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.

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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,

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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/.

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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,

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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

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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).

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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 $\boldsymbol{P_B}$ is the horizontal asymptote (i.e., limiting value of minimum cholinesterase activity), expressed as a fraction of the background activity.

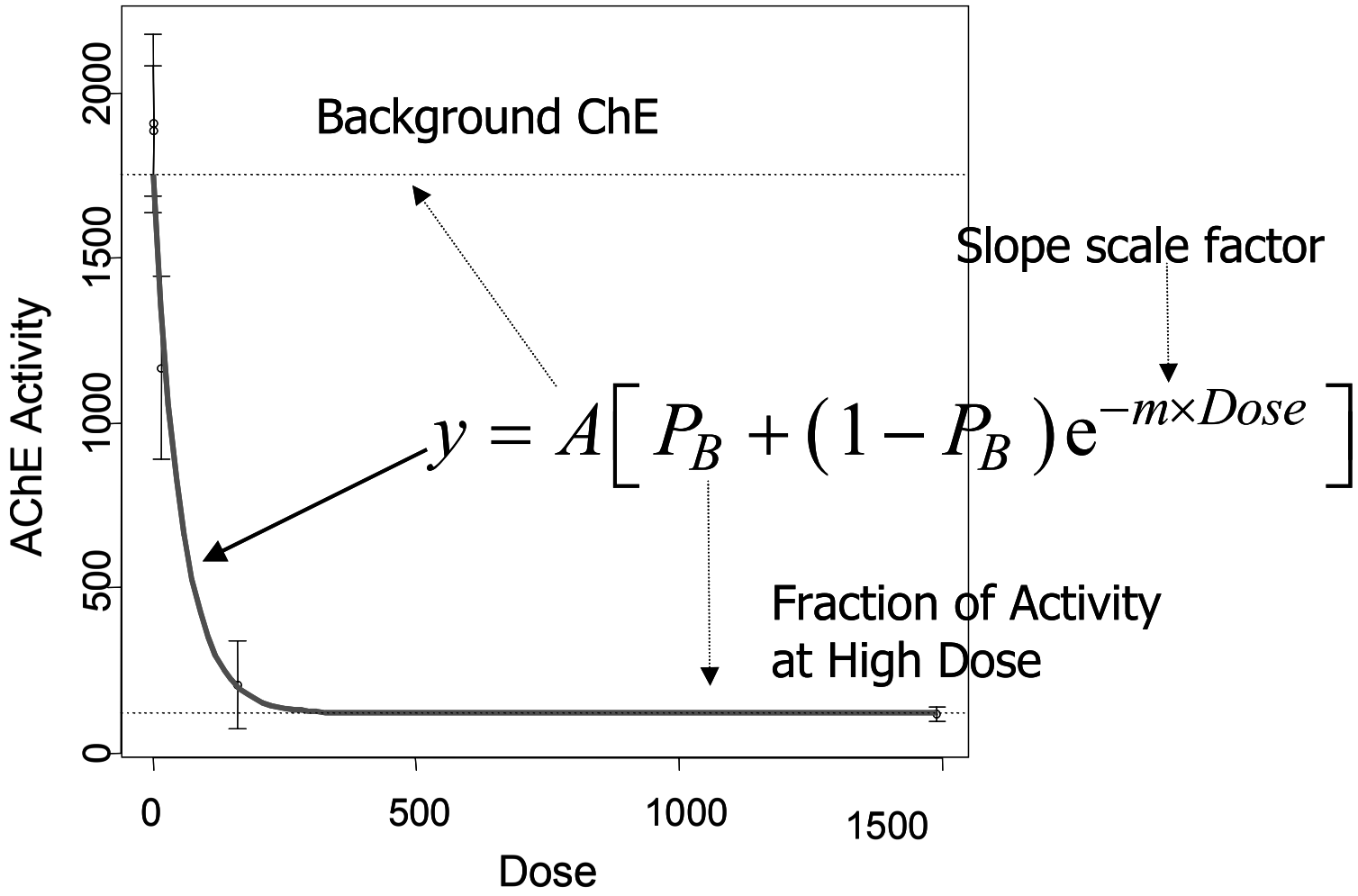
Both *y* (cholinesterase activity) and *dose* were extracted from the oral toxicity studies. P_B expresses the horizontal-asymptote as a fraction of background cholinesterase activity. P_B does not have any units. As described in detail in the technical appendix (III.B.1), Equation I.B-1a was reparameterized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

Equation I.B-1b

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

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*).

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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.

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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.

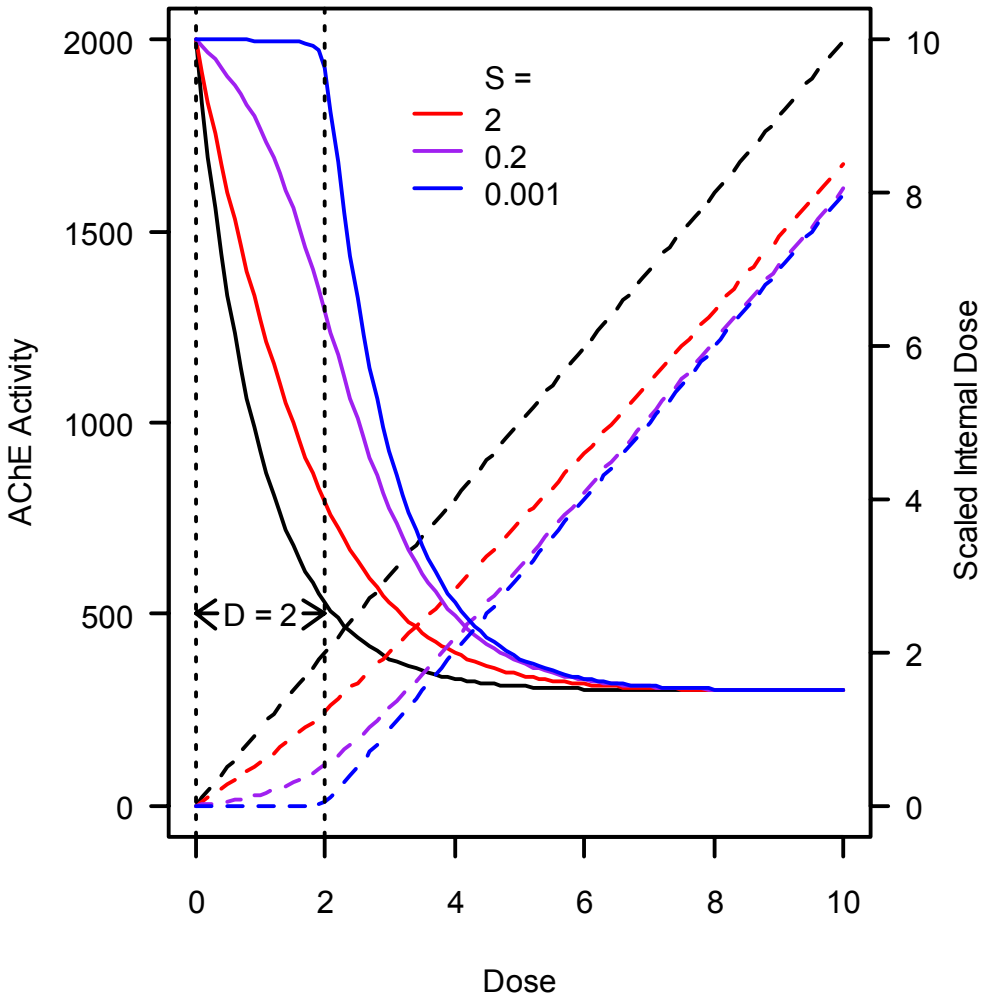

Figure I.B-2. Basic and expanded equations. The black solid curve is the basic equation of Equation I.B-2 with A = 2000, P_B = 0.15, and m = 1. The colored solid curves show the results of the expanded equation with 3 different values of S and D=2. The dotted curves shows the relationship between *idose*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

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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

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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

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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

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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.

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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

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

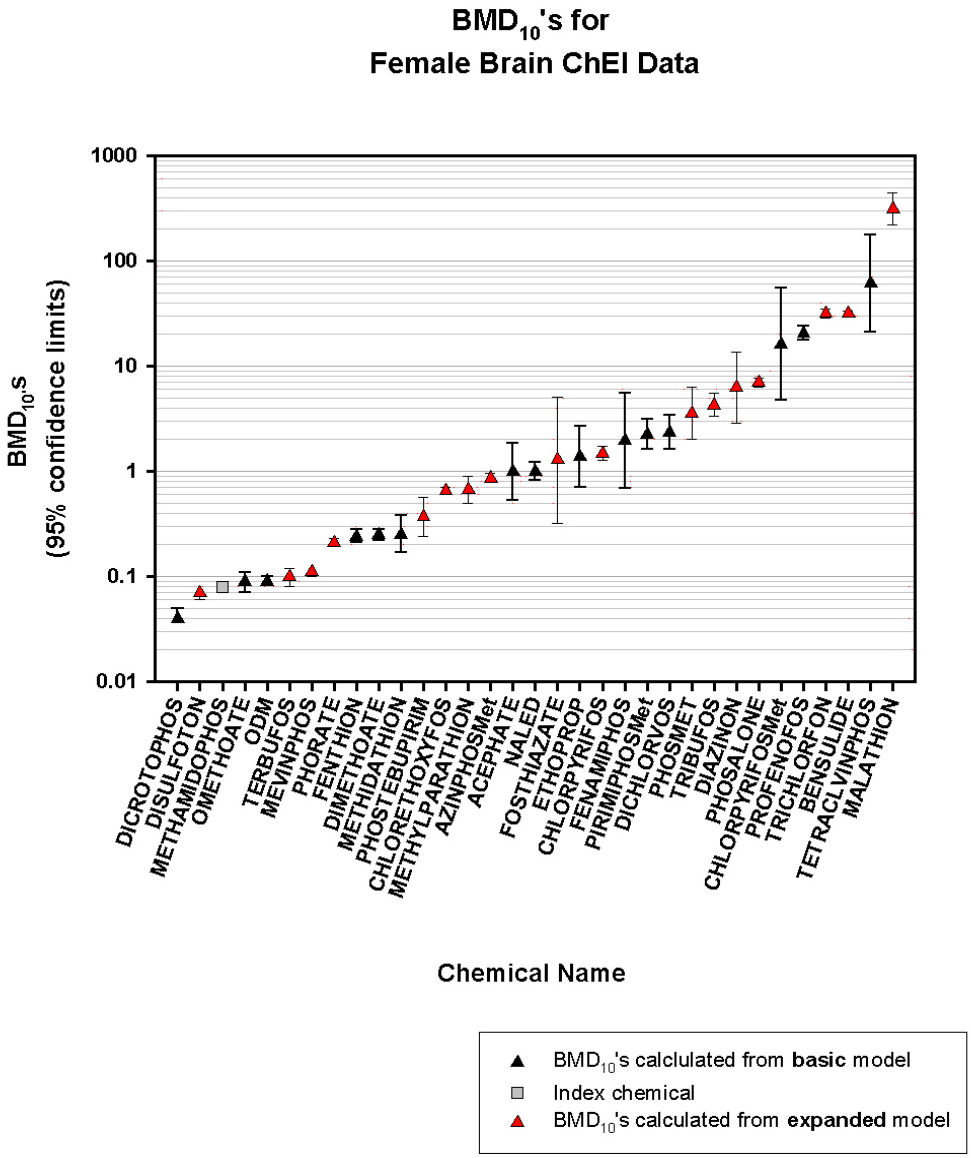

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Figure I.B-4. BMD_{10}s (mg/kg/day) for male brain ChE activity for 33 OPs

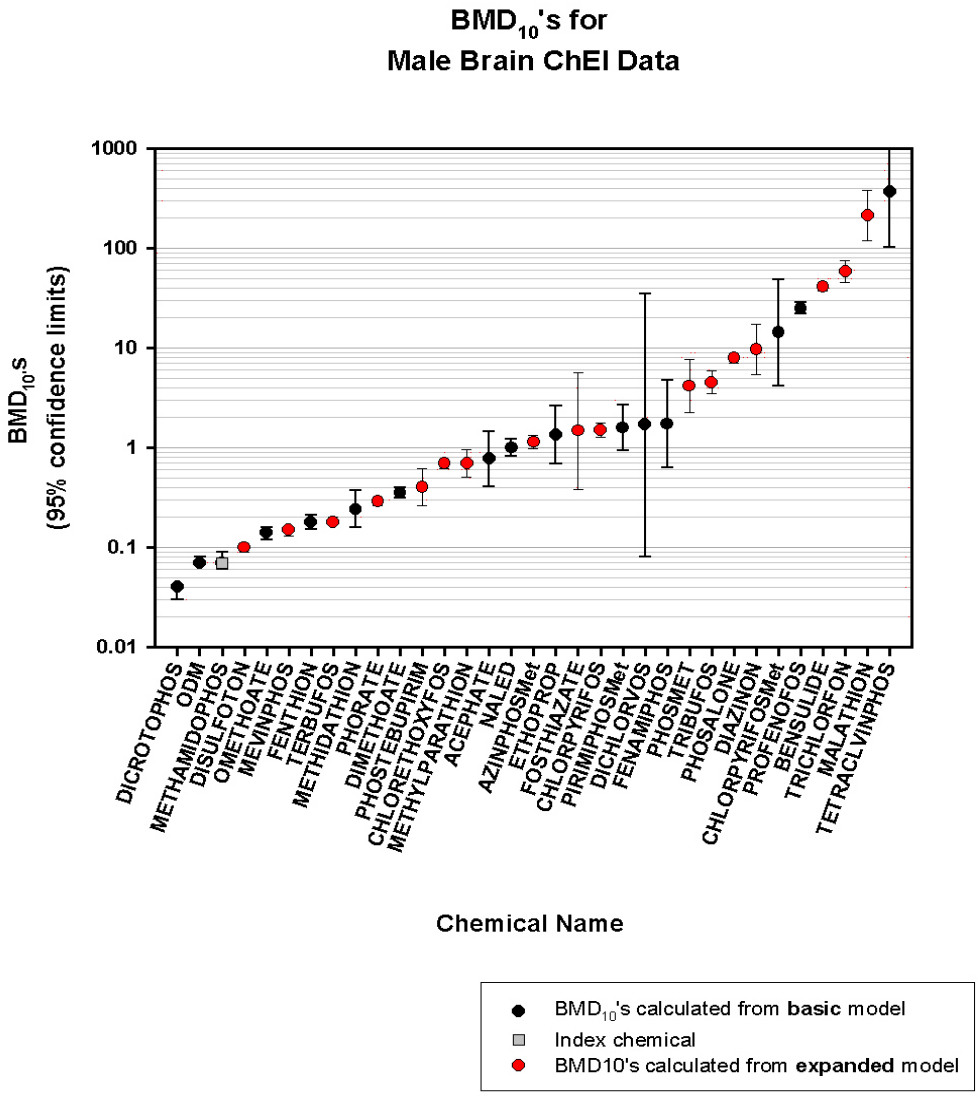

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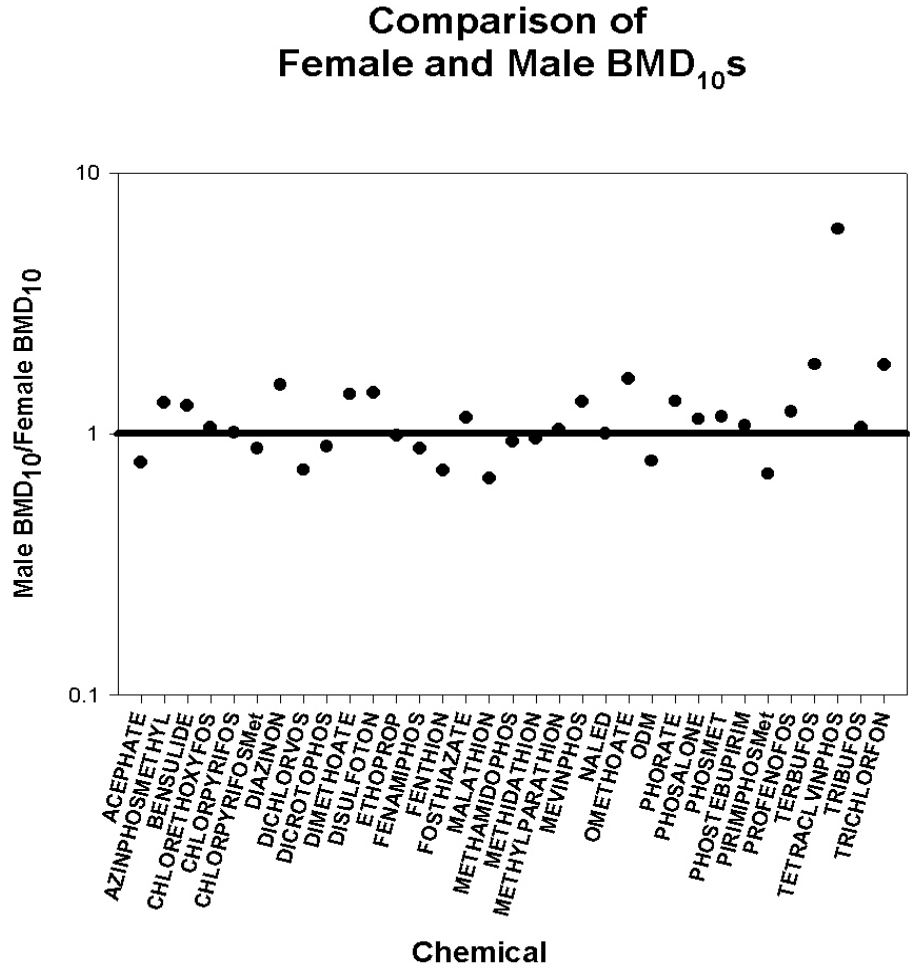
Figure I.B-5. Comparison of BMD_{10}s (mg/kg/day) for female and male brain ChE activity for 33 OPs



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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.

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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.

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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.

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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.

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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

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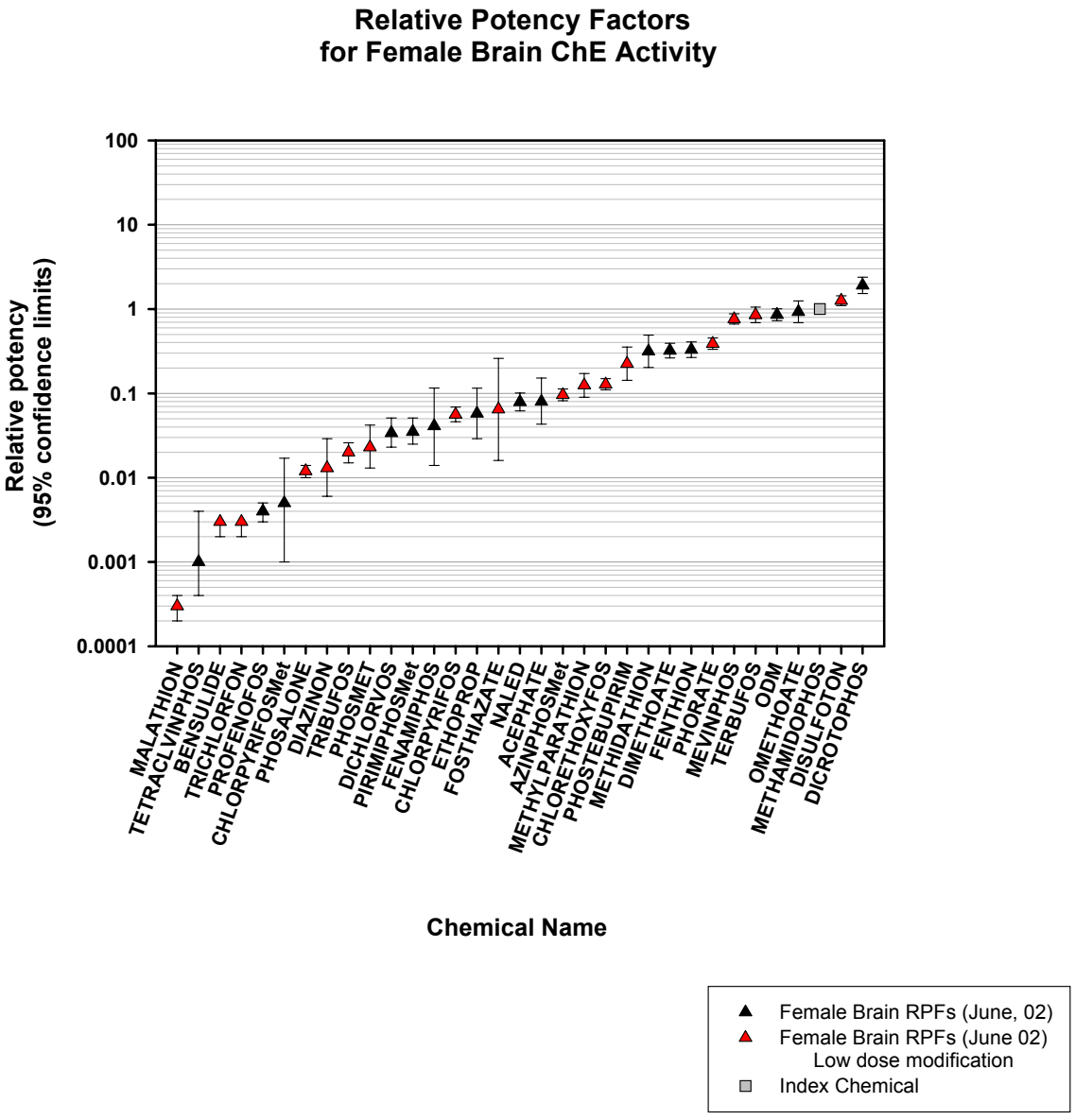
Figure I.B-6. Relative potency factors for female brain ChE activity for 33 OPs



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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

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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.