-05	1.2	8.3E-05	1.1E-04	1.4
Contributors to cumul. OP pulses	Phorate + sulfoxide/ sulfone; ethoprop			Ethoprop; azinphos methyl; chlorpyrifos			Disulfoton + sulfoxide/ sulfone, Phorate + sulfoxide/ sulfone		
Oxon-formers	Chlorpyrifos, diazinon			AzM, bensulide, chlorpyrifos, diazinon, dimethoate, malathion, MePara, Phosmet			AzM, chlorpyrifos, diazinon, dimethoate, malathion, MePara, Phosmet		
Region	**D (Northeast/ North Central)**			**E (Humid Southeast)**			**F (Lower Midwest)**		
Max	4.9E-03	4.9E-03	1.0	3.7E-03	3.8E-03	1.0	3.7E-03	3.9E-03	1.1
99th	1.5E-03	1.5E-03	1.0	1.1E-03	1.1E-03	1.0	1.3E-03	1.4E-03	1.1
95th	4.8E-04	4.9E-04	1.0	3.6E-04	3.9E-04	1.1	4.7E-04	5.7E-04	1.2
90th	2.0E-04	2.2E-04	1.1	1.6E-04	1.9E-04	1.2	2.3E-04	3.1E-04	1.4
80th	5.5E-05	8.5E-05	1.5	6.5E-05	8.3E-05	1.3	5.7E-05	1.2E-04	2.1
75th	3.1E-05	6.0E-05	2.0	4.9E-05	6.4E-05	1.3	3.0E-05	8.2E-05	2.7
50th	5.5E-06	1.2E-05	2.3	1.8E-05	2.2E-05	1.2	4.6E-06	2.3E-05	5.0
25th	1.5E-06	3.8E-06	2.5	9.6E-06	1.1E-05	1.2	1.8E-06	8.4E-06	4.7
10th	5.8E-07	1.8E-06	3.2	6.2E-06	7.2E-06	1.2	9.7E-07	3.4E-06	3.5
Min	2.0E-08	2.0E-07	10.0	3.9E-07	7.3E-07	1.9	1.5E-07	4.7E-07	3.2
Mean	9.2E-05	1.0E-04	1.1	7.9E-05	8.9E-05	1.1	8.2E-05	1.2E-04	1.4
Contributors to cumul. OP pulses	Terbufos, phorate with sulfoxide/ sulfone transformation products			Terbufos, phorate, & disulfoton with sulfoxide/ sulfone; acephate			Terbufos + sulfoxide/ sulfone; phostebupirim		
Oxon-formers	AzM, chlorpyrifos, dimethoate			Chlorpyrifos, dimethoate			Chlorpyrifos, dimethoate, malathion, MePara, phostebupirim		

	Cumulative OP Distribution, ppm		Ratio no treat: 10X oxon	Cumulative OP Distribution, ppm		Ratio no treat: 10X oxon	Cumulative OP Distribution, ppm		Ratio no treat: 10X oxon
	No treatment effects	Convert to oxon w/ 10X increase in RPF		No treatment effects	Convert to oxon w/ 10X increase in RPF		No treatment effects	Convert to oxon w/ 10X increase in RPF	
Region	G (Mid-south)								
Max	8.7E-03	9.0E-03	1.0						
99th	4.3E-03	4.4E-03	1.0						
95th	1.9E-03	2.0E-03	1.0						
90th	1.0E-03	1.1E-03	1.1						
80th	4.4E-04	5.2E-04	1.2						
75th	3.1E-04	3.8E-04	1.2						
50th	4.1E-05	7.4E-05	1.8						
25th	8.4E-06	1.5E-05	1.8						
10th	4.2E-06	6.8E-06	1.6						
Min	1.4E-06	1.8E-06	1.3						
Mean	3.6E-04	4.1E-04	1.1						
Contributors to cumul. OP pulses	Dicrotofos; acephate; terbufos + sulfoxide/ sulfone								
Oxon-formers	Chlorpyrifos, dimethoate, malathion, MePara, phostebupirim								

The assumption of oxon conversion with a 10X increase in toxicity had no impact on the upper percentile of the concentration distributions for OPs in water in the two regions with the highest estimated cumulative OP load in drinking water – Region A or Region G . In Region B, the assumptions regarding oxon transformation increased the maximum estimated cumulative OP concentration by a factor of 2, but had little effect on the 99th or lower percentiles of the water concentration distribution. This resulted in two spikes off the peak OP pulses in two years of simulations, but a lower impact during other times.

7. Conclusions

A multi-route, calendar-based risk assessment for a single chemical requires the assessor to consider a variety of new issues in designing and interpreting a risk assessment. The issues are more complex when the analyses address the simultaneous exposures to more than one pesticide. OPP advanced its risk assessment methods, across the board, as it developed this specific OP cumulative risk assessment.

Many questions arise when interpreting results generated in a complex, highly refined assessment. The detailed outputs allow in-depth analysis of interactions of data sets to estimate the possible risk concerns and identify the sources of exposures. In this assessment, assumptions are replaced with data from surveys and monitoring studies and, as a result, the assessment provides a more refined picture of what is likely to be encountered in the real world. In most cases the assessment uses distributions of data. This practice permits expression of the full range of values for each parameter.

This revised assessment presents results as a range of estimated Margins of Exposure (MOEs) using one-day and seven-day rolling averages at different percentiles of exposure distribution. After careful analysis, the Agency believes that the real world exposure is somewhere between the one-day and seven-day rolling average, and generally these MOEs do not represent a concern. OPP is analyzing the sources of exposure that are significant at the lower end of the MOE range at the high percentiles of exposure distribution.

One of the major factors influencing the results at the highest portion of the range (99.9th percentile) of exposure is the fact that for a few individual OPs, risk assessments and mitigation actions have not been finalized. This is particularly true for DDVP and dimethoate. This conclusion is supported by the results of the analysis that removed pest strips containing DDVP from the assessment. The resulting total (food, water and residential) MOE is essentially identical to that for a food-only MOE analysis.

OPP has identified that a few uses of OP pesticides on food crops generally play a larger role in the results of the food risk assessment. Overall evaluation of the risk from exposure to OPs in foods suggests that, with the exception of completion of outstanding single chemical assessments, the cumulative MOEs from exposure to OPs in foods do not raise a concern.

The results of the residential risk assessment indicate that remaining uses of OPs in a residential setting are anticipated to provide only minimal contributions to the cumulative risks from OPs with the exception of pest strips containing DDVP. The single chemical risk mitigation activities for DDVP have not been completed. The impact of these activities may significantly reduce the contribution of DDVP to the cumulative risk assessment.

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 95th for all subpopulations evaluated. As the percentile of exposure increases, the difference between the food and water contributions increase. Below the 95th percentile of exposure, the water risk comes within one order of magnitude of the food contribution. This pattern is consistent for all regions in the current risk assessment. OP exposure from drinking water does not play a significant role in the cumulative risk from OP use in the US

I. Revised OP Cumulative Risk Assessment

I. Future Work

The Revised OP Cumulative Risk Assessment provides a detailed picture of possible exposure to 32 OPs. Details retained in the assessment are sufficient to evaluate the impact of the methods and assumptions on the results of the assessment. This process is particularly important for a cumulative OP assessment because of its complexity and much additional data compared to single-chemical assessments. It uses distributions of data in place of point estimates to the extent possible. Appropriate information submitted during the comment period has been incorporated as appropriate as have comments from the March 2002 SAP review. This revised assessment utilizes the same innovative methodologies as that in the preliminary document. Since the issuance of the preliminary assessment OPP has analyzed the results presented therein and revised the outputs as necessary. Also further risk mitigation on individual chemicals which has occurred since December 2001 is incorporated in this revised assessment. This document also contains a section discussing the FQPA safety factor as it was applied in this cumulative assessment. That Section of the assessment will be reviewed by the SAP in June of 2002. This revised assessment will undergo an additional comment period during June and July. EPA will evaluate the SAP's comments as well as other comments or data that it receives and will modify this assessment as appropriate. In addition, as existing analyses are revised or new information is obtained, EPA will review this assessment and make further changes as appropriate.

With respect to the next steps discussed in the preliminary assessment, the revised document reflects essentially all of the proposed short term actions. In that document some of the activities were flagged as long term activities. These activities are not necessary for completion of the OP cumulative risk assessment, but are actively being pursued by OPP at present in the interest of improving OPP's risk assessment process. These long term steps are listed below categorized by discipline. Please note that no long term steps were discussed in the food and risk assessment methodology sections of the preliminary cumulative risk assessment and therefore there are no listings in these sections below.

As with the preliminary assessment, new information submitted during the comment period that will serve to improve the accuracy of the assessment will be incorporated into the assessment as appropriate. Also, further risk mitigation on individual chemicals which may have occurred since December of 2001 is incorporated in this revised assessment.

1. Hazard Assessment

① Long term: Research to develop and implement physiologically based pharmacokinetic [PBPK] models, which describe the time course disposition of chemicals and their metabolites, are well suited to provide more refined estimates of relative toxic potencies and points of departure for future cumulative risk assessment. OPP is currently working with the EPA's Office of Research and Development on the development and testing of such models for common mechanism pesticides.

② Long term: Pursue with ORD investigations on the interactions among simple mixtures of common mechanism pesticides to better understand the concept and application of dose additivity.

2. Food Exposure Assessment

To be determined.

3. Drinking Water Exposure Assessment

① Long term: What aspects of the modifications to the water residue modeling process can be applied to the conduct of single chemical aggregate assessments? What differences in assumptions may be needed for implementation of that process for single chemical assessments?

4. Residential Exposure Assessment

① Long term: Develop a science-based process for incorporation of spray drift and other sources of exposure into residential exposure assessment.

② Long term: What aspects of the modifications to the residential exposure estimation process can be applied to the conduct of single chemical aggregate assessments? What differences in assumptions may be needed for implementation of that process for single chemical assessments?

③ Long term: Develop better data defining the hand to mouth behavior of children in a variety of settings and for active and quiet play.

5. Risk Assessment Methodology

To be determined.

I. Draft OP Cumulative Risk Assessment

(*Please note: This section is still undergoing editing*)

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