

A Note to Readers:

This draft report contains the most current acute and chronic toxicological information on the organophosphates for the purpose of conducting human health risk assessments. This report represents the Office of Pesticide Programs' science on hazard identification for the organophosphates at this point in time. However, it should be recognized that we are beginning a process of public comment on the full preliminary risk assessments for each of the organophosphate pesticides. Hazard identification is the first step of the risk assessment process and is subject to change based on information we receive in response to the full preliminary risk assessments.

Also contained in this document are some preliminary suggestions on the 10X margin of safety for children. The Pesticide Programs' FQPA Safety Factor Committee is refining these safety factors for the organophosphates based on our current science policy and standard operating procedures. Therefore, we caution against any use of this portion of the document out of context. This FOIA did also request the completed review from the FQPA Safety Factor Committee, which the Agency is currently working to complete and will make available shortly.

Indeed, scientific documents of this sort always reflect only the work and analysis conducted at the time they are produced. It is common and appropriate that, as new information becomes available and/or additional analyses are performed, the conclusions may change.

The U.S. food supply is among the safest in the world. Leading health experts recommend that people eat five servings of fruits and vegetables a day, along with a variety of foods. Through implementation of the Agency's tolerance reassessment program, as mandated by Food Quality Protection Act, the food supply will become even safer.

July 22, 1998

HAZARD ASSESSMENT OF THE ORGANOPHOSPHATES

REPORT OF THE
HAZARD IDENTIFICATION ASSESSMENT REVIEW COMMITTEE

HAZARD IDENTIFICATION ASSESSMENT REVIEW COMMITTEE

HEALTH EFFECTS DIVISION
OFFICE OF PESTICIDE PROGRAMS
U.S. ENVIRONMENTAL PROTECTION AGENCY

July 7 , 1998

Committee Members in Attendance

Members present were: Karl Baetcke, William Burnam, Steven Dapson (for Sue Makris), Karen Hamernik, Robert Fricke, Nancy McCarroll, Michael Metzger (Co-Chairman), Melba Morrow, John Redden, Jess Rowland (Executive Secretary) and Clark Swentzel (Chairman),

HED staff (non-members) who participated in this reassessment were: Kathleen Raffaele of Toxicology Branch 2 and William Sette of Science Analysis Branch.

FQPA Safety Committee members in attendance (as observers) were Ray Kent and Brenda Tarplee (Executive Secretary)

Report Preparation:

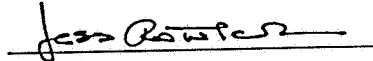

Jess Rowland
Executive Secretary

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I. INTRODUCTION

The Hazard Identification Assessment Review Committee (HIARC) convened on May 12, 13 and 14, 1998 for a comprehensive review of 40 Organophosphates which were reviewed by this Committee during September 97 thru May 1998. HIARC's objective for this reassessment was to evaluate the following factors for consistency: 1) assessment of the neurotoxicity studies for evidence of neuropathology; 2) quantitative and qualitative assessment of the developmental and reproductive toxicity studies for enhanced susceptibility to infants and children as required by FQPA; 3) use of literature data in hazard identification; 4) identification of data gaps; 5) the criteria used in requiring a developmental neurotoxicity study; 6) recommendations on FQPA Safety Factor to the FQPA Safety Committee; 7) the toxicological endpoints and doses selected for acute and chronic dietary as well as occupational and residential exposure risk assessments; 8) selection of the dermal absorption factors for dermal risk assessments; and 9) application of FIFRA-related Uncertainty Factors.

The toxicology database was evaluated for the neurotoxic, developmental and reproductive toxic potential of the 40 organophosphates. Of the 40, the data base was inadequate for Chlorpyrifos methyl, Dicrotophos and Temephos and no data were available for Fonophos, Isazophos and Sulfotepp.

In order to maintain consistency, determination of susceptibility was performed for each pesticide on a case-by-case basis by always employing a weight-of-the evidence assessment. The two primary concerns or factors that contributed to the decision making process were: 1) enhanced susceptibility of the developing organism or offspring as observed in the prenatal developmental toxicity studies in rodents and non-rodents, and the multi-generation reproduction studies in rodents in conjunction with the rest of the toxicity data base; as well as evidence of neuropathology seen in the hen and rat neurotoxicity studies and other neuropathological findings (e.g., decreases in brain weights), which might be indicative of enhanced susceptibility of the developing nervous system and 2) uncertainty related to the absence of a complete data base (e.g., neurotoxicity studies in hen and/or rats) for the assessment of potential effects on infants and children. The HIARC did not consider these two factors to be separate distinct entities, but rather, they represented two aspects of an information continuum that defined the uncertainties in the scientific knowledge of the effects of any pesticide on the human population. Thus in recommending the FQPA Safety Factor, an evaluation of uncertainty and the susceptibility issues may be altered by weight-of-the-evidence considerations. This could include such factors as: the severity of toxic effects on the offspring; the presence of confounding factors such as severe maternal toxicity; a characterization of the dose response curve for effects related to offspring; concordance of treatment-related effects between species and/or strains; data or knowledge of mode of action; and the level of confidence in the data base or critical studies.

II. EVALUATION OF NEUROTOXICITY

The neurotoxicity data requirements include an acute delayed neurotoxicity study in hens, an acute neurotoxicity study in rats and a subchronic neurotoxicity study in rats.

The acute delayed neurotoxicity study in hens was evaluated for organophosphate induced delayed neurotoxicity (OPIDN), neurochemical assessment of inhibition of acetylcholinesterase and neurotoxic esterase (NTE) and histopathological assessment of brain, peripheral nerve, and spinal cord. The acute and the subchronic neurotoxicity studies in rats were usually evaluated for cholinesterase inhibition, neurobehavioral effects (FOB), and histopathology of the central and peripheral nervous system following single (acute) or repeated (subchronic) exposures.

All of the organophosphates are neurotoxic in that they may cause cholinesterase inhibition and related clinical signs, up to and including death following exposure. Organophosphates also may cause neuropathology of the visual system or effects on cognitive function, i.e. learning and memory as well as other effects on the nervous system. While the acute and subchronic neurotoxicity studies might show some gross effects on the visual system or sensory function, these and other effects were not systematically evaluated at this meeting since the cause/effect relationship between cholinesterase inhibition and visual system effects has not been verified.

Of the 33 organophosphates evaluated, evidence of neuropathology was seen for the following:

CHEMICAL	EVIDENCE OF NEUROPATHOLOGY
CHLORPYRIFOS	Published studies have reported OPIDN in humans and animals (at lethal doses) and there have been case reports that indicate possible correlation of neurophysiological effects in humans.
METHAMIDOPHOS	Positive neurotoxic esterase in a subchronic toxicity study in hens and delayed peripheral neuropathy in humans as well as polyneuropathy in hens at extremely high dose levels (greatly in excess of the hen LD ₅₀) reported in published studies.
METHYL PARATHION	Neuropathology in acute and subchronic neurotoxicity studies in rats as well as in chronic toxicity studies in rats.
NALED	In an acute delayed neurotoxicity study, axonal degeneration of the spinal cord was seen following a single oral dose. However, no neuropathy was seen after repeated dosing in the subchronic neurotoxicity study in hens. No evidence of neuropathology was seen following single or repeated dosing in rats.
ODM	Evidence of neuropathology was seen in hens following a single dose but no neuropathology was seen following repeated dose in hens. No evidence of neuropathology was seen following single or repeated dosing in rats.
TRIBUFOS	Evidence of OPIDN and neuropathology following repeated dermal applications in a subchronic delayed neurotoxicity study in hens
TRICHLORFON	Evidence of OPIDN and neuropathology in the acute delayed neurotoxicity study in hens and neuropathology in the subchronic neurotoxicity study in hens.

A study that evaluates the effects on the NTE is required for the following chemicals. The lack of NTE data in an otherwise acceptable negative hen study is not considered a major data gap but rather characterized as the need for confirmatory data (i.e., data to confirm that an effect on NTE does not occur)::

ORGANOPHOSPHATES THAT REQUIRE ASSESSMENT OF NTE				
AZINPHOS METHYL	CADUSAFOS ⁽¹⁾	COUMAPHOS	DIMETHOATE	DISULFOTON ⁽¹⁾
ETHION	ETHOPROP	FENITROTHION	FENAMIPHOS	ISOFENFOS
METHIDATHION	METHYL PARATHION	PHORATE	PHOSTEBUPIRIM	PIRMIMIPHOS METHYL ⁽¹⁾
PROFENFOS	PROPETAMPHOS	TERBUFOS	TETRACHLOR-VINPHOS	TRIBUFOS
TRICHLORFON	⁽¹⁾ Data gap exists for an acute delayed neurotoxicity study for these four chemicals.			

III. DETERMINATION OF SUSCEPTIBILITY

The HIARC evaluated enhanced susceptibility of fetuses as compared to maternal animals following *in utero* exposure in rats and rabbits as well as the enhanced susceptibility of pups as compared to adults in the two generation toxicity study in rats. For most of the organophosphates, following *in utero* exposure developmental effects were observed at or above treatment levels which resulted in evidence of maternal toxicity. Following pre and/or post natal exposure in the two-generation reproduction toxicity study, general, effects in the offspring were most often manifested as decreased pup viability at doses that caused considerable inhibition of cholinesterase activity and cholinergic signs in the parental animals. Since the effects seen in the offspring (e.g., decreased pup viability) are confounded by the presence of maternal toxicity, it is difficult to regard the offspring effects as indicative of developmental toxicity or enhanced susceptibility of young animals. In addition, in the prenatal developmental toxicity studies, the parameters evaluated are not comparable between the dams and the fetuses. While the dams are routinely evaluated for survival, clinical signs, body weight, body weight gain and food consumption and certain reproductive parameters during the cesarian section, the fetuses undergo much more critical and more detailed evaluation. The primary effect for the organophosphates is the inhibition of cholinesterase activity. For most of the pesticides, however, comparative cholinesterase inhibition data for the dams and the pups were not available thus precluding an evaluation of susceptibility based on this endpoint. When these data (i.e., comparative cholinesterase) were available, however, no evidence of enhanced susceptibility was seen in the pups compared to maternal animals (i.e., cholinesterase inhibition occurred at the same doses in the pups as in the parental animals).

1. Prenatal Developmental Toxicity Study in Rats

- (a) The NOELs, LOELs and endpoints selected for maternal and developmental toxicity in the prenatal developmental toxicity studies in rats are provided in **Attachment 1**. No evidence of enhanced susceptibility was observed for 33 of 40 organophosphate following *in utero* exposure to pregnant rats. For these chemicals, there was no evidence of effects being produced in fetuses at lower doses as compared to maternal animals nor was there evidence of an increase in severity of effects at or below maternally toxic doses. Of the remaining 7, an acceptable prenatal developmental toxicity study in rats was not available for Chlorpyrifos methyl, Dicrotophos, Temephos and Trichlorfon, and no data were available for Fonophos, Isazophos and Sulfotepp. It is noted that in pre/postnatal studies published in the open literature, evidence of enhanced susceptibility was demonstrated in rats for Chlorpyrifos following oral, subcutaneous and intraperitoneal administration and for Methyl Parathion via the subcutaneous and intraperitoneal routes.
- (b) For four chemicals (tabulated below), the NOELs and LOELs were the same for maternal and developmental toxicity (i.e., fetal effects were seen at the same dose that caused maternal toxicity) but the developmental (fetal) effects appeared to be more severe. Following a qualitative evaluation of the effects observed, the HIAR concluded that fetal effects occurred at dose levels causing similar or more severe maternal toxicity. The rationale for this conclusion is provided for each chemical.

DEVELOPMENTAL TOXICITY SEEN IN THE PRESENCE OF MATERNAL TOXICITY	
CADUSAFOS	Decreased fetal body weights occurred at levels causing cholinergic signs in the dams characterized as tremors, muscle fasciculations, exophthalmus and decreased activity.
FENTHION	Increased post implantation losses were not accompanied by decreased litter sizes and no developmental effects were seen in the other parameters examined. Dams exhibited clinical signs and decreased body weights at the same dose that induced fetal effects. In addition, plasma, erythrocyte and brain cholinesterase inhibition was seen in dams at doses lower than those causing fetal effects indicating that the dams were under "stress".
FENITROTHION	At the dose that caused severe maternal toxicity characterized as tremors and decreases in body weight and body weight gains, there was an increased incidence of fetuses with skeletal variation.
TERBUFOS	The biological significance of the fetal effects (increases in early fetal resorptions and postimplantation losses) are questionable since similar effects (i.e., decreased litter size) were not seen in the two-generation study in rats. In addition, based on the results of other studies with this chemical, substantial cholinesterase inhibition may have occurred in dams (not measured in this study) and thus most likely contributed to the fetal effects.

2. Prenatal Developmental Toxicity Study in Rabbits

- (a) The NOELs, LOELs and endpoints selected for the maternal and development toxicity in the prenatal developmental toxicity study in rabbits are provided **Attachment 2**. No evidence of enhanced susceptibility was observed for 34 of 4 organophosphates following *in utero* exposure to pregnant rabbits. For the chemicals, there was no evidence of effects being produced in fetuses at lower doses as compared to maternal animals nor was there evidence of an increase in severity effects at or below maternally toxic doses. Of the remaining 6, an acceptable prenatal developmental toxicity study in rabbits was not available for Chlorpyrifos methyl, Dicrotophos and Temephos, and no data was available for Fonophos, Isazophos and Sulfotepp.
- (b) For five chemicals (tabulated below), the NOELs and LOELs were the same for maternal and developmental toxicity (i.e., fetal effects were seen at the same dose that caused maternal toxicity) but the developmental (fetal) effects appeared to be more severe. Following a qualitative evaluation of the effects observed, the HIAF concluded that fetal effects occurred at dose levels causing similar or more severe maternal toxicity. The rationale for this conclusion is provided for each chemical.

DEVELOPMENTAL TOXICITY SEEN IN THE PRESENCE OF MATERNAL TOXICITY	
CADUSAFOS	Severe maternal toxicity manifested as increased mortality and cholinergic signs at the same dose that caused an increase in total number of resorptions, decrease in total number of fetuses and fetal death.
ETHYL PARATHION	The same dose that caused maternal deaths, increased moribundity as well as decrease in body weight and body weight gains also caused a decrease in litter size.
MALATHION	The slight increase in mean resorption sites was not accompanied by alteration in litter size and occurred at the same doses that caused decreased maternal body weights.
PHOSMET	The dose that induced clinical signs and decreased body weight in dams also resulted skeletal variations observed in the fetuses .
PROPETAMPHOS	The increased resorptions were not accompanied by decreases in litter size.

3. Two-Generation Reproduction Study in Rats

- (a) The NOELs, LOELs and endpoints selected for the parental systemic and offspring toxicity in the two-generation reproduction study is provided in **Attachment 3**. No evidence of enhanced susceptibility was observed for 35 of 40 organophosphate following pre and/or post natal exposure in the two-generation reproduction study in rats (i.e., effects noted in offspring occurred at maternally toxic doses or higher). Of the remaining 5, an acceptable reproduction toxicity study in rats was not available for Chlorpyrifos methyl, and Temephos and no data were available for Fonophos, Isazophos and Sulfotepp.
- (b) For the following chemicals, the NOELs and LOELs were same for parental system toxicity and offspring toxicity (i.e., offspring effects were seen at the same dose that caused parental effects) but the offspring (pup) effects appeared to be more severe. Following a qualitative evaluation of the effects observed, the HIARC concluded that the effects in the pups occurred at dose levels causing similar or more severe parental systemic toxicity. The rationale for this conclusion is provided for each chemical.

OFFSPRING TOXICITY SEEN IN THE PRESENCE OF PARENTAL TOXICITY	
ACEPHATE	Decreased viability index and decreased pup body weight gain were seen at the same dose that caused parental toxicity characterized by clinical signs (alopecia and soft stools) and decreased body weight gain. Although the clinical signs in parental animals are not severe, comparison to other studies (subchronic) indicated that cholinesterase inhibition (not measured in this study) would have occurred in dams at the dose that caused offspring toxicity and thus most likely contributed to offspring toxicity. Also, the offspring effects were seen in the first generation only and not repeated in the second generation (i.e., not a consistent finding).
DICHLORVOS	The abnormal estrous cycles observed in maternal animals most likely contributed to the offspring effects (reduced dams bearing litters, decreases in fertility and pregnant indices) observed at the same dose.
DIAZINON	Cholinesterase inhibition (ChEI) has occurred at lower doses with this chemical in other toxicity studies. ChEI was not measured in parental animals in the reproduction study. Therefore it is postulated that ChEI occurred in the maternal animals at the same doses causing pup mortality and decreased pup weight gain observed during lactation at which time the pup were exposed to the chemical via the milk.
FENITROTHION	The dose that caused severe parental systemic toxicity (decreases in body weight and body weight gain as well as food consumption) was also associated with offspring toxicity (decreases in fertility index, number of implantation sites and viability) in one generation. However, similar offspring toxicity was not seen in the second generation (i.e., not replicated in the second generation).
ISOFENPHOS	Offspring toxicity manifested as increased pup mortality (reductions in lactation indices and mean litter size) and clinical signs (small to very small emaciated pups) were observed at the same dose that caused parental systemic toxicity (inhibition of plasma, erythrocyte and brain cholinesterase). The offspring toxicity was not considered to be more severe since 1) the effects were observed only after postnatal Day 14 and not on other days (i.e., a single occurrence) and thus the biological significance is not known; 2) during that period (i.e., later portion of lactation), young rats consume approximately twice the diet per unit body weight as an adult rat consumes. Estimation of the test substance intake in pre-weaning animals is likely to be more than double the adult intake because of the availability of the test material both via the milk (lactation) and food, particularly after the mid point of lactation. and 3) the dose that caused the offspring toxicity also caused cholinesterase inhibition (all three compartments) in parental animals.

OFFSPRING TOXICITY SEEN IN THE PRESENCE OF PARENTAL TOXICITY	
MALATHION	The decreases in the F1a and F2b pup body weight occurred at a lower dose than the dose that caused parental toxicity; this was not a true indication of enhanced susceptibility because: 1) pup body weight decrements were primarily observed at postnatal Day 21; 2) during that period, young rats consume approximately twice the diet per unit body weight as an adult rat consumes; and 3) the estimation of the test substance intake in pre-weaning animals is likely to be more than double the adult intake because of the availability of the test material both via the milk (lactation) and food, particularly after the mid point of lactation.
METHAMIDAPHOS	Substantial cholinesterase inhibition was seen at lower doses in other toxicity studies conducted with rats indicating that cholinesterase inhibition most likely occurred in parental animals at the dose that caused offspring toxicity (decreased pup viability). Also this effect was seen only on postnatal Day 14 and only in one generation. It is noted that decreased pup viability was also seen with Acephate, a related organophosphate, at the same dose that caused parental toxicity.
ODM	The same dose that caused cholinesterase inhibition in parental animals also caused the offspring toxicity (decreased viability index, decreased litter size at birth and decreased pup body weight gain during lactation). In addition, no enhanced susceptibility was seen in adults vs. fetuses based on comparative cholinesterase inhibition data (i.e., cholinesterase inhibition occurred at the same doses in the pups and the parental animals).
PHORATE	The same dose that caused severe parental toxicity (tremors and inhibition of plasma and brain cholinesterase activity) also caused decreased pup survival and pup body weight.

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IV. SUMMARY OF FQPA ASSESSMENT

CHEMICAL	ACUTE DELAYED NEUROTOXICITY HEN	MAMMALIAN NEUROTOXICITY - RAT		EVIDENCE OF ENHANCED SUSCEPTIBILITY IN DEVELOPMENTAL STUDIES RAT & RABBIT	EVIDENCE OF ENHANCED SUSCEPTIBILITY IN THE 2-GENERATION REPRODUCTION RAT	REQUIREMENT OF A DEVELOPMENTAL NEUROTOXICITY STUDY IN RATS	DATA GAPS
		ACUTE	SUBCHRONIC				
1) ACEPHATE	OPIDN: Negative Neuropathology: Negative NTE: Negative <u>Literature Data</u> NTE: Positive	Neuropathology: Negative Cholinesterase activity measured (ChEI): Yes	Neuropathology: Negative ChEI measured: Yes	No increased Susceptibility	No increased Susceptibility	Not Required	None
2) AZINPHOS METHYL	OPIDN: Negative Neuropathology: Negative Confirmatory NTE Study Required	Neuropathology: Negative ChEI measured: Yes	Neuropathology: Negative ChEI measured: Yes	No increased Susceptibility	No increased Susceptibility	Not Required	None
3) BENSULIDE	OPIDN: Negative NTE: Negative	Neuropathology: Negative ChEI measured: Yes	Study Waived	No increased Susceptibility	No increased Susceptibility	Not Required	None

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CHEMICAL	ACUTE DELAYED NEUROTOXICITY HEN	MAMMALIAN NEUROTOXICITY - RAT		EVIDENCE OF ENHANCED SUSCEPTIBILITY IN DEVELOPMENTAL STUDIES RAT & RABBIT	EVIDENCE OF ENHANCED SUSCEPTIBILITY IN THE 2-GENERATION REPRODUCTION RAT	REQUIREMENT OF A DEVELOPMENTAL NEUROTOXICITY STUDY IN RATS	DATA GAPS
		ACUTE	SUBCHRONIC				
4) CADUSAFOS	Inadequate Study	Not available	Not available	No increased Susceptibility	No increased Susceptibility	Reserved Pending Acute Hen, Acute & 90-day rat neurotoxicity studies	Acute-Hen Acute -Rat Neurotoxicity 90-Day -Rat Neurotoxicity
	(No histopathology or NTE data) Confirmatory NTE Study Required	No data to assess neurotoxicity, cholinesterase inhibition, behavioral effects, or neuropathology					
5) CHLOR- ETHOXYFOS	OPIDN: Negative	Neuropathology: Negative	Waived since other studies showed no evidence of neuropathology	No increased Susceptibility	No increased Susceptibility	Not Required	None
	Neuropathology: Negative	ChEI measured: Yes	Neuropathology: Negative ChEI measured: Yes				
6) CHLORPYRIFOS	OPIDN: Negative	Neuropathology: Negative	Neuropathology: Negative	No increased Susceptibility <u>Literature Data</u> Enhanced susceptibility seen in young rats (ChEI, behavioral and other developmental neurotoxic effects).	No increased Susceptibility	Required Literature Data OPIDN: Positive	Develop- mental Neurotoxicity Study in Rats
	<u>Literature Data</u> OPIDN: Positive NTE: Positive	ChEI measured: Yes	ChEI measured: Yes				

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CHEMICAL	ACUTE DELAYED NEUROTOXICITY HEN	MAMMALIAN NEUROTOXICITY - RAT		EVIDENCE OF ENHANCED SUSCEPTIBILITY IN DEVELOPMENTAL STUDIES RAT & RABBIT	EVIDENCE OF ENHANCED SUSCEPTIBILITY IN THE 2-GENERATION REPRODUCTION RAT	REQUIREMENT OF A DEVELOPMENTAL NEUROTOXICITY STUDY IN RATS	DATA GAPS
		ACUTE	SUBCHRONIC				
7) CHLORPYRIFOS METHYL	Equivocal evidence of neuropathology	Not available	Not available	Studies Unacceptable To Assess Susceptibility	Study Unacceptable To Assess Susceptibility	Can Not Be Ascertained Due to Inadequate Data Base	Acute Rat 90-Day Rat Neurotoxicity Develop- mental -Rat & Rabbit 2-Generation Reproduction
		No data to assess neurotoxicity, cholinesterase inhibition, behavioral effects, or neuropathology					
8) COUMAPHOS	OPIDN: Negative Neuropathology: Negative Confirmatory NTE Study Required	Not available	Not available	No increased Susceptibility	No increased Susceptibility	Reserved Pending Acute & 90-day neurotoxicity studies	Acute - Rat 90-Day-Rat

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CHEMICAL	ACUTE DELAYED NEUROTOXICITY HEN	MAMMALIAN NEUROTOXICITY - RAT		EVIDENCE OF ENHANCED SUSCEPTIBILITY IN DEVELOPMENTAL STUDIES RAT & RABBIT	EVIDENCE OF ENHANCED SUSCEPTIBILITY IN THE 2-GENERATION REPRODUCTION RAT	REQUIREMENT OF A DEVELOPMENTAL NEUROTOXICITY STUDY IN RATS	DATA GAPS
		ACUTE	SUBCHRONIC				
9) DDTVP	Acute OPIDN: Equivocal 28-day Neuropathology: Negative NTE: Negative	Neuropathology Negative ChEI measured: Yes	Neuropathology Negative ChEI measured: Yes	No increased Susceptibility	No increased Susceptibility	Reserved Pending results of developmental toxicity study in Guinea Pigs requested by HIARC. See HIARC Report.	None
10) DIAZINON	OPIDN: Negative Neuropathology: Negative NTE: Negative	Neuropathology Negative ChEI measured: Yes	Neuropathology Negative ChEI measured: Yes	No increased Susceptibility	No increased Susceptibility	Not Required	None
11) DICROTOPHOS	Unacceptable study	Neuropathology: Negative	Neuropathology Negative	FQPA ASSESSMENT COULD NOT BE MADE DUE TO INADEQUATE DATA BASE			

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CHEMICAL	ACUTE DELAYED NEUROTOXICITY HEN	MAMMALIAN NEUROTOXICITY - RAT		EVIDENCE OF ENHANCED SUSCEPTIBILITY IN DEVELOPMENTAL STUDIES RAT & RABBIT	EVIDENCE OF ENHANCED SUSCEPTIBILITY IN THE 2-GENERATION REPRODUCTION RAT	REQUIREMENT OF A DEVELOPMENTAL NEUROTOXICITY STUDY IN RATS	DATA GAPS
		ACUTE	SUBCHRONIC				
12) DIMETHOATE	OPIDN: Negative Neuropathology: Negative NTE: Equivocal Confirmatory NTE study Required	Neuropathology: Negative ChEI measured: No.	Neuropathology: Negative ChEI measured: Yes	No increased Susceptibility	No increased Susceptibility	Not Required	None
13) DISULFOTON	Unacceptable Study	Neuropathology: Negative ChEI measured: Yes	Neuropathology: Equivocal ChEI measured: Yes	No increased Susceptibility	No increased Susceptibility	Reserved Pending Acute Hen study	Acute Hen
14) ETHION	OPIDN: Negative Neuropathology: Negative Confirmatory NTE Study Required	Neuropathology: Negative ChEI measured: No	Equivocal neuropathology at high dose ChEI measured: No	No increased Susceptibility	No increased Susceptibility	Not required	None

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CHEMICAL	ACUTE DELAYED NEUROTOXICITY HEN	MAMMALIAN NEUROTOXICITY - RAT		EVIDENCE OF ENHANCED SUSCEPTIBILITY IN DEVELOPMENTAL STUDIES RAT & RABBIT	EVIDENCE OF ENHANCED SUSCEPTIBILITY IN THE 2-GENERATION REPRODUCTION RAT	REQUIREMENT OF A DEVELOPMENTAL NEUROTOXICITY STUDY IN RATS	DATA GAPS
		ACUTE	SUBCHRONIC				
15) ETHOPROP	OPIDN: Negative Neuropathology: Negative NTE requested by RfD Committee 5/96	Neuropathology: Negative ChEI measured: Yes	Neuropathology: Negative ChEI measured: Yes	No increased Susceptibility	No increased Susceptibility	Not Required	None
16) ETHYL PARATHION	OPIDN: Negative NTE : Negative Neuropathology: Negative	Neuropathology: Negative ChEI measured: Yes	Neuropathology: Negative ChEI measured: Yes	No increased Susceptibility	No increased Susceptibility	Not Required	None
17) FENAMIPHOS	OPIDN: Negative Neuropathology: Negative Confirmatory NTE Study Required	Neuropathology: Negative ChEI measured: Yes	Neuropathology: Negative ChEI measured: Yes	No increased Susceptibility	No increased Susceptibility	Not required	None

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CHEMICAL	ACUTE DELAYED NEUROTOXICITY HEN	MAMMALIAN NEUROTOXICITY - RAT		EVIDENCE OF ENHANCED SUSCEPTIBILITY IN DEVELOPMENTAL STUDIES RAT & RABBIT	EVIDENCE OF ENHANCED SUSCEPTIBILITY IN THE 2-GENERATION REPRODUCTION RAT	REQUIREMENT OF A DEVELOPMENTAL NEUROTOXICITY STUDY IN RATS	DATA GAPS
		ACUTE	SUBCHRONIC				
18) FENTROTHION	OPIDN: Negative Neuropathology: Negative Confirmatory NTE Study Required	Neuropathology: Negative ChEI measured: No	Neuropathology: Negative ChEI measured: Yes	No increased Susceptibility	No increased Susceptibility	Not required	None
19) FENTHION	Acute (Oral & Dermal) OPIDN: Negative Neuropathology: Negative NTE: Negative Subchronic OPIDN: Negative Neuropathology: Negative	Neuropathology: Negative ChEI measured: Yes	Neuropathology: Negative ChEI measured: Yes	No increased Susceptibility	No increased Susceptibility	No Required	None
20) FONOFOS	NO DATA AVAILABLE						

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CHEMICAL	ACUTE DELAYED NEUROTOXICITY HEN	MAMMALIAN NEUROTOXICITY - RAT		EVIDENCE OF ENHANCED SUSCEPTIBILITY IN DEVELOPMENTAL STUDIES RAT & RABBIT	EVIDENCE OF ENHANCED SUSCEPTIBILITY IN THE 2-GENERATION REPRODUCTION RAT	REQUIREMENT OF A DEVELOPMENTAL NEUROTOXICITY STUDY IN RATS	DATA GAPS
		ACUTE	SUBCHRONIC				
21) ISOFENPHOS	<u>Acute</u> OPIDN: Negative Neuropathology: Negative Confirmatory NTE Study Required <u>Subchronic</u> OPIDN: Negative Neuropathology: Negative	Neuropathology: Negative ChEI measured: Yes	Neuropathology: Negative ChEI measured: Yes	No increased Susceptibility	No increased Susceptibility	Not Required	None
22) TRIUMPH (ISAZOPHOS)	NO DATA AVAILABLE						

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CHEMICAL	ACUTE DELAYED NEUROTOXICITY HEN	MAMMALIAN NEUROTOXICITY - RAT		EVIDENCE OF ENHANCED SUSCEPTIBILITY IN DEVELOPMENTAL STUDIES RAT & RABBIT	EVIDENCE OF ENHANCED SUSCEPTIBILITY IN THE 2-GENERATION REPRODUCTION RAT	REQUIREMENT OF A DEVELOPMENTAL NEUROTOXICITY STUDY IN RATS	DATA GAPS
		ACUTE	SUBCHRONIC				
23) MALATHION	OPIDN: Negative	Neuropathology: Negative	Neuropathology: Negative	No increased Susceptibility	No increased Susceptibility	Not required	None
	Neuropathology: Negative <u>Literature Data</u> NTE:-Negative	ChEI measured: Yes	ChEI measured: Yes				

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CHEMICAL	ACUTE DELAYED NEUROTOXICITY HEN	MAMMALIAN NEUROTOXICITY - RAT		EVIDENCE OF ENHANCED SUSCEPTIBILITY IN DEVELOPMENTAL STUDIES RAT & RABBIT	EVIDENCE OF ENHANCED SUSCEPTIBILITY IN THE 2-GENERATION REPRODUCTION RAT	REQUIREMENT OF A DEVELOPMENTAL NEUROTOXICITY STUDY IN RATS	DATA GAPS
		ACUTE	SUBCHRONIC				
24) METHA- MIDOPHOS	<u>Acute & Subchronic</u> OPIDN: Negative	Neuropathology: Negative	Neuropathology: Negative	No increased Susceptibility	No increased Susceptibility	Required Positive NTE Polyneuropathy in hens and Delayed peripheral neuropathy in humans in published studies	Develop- mental Neurotoxicity Study in Rats
	Neuropathology: Negative	ChEI measured: Yes	ChEI measured: Yes				
	NTE: Negative (Acute) Positive (subchronic)						
	<u>Racemate & Enantiomers</u>						
	Positive for OPIDN at extremely high levels						
	<u>Literature Data</u> Polyneuropathy & peripheral neuropathy in humans at high doses.						

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CHEMICAL	ACUTE DELAYED NEUROTOXICITY HEN	MAMMALIAN NEUROTOXICITY - RAT		EVIDENCE OF ENHANCED SUSCEPTIBILITY IN DEVELOPMENTAL STUDIES RAT & RABBIT	EVIDENCE OF ENHANCED SUSCEPTIBILITY IN THE 2-GENERATION REPRODUCTION RAT	REQUIREMENT OF A DEVELOPMENTAL NEUROTOXICITY STUDY IN RATS	DATA GAPS
		ACUTE	SUBCHRONIC				
25) METHIDATHION	OPIDN: Negative Neuropathology: Negative Confirmatory NTE Study Required	Neuropathology: Negative ChEI measured: Yes	Negative for neuropathology ChEI measured: Yes	No increased Susceptibility	No increased Susceptibility	Not required	None
26) METHYL PARATHION	OPIDN: Negative Neuropathology: Negative Confirmatory NTE Study Required	Positive for neuropathology ChEI measured: Yes	Equivocal for neuropathology ChEI measured: Yes	No increased Susceptibility in Subdivision F studies. <u>Literature Data</u> Qualitative evidence of increased Susceptibility seen in open literature rat studies via subcutaneous. & intraperitoneal routes at high doses.	No increased Susceptibility	Required Positive neuropathology in acute rat. Equivocal neuropathology in subchronic rat Positive Neuropathology in Chronic Rat and 1-Year Rat	Develop- mental Neurotoxicity Study in Rats

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CHEMICAL	ACUTE DELAYED NEUROTOXICITY HEN	MAMMALIAN NEUROTOXICITY - RAT		EVIDENCE OF ENHANCED SUSCEPTIBILITY IN DEVELOPMENTAL STUDIES RAT & RABBIT	EVIDENCE OF ENHANCED SUSCEPTIBILITY IN THE 2-GENERATION REPRODUCTION RAT	REQUIREMENT OF A DEVELOPMENTAL NEUROTOXICITY STUDY IN RATS	DATA GAPS
		ACUTE	SUBCHRONIC				
27) NALED	Acute	Neuropathology: Negative	Neuropathology: Negative	No increased Susceptibility	No increased Susceptibility	Not Required	None
	OPIDN: Positive	ChEI measured: No	ChEI measured: No				
	Neuropathology: Positive						
	NTE: Negative						
	Subchronic						
	OPIDN: Negative						

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CHEMICAL	ACUTE DELAYED NEUROTOXICITY HEN	MAMMALIAN NEUROTOXICITY - RAT		EVIDENCE OF ENHANCED SUSCEPTIBILITY IN DEVELOPMENTAL STUDIES RAT & RABBIT	EVIDENCE OF ENHANCED SUSCEPTIBILITY IN THE 2-GENERATION REPRODUCTION RAT	REQUIREMENT OF A DEVELOPMENTAL NEUROTOXICITY STUDY IN RATS	DATA GAPS
		ACUTE	SUBCHRONIC				
28) ODM	<u>Acute</u> Neuropathology: Positive Confirmatory NTE Study Required	Neuropathology: Negative ChEI measured: Yes	Neuropathology: Negative ChEI measured: Yes	No increased Susceptibility	No increased Susceptibility	Not Required	Mouse Specific Locus Test.
	<u>Subchronic</u> Neuropathology: Negative	Not available	Not available	No increased Susceptibility	No increased Susceptibility	Reserved Pending Acute & 90-day rat neurotoxicity studies	Acute-Rat Neurotoxicity 90-day Rat Neurotoxicity
29) PHORATE	OPIDN: Negative Neuropathology: Negative Confirmatory NTE Study Required.	No data to assess neurotoxicity, cholinesterase inhibition, behavioral effects, or neuropathology					

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CHEMICAL	ACUTE DELAYED NEUROTOXICITY HEN	MAMMALIAN NEUROTOXICITY - RAT		EVIDENCE OF ENHANCED SUSCEPTIBILITY IN DEVELOPMENTAL STUDIES RAT & RABBIT	EVIDENCE OF ENHANCED SUSCEPTIBILITY IN THE 2-GENERATION REPRODUCTION RAT	REQUIREMENT OF A DEVELOPMENTAL NEUROTOXICITY STUDY IN RATS	DATA GAPS
		ACUTE	SUBCHRONIC				
30) PHOSMET	OPIDN: Negative	Not available	Not available	No increased Susceptibility	No increased Susceptibility	Reserved Pending Acute & 90-day rat neurotoxicity studies & Confirmation of results of hen studies	Acute-Rat Neurotoxicity 90-day Rat Neurotoxicity
	Neuropathology: Negative NTE: Negative Need re-review	No data to assess neurotoxicity, cholinesterase inhibition, behavioral effects, or neuropathology					
31) PHOSTE- BUPIRIM	OPIDN: Negative	Not available	Not available	No increased Susceptibility	No increased Susceptibility	Reserved Pending Acute & 90-day rat neurotoxicity studies	Acute-Rat Neurotoxicity 90-day Rat Neurotoxicity
	Neuropathology: Negative Confirmatory NTE Study Required	No data to assess neurotoxicity, cholinesterase inhibition, behavioral effects, or neuropathology					
32) PIRIMIPHOS- METHYL	No Acute study	Neuropathology: Negative	Neuropathology: Negative	No increased Susceptibility	No increased Susceptibility	Reserved Pending Acute Hen & Chronic Dog/Rat	Acute-Hen Chronic Toxicity-Dog
	Subchronic: Unacceptable	ChEI measured: Yes	ChEI measured: Yes				
							Chronic Toxicity-Rat

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CHEMICAL	ACUTE DELAYED NEUROTOXICITY HEN	MAMMALIAN NEUROTOXICITY - RAT		EVIDENCE OF ENHANCED SUSCEPTIBILITY IN THE DEVELOPMENTAL STUDIES RAT & RABBIT	EVIDENCE OF ENHANCED SUSCEPTIBILITY IN THE 2-GENERATION REPRODUCTION RAT	REQUIREMENT OF A DEVELOPMENTAL NEUROTOXICITY STUDY IN RATS	DATA GAPS
		ACUTE	SUBCHRONIC				
33) PROFENFOS	OPIDN: Negative Neuropathology: Negative Confirmatory NTE Study Required	Neuropathology: Negative ChEI measured: Yes	Neuropathology: Negative ChEI measured: Yes	No increased Susceptibility	No increased Susceptibility	Not Required	None
34) PROPETAMPHOS	OPIDN: Negative Neuropathology: Negative Confirmatory NTE Study Required	Neuropathology: Negative ChEI measured: No	Neuropathology: Negative ChEI measured: No	No increased Susceptibility	No increased Susceptibility	Not Required	None
35) SULFOTEPP	NO DATA AVAILABLE - INADEQUATE DATA BASE						
36) TEMEPHOS	Study Unacceptable Confirmatory NTE Study Required	Not available	Not available	There are no food uses for this chemical thus requiring only a minimal data base. However, both the oral and dermal developmental toxicity study in rats as well as a three generation reproduction study in rats are unacceptable. Thus, an adequate assessment for FQPA can not be made with the existing database.			

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CHEMICAL	ACUTE DELAYED NEUROTOXICITY HEN	MAMMALIAN NEUROTOXICITY - RAT		EVIDENCE OF ENHANCED SUSCEPTIBILITY IN DEVELOPMENTAL STUDIES RAT & RABBIT	EVIDENCE OF ENHANCED SUSCEPTIBILITY IN THE 2-GENERATION REPRODUCTION RAT	REQUIREMENT OF A DEVELOPMENTAL NEUROTOXICITY STUDY IN RATS	DATA GAPS
		ACUTE	SUBCHRONIC				
37) TERBUFOS	OPIDN: Negative Neuropathology: Negative Confirmatory NTE Study Required	Not available	Not available	No increased Susceptibility	No increased Susceptibility	Reserved Pending Acute & 90-day rat neurotoxicity studies	Acute-Rat Neurotoxicity 90-day Rat Neurotoxicity
		No data to assess neurotoxicity, cholinesterase inhibition, behavioral effects, or neuropathology					
38) TETRACHLOR- VINPHOS	OPIDN: Negative Neuropathology: Negative Confirmatory NTE Study Required	Neuropathology: Negative	Neuropathology: Negative	No increased Susceptibility	No increased Susceptibility	Not required	None
		ChEI measured: No	ChEI measured: No				

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CHEMICAL	ACUTE DELAYED NEUROTOXICITY HEN	MAMMALIAN NEUROTOXICITY - RAT		EVIDENCE OF ENHANCED SUSCEPTIBILITY IN DEVELOPMENTAL STUDIES RAT & RABBIT	EVIDENCE OF ENHANCED SUSCEPTIBILITY IN THE 2-GENERATION REPRODUCTION RAT	REQUIREMENT OF A DEVELOPMENTAL NEUROTOXICITY STUDY IN RATS	DATA GAPS
		ACUTE	SUBCHRONIC				
39) TRIBUFOS	Subchronic Dermal OPIDN: Positive Neuropathology: Positive Confirmatory NTE Study Required	Not available	Not available	No increased Susceptibility	No increased Susceptibility	Required Evidence of neuropathology in the subchronic hen study	Acute - Hen (subchronic is via the dermal route). Acute - Rat Neurotoxicity 90-day - Rat Neurotoxicity Develop- mental Neurotoxicity Study in Rats
		No data to assess neurotoxicity, cholinesterase inhibition, behavioral effects, or neuropathology					

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CHEMICAL	ACUTE DELAYED NEUROTOXICITY HEN	MAMMALIAN NEUROTOXICITY - RAT		EVIDENCE OF ENHANCED SUSCEPTIBILITY IN DEVELOPMENTAL STUDIES RAT & RABBIT	EVIDENCE OF ENHANCED SUSCEPTIBILITY IN THE 2-GENERATION REPRODUCTION RAT	REQUIREMENT OF A DEVELOPMENTAL NEUROTOXICITY STUDY IN RATS	DATA GAPS
		ACUTE	SUBCHRONIC				
40) TRICHLORFON	Acute OPIDN: Positive Neuropathology: Positive Confirmatory NTE Study Required Subchronic OPIDN: Negative Neuropathology: Positive	Not available	In Review	No increased Susceptibility (Rabbit) Rat (unacceptable)	No increased Susceptibility	Reserved 1) Pending results of the developmental toxicity study in Guinea Pig required by HIARC. 2) Receipt and review of the Developmental toxicity study in rats	Acute-Rat Neurotoxicity 90-day Rat Neurotoxicity Develop- mental Toxicity -Rat
		No data to assess neurotoxicity, cholinesterase inhibition, behavioral effects, or neuropathology					

V. HIARC's RECOMMENDATIONS FOR THE FQPA SAFETY FACTOR COMMITTEE.

The toxicology database was evaluated for the neurotoxic, developmental and reproductive toxic potential of the 40 organophosphates. The data base was inadequate for Chlorpyrifos methyl, Dichrotophos and Temephos. No data were available for Fonophos, Isazophos and Sulfotepp. For one chemical (Dichlorvos or DDVP), the FQPA Safety Factor was determined by the Division Directors. Thus, HIARC's recommendation of the FQPA Safety Factor to the FQPA Safety Committee for 33 organophosphates are presented below:

1. Recommendation to the FQPA Safety Committee for *REMOVAL* of the additional 10 x Factor Based on Hazard Alone

The HIARC, based on hazard assessment, recommends, that the additional 10 x factor for enhanced susceptibility of infants and children should be **removed** for the organophosphates listed below based on the following weight-of-the-evidence considerations:

- (a) In prenatal developmental toxicity studies following *in utero* exposure in rats and rabbits, there was no evidence of effects being produced in fetuses at lower doses as compared to maternal animals nor was there evidence of an increase in severity of effects at or below maternally toxic doses.
- (b) In the pre/post natal two-generation reproduction study in rats, there was no evidence of enhanced susceptibility in pup when compared to adults (i.e., effects noted in offspring occurred at maternally toxic doses or higher)..
- (c) There was no evidence of abnormalities in the development of the fetal nervous system in the pre/post natal studies. .
- (d) There was no convincing evidence for requiring a developmental neurotoxicity study in rats.
- (e) The toxicology data base is complete and there are no data gaps according to Subdivision F Guideline requirements including meeting any of the triggers for requiring a developmental neurotoxicity study in rats.

ORGANOPHOSPHATES FOR WHICH THE 10 X FACTOR SHOULD BE REMOVED		
ACEPHATE	AZINPHOS METHYL	BENSULIDE ⁽¹⁾
CHLORETHOXYFOS ⁽²⁾	DIAZINON	DIMETHOATE
ETHION	ETHOPROP	ETHYL PARATHION
FENAMIPHOS	FENTHION	FENITROTHION
ISOFENFOS	MALATHION	METHIDATHION
NALED ⁽³⁾	PROFENFOS	PROPETAMPHOS
TETRACHLORVINPHOS		

⁽¹⁾ Bensulide: The HIARC determined that the absence of a subchronic neurotoxicity study in rats alone does not warrant retaining or reducing the FQPA Safety Factor because neuropathology was not observed either in the acute delayed neurotoxicity study in hen or in the acute neurotoxicity study in rats or any other studies. This chemical will be re-evaluated upon receipt and evaluation of the subchronic neurotoxicity study.

⁽²⁾ Chlorethoxyfos: The requirement for a subchronic neurotoxicity study in rats was waived because several other studies in the data base provided adequate evidence for the absence of neuropathology. Therefore, this is not considered to be a data gap requiring a FQPA Safety Factor.

⁽³⁾ Naled: The acute delayed neurotoxicity study in hens revealed neurotoxicity (clinical signs and brain cholinesterase inhibition) and neuropathology (axonal degeneration of the spinal cord). These effects, however, were not seen following repeated dosing in the subchronic neurotoxicity study in hens. Also, there was no evidence of neuropathology in rats following single and multiple exposures and there was no evidence of enhanced susceptibility following *in utero* exposures in rats and rabbits as well as pre and/or post natal exposures in the two generation reproduction study in rats. Based on these weight-of-the-evidence considerations, it is recommended that the FQPA Safety Factor can be removed for this chemical

2. Recommendation to the FQPA Safety Committee for REDUCTION of the additional 10 x Factor Based on Hazard Alone

The FQPA requires that an additional 10 x margin of safety be applied for infants and children to take into account the potential pre-and postnatal toxicity and the completeness of the data with respect to exposure and toxicity:

For the organophosphates, in general, the neurotoxicity data requirement include an acute delayed neurotoxicity study in hens (§81-7), an acute neurotoxicity study in rats (§81-8) and a subchronic neurotoxicity study in rats (§82-5).[Reference: OMB 2070-0107; 5/8/91].

Data from these studies are used for hazard characterization as well as in determining the need for a developmental neurotoxicity study. The "trigger" for a developmental neurotoxicity study for example, will be "positive" histopathology in these studies as well as central nervous system effects (e.g., decrease in brain weights) in these or other toxicology studies (e.g., 90-day or chronic studies). When a developmental neurotoxicity study is required, it is because this study will provide additional data (e.g., functional parameter development, potential increased susceptibility, effects on the development of the fetal nervous system, etc.). When the requirement for a developmental neurotoxicity study is placed in reserve status, the Agency will make the final requirement decision following evaluation of the results of the neurotoxicity studies (i.e., datagaps).

For the organophosphates listed below, the neurotoxicology data base is not considered to be incomplete since none of them are missing all three neurotoxicity studies. Two are missing the hen study but have the rat studies while five are missing the rat studies but have the hen study. Thus, the lack of a "complete" data base for these chemicals requires an FQPA Safety Factor. The HIARC, however, recommends that the 10 x factor can be reduced (to be determined) and this recommendation is based on the following weight-of-the-evidence considerations:

- (a) In prenatal developmental toxicity studies following *in utero* exposure in rats and rabbits, there was no evidence of effects being produced in fetuses at lower doses as compared to maternal animals nor was there evidence of an increase in severity of effects at or below maternally toxic doses.
- (b) In the pre/post natal two-generation reproduction study in rats, there was no evidence of enhanced susceptibility in pup when compared to adults (i.e., effects noted in offspring occurred at maternally toxic doses or higher).
- (c) There was no evidence of abnormalities in the development of the fetal nervous system in the pre/post natal studies.
- (d) There is no concern for positive neurological effects from the available neurotoxicity studies or for histopathology in the central nervous system from the other toxicological studies (e.g., subchronic rat, chronic dog, chronic mouse and rat).
- (e) The doses selected for dietary and non-dietary exposure risk assessments are based on the most sensitive endpoint (cholinesterase inhibition) occurring at low dose levels (0.005 to 1.1 mg/kg/day).
- (f) The dose level selected for acute dietary exposure risk assessments are from multiple dosing regimen.
- (g) Historical experience shows that neuropathology appears at higher doses relative to cholinesterase inhibition (the endpoint that is currently used for risk assessments).

The HIARC determined that the "missing" neurotoxicity studies for these organophosphates are necessary for completion of hazard characterization as well as to confirm the doses that are currently used for risk assessment/regulatory purposes are fully protected.

If the neurotoxicity studies provide no evidence of neuropathology and/or there was no convincing evidence for requiring a developmental neurotoxicity study, then HIARC would recommend that the FQPA Safety Factor (yet to be determined) be removed for these organophosphates based on hazard alone. However, until that decisions can be made, HIARC considers the lack of neurotoxicity studies as datagaps thus requiring an FQPA Safety Factor.

The Table below is a summary of the specific studies that are missing in the toxicology data base. However, all of the weight-of-the-evidence considerations discussed above also apply (e.g., lack of enhanced susceptibility in the critical development and reproduction toxicity studies etc.,). Therefore, the Committee considers the reduction of the FQPA Safety Factor to be an appropriate recommendation.

CHEMICAL	RATIONALE FOR REDUCING THE FQPA SAFETY FACTOR (UNDETERMINED)
PIRIMIPHOS METHYL	1) Data gap for an Acute Delayed Neurotoxicity Study in Hen, Chronic toxicity studies in dogs and rats. 2) No evidence of neuropathology in rats following single or repeated exposures. 3) The requirement for a Developmental Neurotoxicity Study in Rats placed in <i>Reserve</i> status pending receipt of acute delayed neurotoxicity study in hens.
DISULFOTON	1) Data gap for Acute Delayed Neurotoxicity Study in Hen 2) Equivocal evidence of neuropathology in the Subchronic Neurotoxicity Study in Rats. 3) The requirement for a Developmental Neurotoxicity Study in Rats placed in <i>Reserve</i> status pending receipt and review of a repeated acute delayed neurotoxicity study in hens.

CHEMICAL	RATIONALE FOR REDUCING THE FQPA SAFETY FACTOR (UNDETERMINED)
COUMAPHOS	1) Negative for OPIDN and neuropathology; a NTE study required as confirmatory data. 2) Data gap for Acute and Subchronic Neurotoxicity Studies in Rats. 3) Therefore, data on cholinesterase inhibition, neurobehavioral effects (FOB), and histopathology of the central and peripheral nervous system were not available for evaluation following single (acute) or repeated (subchronic) exposures to Coumaphos. 4) The requirement for a Developmental Neurotoxicity Study in Rats placed in <i>Reserve</i> status pending receipt and review of the acute and subchronic neurotoxicity studies.
PHORATE	1) Negative for OPIDN and neuropathology; a NTE study is required as confirmatory data. 2) Data gap for Acute and Subchronic Neurotoxicity Studies in Rats. 3) Therefore, data on cholinesterase inhibition, neurobehavioral effects (FOB), and histopathology of the central and peripheral nervous system were not available for evaluation following single (acute) or repeated (subchronic) exposures to Phorate. 4) The requirement for a Developmental Neurotoxicity Study in Rats placed in <i>Reserve</i> status pending receipt and review of the acute and subchronic neurotoxicity studies.
PHOSMET	1) Negative for OPIDN and neuropathology; a NTE study is required as confirmatory data. 2) Data gap for Acute and Subchronic Neurotoxicity Studies in Rats. 3) Therefore, data on cholinesterase inhibition, neurobehavioral effects (FOB), and histopathology of the central and peripheral nervous system were not available for evaluation following single (acute) or repeated (subchronic) exposures to Phosmet. 4) The requirement for a Developmental Neurotoxicity Study in Rats placed in <i>Reserve</i> status pending receipt and review of the acute and subchronic neurotoxicity studies.

CHEMICAL	RATIONALE FOR REDUCING THE FQPA SAFETY FACTOR (UNDETERMINED)
PHOSTEBUPIRIM	1) Negative for OPIDN and neuropathology; a NTE study is required as confirmatory data. 2) Data gap for Acute and Subchronic Neurotoxicity Studies in Rats. 3) Therefore, data on cholinesterase inhibition, neurobehavioral effects (FOB), and histopathology of the central and peripheral nervous system were not available for evaluation following single (acute) or repeated (subchronic) exposures to Phostebupirim. 4) The requirement for a Developmental Neurotoxicity Study in Rats placed in <i>Reserve</i> status pending receipt and review of the acute and subchronic neurotoxicity studies.
TERBUFOS	1) Negative for OPIDN and neuropathology; a NTE study is required as confirmatory data. 2) Data gap for Acute and Subchronic Neurotoxicity Studies in Rats. 3) Therefore, data on cholinesterase inhibition, neurobehavioral effects (FOB), and histopathology of the central and peripheral nervous system were not available for evaluation following single (acute) or repeated (subchronic) exposures to Terbufos. 4) The requirement for a Developmental Neurotoxicity Study in Rats placed in <i>Reserve</i> status pending receipt and review of the acute and subchronic neurotoxicity studies.
METHAMIDAPHOS	1) Evidence of positive effects in the NTE assay in hens in Subchronic Toxicity Studies.. 2) In studies from <i>open literature</i>, ingestion of Methamidaphos has been shown to result in delayed peripheral neuropathy in humans. Similarly, adult hens developed poly neuropathy but only after ingestion of doses 12-16 times the LD₅₀. 3) The HIARC recognized that the dose levels causing delayed neuropathy in humans are NOT well characterized. Exposures occurred at high doses through accidental occupational poisoning, suicide attempts or ingestion of contaminated vegetables. 4) Based on this evidence, a Developmental Neurotoxicity Study in Rats is required.

3. **Recommendation to the FQPA Safety Committee for *RETAINING* the additional 10 Factor Based on Hazard Alone**

The HIARC, based on hazard assessment, recommends that the additional **10 x factor** for enhanced susceptibility of infants and children should be **retained** for the organophosphates listed below. The rationale for this recommendation is provided in the table.

CHEMICAL	RATIONALE FOR RETAINING THE 10 X FQPA SAFETY FACTOR
CADUSAFOS	1) Data gap for Acute Delayed Neurotoxicity Study in Hen as well as Acute and Subchronic Neurotoxicity Studies in Rats. 2) Therefore, data on organophosphate induced delayed neurotoxicity (OPIDN), NTE and neuropathology in hens as well as cholinesterase inhibition, neurobehavioral effects (F0) and histopathology of the central and peripheral nervous system in rats were not available for evaluation following single (acute) or repeated (subchronic) exposures to Cadusofos. 3) The requirement for a Developmental Neurotoxicity Study in Rats placed in <i>Reserve</i> status pending receipt and review of the acute delayed neurotoxicity study in hens as well as the acute and subchronic neurotoxicity studies in rats.
CHLORPYRIFOS	1) Chlorpyrifos is a neurotoxicant with evidence of OPIDN in humans and animals; there have been case reports of neurophysiological effects in humans. 2) In studies (published/unpublished) conducted in various reputable scientific research laboratories and reported in the open literature, increased susceptibility of offspring to the effects of Chlorpyrifos has been identified. 3) A Developmental Neurotoxicity Study in Rats is required and thus there are data gaps for the assessment of functional development of young animals following pre- and/or postnatal exposure.

CHEMICAL	RATIONALE FOR RETAINING THE 10 X FQPA SAFETY FACTOR
METHYL PARATHION	1) Evidence of neuropathology in acute and subchronic neurotoxicity studies in rats as well as in the chronic toxicity studies in rats. 2) In studies (published) conducted in various reputable scientific research laboratories reported in the open literature, qualitative evidence of enhanced susceptibility to perinatal effects in rats has been identified following subcutaneous and intraperitoneal administration at high doses. 3) The HIARC noted that open literature data for another organophosphate, chlorpyrifos, has also demonstrated differences in susceptibility in the offspring following oral, subcutaneous and intraperitoneal administrations. 4) Even though these routes of exposure (i.e., subcutaneous and intraperitoneal) are not traditional (i.e., oral), enhanced susceptibility was seen in studies published in the open literature and also, neuropathology was seen in two chronic studies in rats submitted to the Agency. Therefore, based on these considerations, a Developmental Neurotoxicity Study in Rats is required.
ODM	Concern for possible adverse heritable effects based in the <i>in vivo</i> mouse spot test which was positive for the induction of somatic cell mutations following prenatal administration. Also, there was clear evidence of DNA strand breaks in rat testes cells in an <i>in vitro</i> alkaline elution assay (not confirmed <i>in vivo</i>). Based on this, HIARC recommended a mouse specific locus test.
TRIBUFOS	1) Evidence of OPIDN and neuropathology in hens following repeated dermal application in a Subchronic Delayed Neurotoxicity Study. 2) Data gap for Acute Delayed Neurotoxicity Study in Hen Acute and Subchronic Neurotoxicity Studies in Rats. 3) Therefore, data on OPIDN and neuropathology in hens as well as cholinesterase inhibition, neurobehavioral effects (FOB), and histopathology of the central and peripheral nervous system in rats were not available for evaluation following single (acute) or repeated (subchronic) exposures to TRIBUFOS. 4) Ocular effects and neuropathology at low doses in various other studies. 5) Based on the neuropathology observed in the subchronic study, a Developmental Neurotoxicity Study in Rats is required.

CHEMICAL	RATIONALE FOR RETAINING THE 10 X FQPA SAFETY FACTOR
TRICHLORFON	1) Evidence of OPIDN and neuropathology in hens in the Acute Delayed Neurotoxicity Study. 2) Evidence of neuropathology in hens in the Subchronic Delayed Neurotoxicity Study. 3) Data gap for Acute and Subchronic Neurotoxicity Studies in Rats. 4) Therefore, data on cholinesterase inhibition, neurobehavioral effects (FOB), and histopathology of the central and peripheral nervous system in rats were not available for evaluation following single (acute) or repeated (subchronic) exposures to Trichlorfon. 5) Data gap for a Prenatal Developmental Toxicity Study in Rats which precluded an assessment of susceptibility in rat fetuses as compared to maternal animals. 6) Open literature identified a developmental toxicity in Guinea Pigs in which oral administration of Trichlorfon resulted in decreases in brain weights. 7) A Developmental Neurotoxicity Study in Rats is reserved pending the results of the prenatal developmental toxicity study in Guinea Pigs, acute and subchronic neurotoxicity studies in rats and a prenatal developmental toxicity study in rats.

VI. EVALUATION OF THE TOXICOLOGY ENDPOINTS SELECTION

The toxicological endpoints selected for the various exposure scenarios are provided in Attachment 4. The dose levels selected for the various exposure risk assessments are provided in Attachment 5.

The conventional Uncertainty Factor (UF) of 100 (i.e., 10 x for intra-species variation and 10 x for inter-species extrapolation) is adequate for 25 of the 35 organophosphates evaluated. For the remaining 10, the HIARC applied an additional UF for various reasons. A re-evaluation found the rationale that was used in the application of the additional UF's to be consistent. The 10 chemicals for which the additional UF's were applied are tabulated below:

The use of additional Uncertainty Factors for Toxicology Endpoints Selected

CHEMICAL NAME	EXPOSURE SCENARIO	UF	RATIONALE FOR USE OF ADDITIONAL UNCERTAINTY FACTOR
AZINPHOS METHYL	Acute Dietary	3	Use of a LOEL in the critical (acute neurotoxicity) study.
DIAZINON	Chronic Dietary, Residential, Short, Intermediate and Long-Term Dermal and Inhalation.	3	Closeness of the NOEL/LOEL and the use of one sex (males) in the critical (human) study..
ETHION	Chronic Dietary Residential, Short, Intermediate and Long-Term Dermal	10	Use of a LOEL for in the critical (human) study. Use of the human study with a LOEL and results of 21-day dermal toxicity study in rabbits indicated that brain cholinesterase activity may be inhibited at lower doses than plasma and erythrocyte inhibition.
ETHYL PARATHION	Chronic Dietary	3	Use of a LOEL in the critical study (1-year dog).
FENAMIPHOS	Acute Dietary	3	Use of a LOEL in the critical (acute neurotoxicity) study.
FENTHION	Chronic Dietary	3	Use of threshold NOEL/LOEL in the critical (monkey and co-critical (human) studies
ISOFENPHOS	Acute Dietary, Residential, Short-Term Dermal and Inhalation	3	Use of a LOEL in the critical (acute neurotoxicity) study.
ODM	Acute Dietary	3	Use of a LOEL in the critical (acute neurotoxicity) study.
	Inhalation (any time period)		Use of a LOEL in the critical study
PIRIMIPHOS METHYL	Chronic Dietary	30	Use of a LOEL in the critical (human) study (3x) as well as data gaps for chronic studies in dogs and rats (10x).
	Intermediate-Term Dermal	3	Use of a LOEL in the critical (human) study.
	Long-Term Dermal	30	Use of a LOEL in the critical (human) study (3x) as well as data gaps for chronic studies in dogs and rats (10x).
TRIBUFOS	Short and Intermediate-Term Dermal	10	Use of a LOEL in the critical (21-day dermal) study via the relevant route (dermal) of exposure.

During the evaluation, the HIARC identified and/or modified some of the toxicological endpoints selected previously by the Toxicology Endpoint Selection Committee (TESC). This was done (for a few chemicals) because doses and endpoints were not selected for certain exposure scenarios (e.g., Long-Term Dermal and/or Inhalation) by the TESC during the "initial-phase" of the TESC process. Modifications made at the meeting for 15 organophosphates are summarized below:

July 7, 1998

MODIFICATIONS MADE IN THE TOXICOLOGY ENDPOINT SELECTION						
CHEMICAL NAME	CHANGED PARAMETER	DOSES		ENDPOINT		RATIONALE FOR CHANGE
		PREVIOUS SELECTION	CHANGED TO	PREVIOUS SELECTION	CHANGED TO	
BENSULIDE	Dermal Absorption	None	100%	NA	NA	A dermal absorption study was not available, thus the default value was selected.
	Inhalation (Any Time Period)	LC50 = 1.75 mg/L	<u>Oral Equivalents</u> Short-Term: Oral NOEL=5.5 mg/kg/day Intermediate & Long-Term: Oral NOEL= 0.5 mg/kg/day	Clinical signs	Cholinesterase inhibition (ChEI).	Selected Oral NOELs since the dose selected previously by the Toxicology Endpoint Selection Committee (TESC) was an LC ₅₀ value which is not appropriate for use in risk assessments.
CHLOR-ETHOXYPHOS	Long-Term Dermal	None selected	Oral NOEL = 0.06 mg/kg/day with 100% Dermal absorption	None selected	ChEI	A dose and endpoint was not selected for Long-Term dermal risk assessment. previously by the Toxicology Endpoint Selection Committee (TESC).
	Inhalation (Any Time Period)	None selected	<u>Oral Equivalents</u> Short-, Intermediate & Long-Term :Oral NOEL= 0.06 mg/kg/day	None selected	ChEI	A dose and endpoint for inhalation risk assessment was not selected previously by TESC.

July 7, 1998

MODIFICATIONS MADE IN THE TOXICOLOGY ENDPOINT SELECTION					
CHEMICAL NAME	CHANGED PARAMETER	DOSES		END POINT	
		PREVIOUS SELECTION	CHANGED TO	PREVIOUS SELECTION	CHANGED TO
COUMOPHOS	Inhalation (Any Time Period)	None selected	Oral Equivalents Short-& , Intermediate: Oral NOEL= 0.2 mg/kg/day	None selected	ChEI
					A dose and endpoint for inhalation risk assessment was not selected previously by TESC. Long-Term inhalation risk assessment is not required based on the use pattern.
DIMETHOATE	Acute Dietary	2.0 mg/kg/day	Oral NOEL = 0.06 mg/kg/day	Absence of pupil response in rats	ChEI
					Lack of confidence in the previous endpoint (absence of pupil response) selected. Also, no ChEI measurement in the acute neurotoxicity study.
	Short-Term Dermal	2.0 mg/kg/day	Oral NOEL = 0.06 mg/kg/day with 11% dermal absorption.	Absence of pupil response in rats	ChEI
					Lack of confidence in the previous endpoint selected (absence of pupil response) as well as lack of ChEI measurement in the acute neurotoxicity study.
	Inhalation (Any Time Period)	None selected	Oral Equivalents Short-and Intermediate Term: Oral NOEL=0.06 mg/kg/day Long-Term :Oral NOEL= 0.05 mg/kg/day	None selected	ChEI
					A dose and endpoint for inhalation risk assessment was not selected previously by TESC.

July 7, 1998

MODIFICATIONS MADE IN THE TOXICOLOGY ENDPOINT SELECTION						
CHEMICAL NAME	CHANGED PARAMETER	DOSES		END POINT		RATIONALE FOR CHANGE
		PREVIOUS SELECTION	CHANGED TO	PREVIOUS SELECTION	CHANGED TO	
ETHION	Long -Term Dermal	None selected	Oral LOEL=0.05 mg/kg/day	None selected	Clinical signs of ChEI.	A dose and endpoint for Long-Term dermal risk assessment was not selected previously by TESC. Human study with a LOEL is used, therefore a MOE of 100 is required..
	Inhalation (Any Time Period)	None selected	<u>Oral Equivalents</u> Short, Intermediate and long.- Term: Oral NOEL=0.05 mg/kg/day	None selected	Clinical signs of ChEI.	A dose and endpoint for inhalation exposure risk assessment was not selected previously by TESC. Human study with a LOEL is used, therefore a MOE of 100 is required..
ETHOPROP	Inhalation (Any Time Period)	None selected	<u>Oral Equivalents</u> Short Term: Oral NOEL = 0.025 mg/kg/day Intermediate and Long-Term: Oral NOEL =0.01 mg/kg/day	None selected	ChEI.	A dose and endpoint for inhalation exposure risk assessment was not selected previously by TESC

MODIFICATIONS MADE IN THE TOXICOLOGY ENDPOINT SELECTION

CHEMICAL NAME	CHANGED PARAMETER	DOSES		END POINT		RATIONALE FOR CHANGE
		PREVIOUS SELECTION	CHANGED TO	PREVIOUS SELECTION	CHANGED TO	
FENTHION	Inhalation (Any Time Period)	None selected	Oral Equivalents Short Term: Oral NOEL = 0.07 mg/kg/day Intermediate and Long-Term: Oral NOEL =0.02 mg/kg/day	None selected	ChEI.	A dose and endpoint for inhalation exposure risk assessment was not selected previously by TESC.
ISOFPENPHOS	Long -Term Dermal	None selected	Oral NOEL=0.06 mg/kg/day	None selected	Clinical signs of ChEI.	A dose and endpoint for Long-Term dermal risk assessment was not selected previously by TESC.
METHA-MIDAPHOS	Short, Intermediate and Long- Term Dermal	Short-Term: Oral NOEL =0.14 mg/kg/day Intermediate & Long-Term: Oral NOEL=0.3 mg/kg/day with 100% dermal absorption.	Dermal NOEL = 1.0 mg/kg/day	ChEI	ChEI	A 21-day dermal toxicity study in rats became available since the HIARC meeting of 1/20/98 at which the oral NOELs were selected for dermal risk assessments.

MODIFICATIONS MADE IN THE TOXICOLOGY ENDPOINT SELECTION						
CHEMICAL NAME	CHANGED PARAMETER	DOSES		END POINT		RATIONALE FOR CHANGE
		PREVIOUS SELECTION	CHANGED TO	PREVIOUS SELECTION	CHANGED TO	
METHIDATHION	Inhalation (Any Time Period)	None selected	Oral Equivalents Short-and Intermediate Term: Oral NOEL=0.2 mg/kg/day Long-Term: Oral NOEL= 0.15 mg/kg/day	None selected	ChEI	A dose and endpoint for inhalation risk assessment was not selected previously by TESC.
PHOSTEBUPIRIM	Long -Term Dermal	None selected	Oral NOEL=0.02 mg/kg/day	None selected	ChEI.	A dose and endpoint for Long-Term dermal risk assessment was not selected previously by TESC.
PROFENOPHOS	Dermal Absorption	50%	100% default	NA	NA	Previously the 50% dermal absorption was estimated based on LD ₅₀ values. The dermal absorption value was changed to 100% (default) to be consistent with other chemicals.
TERBUFOS	Long -Term Dermal	None selected	Oral NOEL=0.005 mg/kg/day	None selected	ChEI.	A dose and endpoint for Long-Term dermal risk assessment was not selected previously by TESC.

MODIFICATIONS MADE IN THE TOXICOLOGY ENDPOINT SELECTION						
CHEMICAL NAME	CHANGED PARAMETER	DOSES		END POINT		RATIONALE FOR CHANGE
		PREVIOUS SELECTION	CHANGED TO	PREVIOUS SELECTION	CHANGED TO	
TETRACHLOR-VINPHOS	Acute dietary	None selected	Oral NOEL = 5.0 mg/kg/day	None selected	ChEI	A dose and endpoint for acute dietary risk assessment was not selected previously by TES.
	Short, Intermediate, and Long-Term Dermal	None selected	Short-and Intermediate Term: Oral NOEL = 5.0 Long-Term: Oral NOEL = 4.23% with a dermal absorption factor of 9.57%	None selected	ChEI	A doses and endpoint for dermal risk assessment was not selected previously by TESC.
	Inhalation (Any Time Period)	None selected	Oral Equivalents Short-and Intermediate Term: Oral NOEL = 5.0 mg/kg/day Long-Term: Oral NOEL = 4.23 mg/kg/day	None selected	ChEI	A doses and endpoint for inhalation risk assessment was not selected previously by TESC.

MODIFICATIONS MADE IN THE TOXICOLOGY ENDPOINT SELECTION					
CHEMICAL NAME	CHANGED PARAMETER	DOSES		END POINT	
		PREVIOUS SELECTION	CHANGED TO	PREVIOUS SELECTION	CHANGED TO
TRICHLORFON	Dermal Absorption	None selected	10%	NA	NA
					A dermal absorption factor was not required since doses and endpoints for dermal risk assessments were not selected previously by TESC. A 10% dermal absorption factor was derived by the ratio of the Oral LOEL of 35 mg/kg/day in the developmental toxicity study in rabbits and the Dermal LOEL of 300 mg/kg/day from the 21-day dermal toxicity study in rabbits.
	Short and, Intermediate-and Long -Term Dermal	Non selected	Dermal NOEL=100 mg/kg/day	None	ChEI
		None selected	Oral NOEL = 0.2 mg/kg/day with 10% dermal absorption.	None	ChEI
	Inhalation (Any Time Period)	None selected	Inhalation NOEL = 0.0127 mg/L	None	ChEI
					A dose and endpoint for dermal risk assessment was not selected previously by TESC.
					A dose and endpoint for inhalation risk assessment was not selected previously by TESC.

VIII. CONCLUSIONS

HED's FQPA Safety Factor Committee met on June 15 -16, 1998 and considered the following recommendations made by the HIARC (based hazard alone) in conjunction with the dietary, drinking water and residential exposure assessments for each of these pesticides. A report from the FQPA Safety Factor Committee will be forthcoming which will include the final recommendations for the FQPA Safety Factors based on hazard and exposure assessments.

The HIARC's recommendations (based only on hazard assessment) to the FQPA Safety Committee are summarized below:

The FQPA Safety Factor can be **removed** for *Acephate, Azinphos Methyl, Bensulide, Chlorethoxyfos, Diazinon, Dimethoate, Ethion, Ethoprop, Ethyl Parathion, Fenamiphos, Fenthion, Fenitrothion, Isofenfos, Malathion, Methidathion, Naled, Profenfos, Propetamphos and Tetrachlorvinphos* since there was not evidence of enhanced susceptibility in fetuses in the prenatal developmental toxicity studies in rodents and non rodents or in the pups in the two-generation reproduction study in rats and the toxicology data base is complete.

The FQPA Safety Factor can be **reduced (value undetermined)**: For *Coumophos, Dichlorvos, DISULFOTON, Phorate, Phomet, Phostebupirim, Pirimiphos methyl, and Terbufos* due to datagaps for acute hen, acute rat and/or subchronic rat neurotoxicity studies as well as placement of the developmental neurotoxicity study in *Reserve* status pending receipt and review of the preceding studies. For *Methamidaphos*, however, the FQPA Safety Factor can be **reduced (to be determined)** due to evidence of neurotoxicity in hens, occurrence of delayed peripheral neuropathy in humans, and the requirement for a developmental neurotoxicity study. The HIARC, however, noted that the dose at which neuropathology occurred in humans was probably high and is not well characterized.

The FQPA Safety Factor should be **retained** for: *Cadusafos* because of datagaps for three studies (acute hen, acute rat and subchronic rat neurotoxicity); for *Chlorpyrifos* and *Methyl parathion* due to evidence of neuropathology as well enhanced susceptibility from the open literature studies and thus the need for a developmental neurotoxicity study; for *ODM* because for the concern for heritable effects and the requirement for a mouse specific locust test; for *Tribufos* due to evidence of OPIDN and neuropathology in hens via the dermal route, ocular effects and neuropathology in several species, datagaps for the acute and subchronic neurotoxicity studies in rats as well as the requirement for a developmental neurotoxicity study; for *Trichlorfon* because of evidence of OPIDN and neuropathology in hens, datagaps for acute and subchronic neurotoxicity as well as a prenatal developmental toxicity study in rats and the placement of the developmental neurotoxicity study in rats in reserve status pending the results of the developmental toxicity study in the guinea pigs.

No recommendations of the FQPA Safety Factor are made for *Chlorpyrifos methyl, Dicrotophos, Fonophos, Isazophos, and Sulfotepp* due to the inadequate toxicology data base and/or absence of data to evaluate the potential enhanced susceptibility to infants and children.

ATTACHMENT 1

HAZARD ID COMMITTEE REPORT

ORGANOPHOSPHATES

ATTACHMENT 1

NOELs/LOELs and ENDPOINTS FOR DEVELOPMENTAL TOXICITY STUDIES IN RATS

HAZARD ID COMMITTEE REPORT

ORGANOPHOSPHATES

NOELs/LOELs & ENDPOINTS FOR DEVELOPMENTAL TOXICITY STUDIES IN RATS						
CHEMICAL	MATERNAL TOXICITY			DEVELOPMENTAL TOXICITY		
	(mg/kg/day)		ENDPOINT	(mg/kg/day)		ENDPOINT
	NOEL	LOEL		NOEL	LOEL	
1) ACEPHATE	5.0	20.0	Decreases in body weight gain, food consumption and food efficiency.	20.0	75.0	Decrease in mean number of ossification on center/litter
2) AZINPHOS METHYL	0.5	1.0	RBC & Brain ChEI	≥2.0	(NA)	No developmental toxicity at HDT.
3) BENSULIDE	23.0	95.0	Clinical sign (tremors), decreases in body weight and body weight gain/food consumption and increased relative liver weights.	≥95.0	NA	No developmental toxicity at HDT.
4) CADUSAFOS	6	18	Cholinergic signs (decreased locomotion, tremors, exothalonus, fasciculation).	6	18	Decreased fetal body weight.
5) CHLORETHOXYFOS	0.25	0.25	Decrease body weight.	NA	50	Delayed ossification of sternbrae.
6) CHLORPYRIFOS	0.1	3.0	Plasma & RBC ChEI.	≥15.0	NA	No developmental toxicity at HDT.
	0.5	2.5	Decreased body weight and food consumption.	2.5	15.0	Increased post implantation loss.
7) CHLORPYRIFOS METHYL	100	200	STUDY UNACCEPTABLE	≥200	NA	STUDY UNACCEPTABLE
8) COUMAPHOS	5	25	Clinical signs of cholinesterase inhibition.	25	NA	No developmental toxicity at HDT.
9) DDVP	3	21	Cholinergic signs (Tremors, hind leg splay, vocalization, prone positioning).	NA	21	No developmental toxicity at HDT.
10) DIAZINON	20	100	Decreased body weight, body weight gain and food consumption.	≥100	NA	No developmental toxicity at HDT.

NOELs/LOELs & ENDPOINTS FOR DEVELOPMENTAL TOXICITY STUDIES IN RATS

CHEMICAL	MATERNAL TOXICITY			DEVELOPMENTAL TOXICITY		
	(mg/kg/day)		ENDPOINT	(mg/kg/day)		ENDPOINT
	NOEL	LOEL		NOEL	LOEL	
11) DICROTOTOPIOS	0.5	1.0	Clinical signs (Fasciculations)	≥2.0	NA	No developmental toxicity at HDT
12) DIMETHOATE	3.0	6.0	Small pellet like feces.	≥18.0	NA	No developmental toxicity at HDT.
13) DISULFOTON	0.1	0.3	Plasma and RBC ChEI.	0.3	1.0	Incomplete ossification of intraparietals and sternbrae
14) ETHION	0.6	2.5	Hyperactivity	0.6	2.5	Delayed ossification of pubes in the fetuses.
15) ETHOPROP	2.0	9.0	Decreases in body weight gain and increased incidence of soft stools.	≥18.0	NA	No developmental toxicity at HDT.
16) ETHIYL. PARATHION	1.0	1.5	Increased mortality and decreased body weights.	1.5	NA	No developmental toxicity at HDT.
17) FENAMIPHOS	0.85	3.0	Increased mortality and decreases in body weight gain and food consumption.	≥3.0	NA	No developmental toxicity at HDT.
18) FENTHION	4.2 <1.0 (ChEI)	18.0	Clinical signs (hypoactivity, urine stains) and decreased body weight gain.	4.2	18.0	Increase in post implantation loss and increase in fetal Brain ChEI.
19) FENITROTHION	8.0	25.0	Plasma, RBC and Brain ChEI.	8.0	25.0	Increased incidence (fetal and litter) fetuses with one full and one rudimentary 13th ribs.
20) FONOFOS	NO DATA AVAILABLE					
21) ISOFPENPHOS	0.05	0.45	Plasma, RBC & Brain ChEI.	≥4.0	NA	No developmental toxicity at HDT.
22) ISAZOPHOS	NO DATA AVAILABLE					

NOELS/LOELS & ENDPOINTS FOR DEVELOPMENTAL TOXICITY STUDIES IN RATS

CHEMICAL	MATERNAL TOXICITY			DEVELOPMENTAL TOXICITY		
	(mg/kg/day)		ENDPOINT	(mg/kg/day)		ENDPOINT
	NOEL	LOEL		NOEL	LOEL	
23) MALATHION	400.0	800.0	Clinical signs (urine stain) and decreases in body weight and food consumption.	≥800.0	NA	No developmental toxicity at HDT.
24) METHIDATHION	1.0	2.25	Increased mortality, cholinergic signs, and decreases in body weight gain and food consumption.	≥2.25	NA	No developmental toxicity at HDT.
25) METHAMIDAPHOS	1.0	3.0	Cholinergic signs and decreases in body weight gain and food consumption.	1.0	3.0	Decreased fetal body weight.
26) METHYL PARATHION	1.0	3.0	Increased mortality, cholinergic signs, plasma, erythrocyte and brain ChEI, decreases in body weight, body weight gain and food consumption.	1.0	3.0	Increased postimplantation loss (early resorptions), decreased fetal body weight, increased incidence of delayed ossification (3rd cervical vertebrae, proximal phalanx of the 2nd right digit, and 1st metatarsal of both hind limbs).
27) NALED	10.0	40.0	Cholinergic signs.	≥40.0	NA	No developmental toxicity at HDT.
28) ODM	NA	0.5	Plasma & Brain ChEI at LDT.	≥4.5	NA	No developmental toxicity at HDT.
29) PHORATE	0.25	0.5	Increased mortality and clinical signs (convulsions and hypothermia).	0.25	0.5	No developmental toxicity at HDT.
	0.3	0.4	Mortality, neurotoxic clinical signs, decreases in body weight, body weight gain, and food consumption and gross pathology.	0.3	0.4	Decreased fetal body weights and increased incidence of skeletal variations (delayed ossification of the sternum and pelvis).

ENDPOINTS FOR DEVELOPMENTAL TOXICITY STUDIES IN RATS

NOELs/LOELs & ENDPOINTS FOR DEVELOPMENTAL TOXICITY STUDIES IN RATS									
CHEMICAL	MATERNAL TOXICITY				DEVELOPMENTAL TOXICITY				
	(mg/kg/day)		ENDPOINT	(mg/kg/day)	ENDPOINT		(mg/kg/day)	ENDPOINT	
	NOEL	LOEL			NOEL	LOEL			
30) PHOSMET	10	15	Decreased body weight gain and food consumption and clinical signs.		≥15	NA	No developmental toxicity at HDT.		
31) PHOSTEBUPIRIM	0.5	0.75	Increased mortality, cholinergic signs, plasma, RBC and brain ChEI, and decreased body weight and food consumption.		≥0.75	NA	No developmental toxicity at HDT.		
32) PIRIMIPHOS METHYL	15.0	150.0	Clinical signs (tremors, abnormal gait, irregular respiration, urinary incontinence)		≥150.0	NA	No developmental toxicity at HDT.		
33) PROFENOPHOS	30.0	60.0	Decreases in body weight gain and food consumption.		≥60.0	NA	No developmental toxicity at HDT.		
34) PROPETAMPHOS	1.5	3.0	Cholinergic signs.		≥6.0	NA	No developmental toxicity at HDT.		
35) SULFOTEP	INADEQUATE DATA BASE								
36) TEMEPHOS	≥30.0	NA	No maternal toxicity at HDT. Study inadequate since high dose did not elicit any toxicity in the dams.		≥30.0	NA	No developmental toxicity at HDT. Study classified inadequate due to lack of maternal toxicity at HDT.		
37) TERBUFOS	≥0.2	NA	No maternal toxicity at HDT		0.1	0.2	Increases in early fetal resorptions, number of litters with two or more resorptions, and postimplantation losses.		
38) TETRACHLORVINPHOS	75.0	150.0	Decreased body weight gain.		≥300.0	NA	No developmental toxicity at HDT.		
39) TRIBUFOS	1.0	7.0	Plasma and RBC ChEI.		≥28.0	NA	No developmental toxicity at HDT.		

NOELs/LOELs & ENDPOINTS FOR DEVELOPMENTAL TOXICITY STUDIES IN RATS

CHEMICAL	MATERNAL TOXICITY				DEVELOPMENTAL TOXICITY	
	(mg/kg/day)		ENDPOINT		(mg/kg/day)	
	NOEL	LOEL			NOEL	LOEL
40) TRICHLORFON	NA	≥45	Plasma and Brain ChEI.		NA	≥45.0
					Increases in delayed ossification of skulls, vertebrae and sternbrae in fetuses. Study supplementary -technical deficiencies)	

ATTACHMENT 2

NOELs/LOELs and ENDPOINTS FOR DEVELOPMENTAL TOXICITY STUDIES IN RABBITS

NOELs/LOELs & ENDPOINTS FOR DEVELOPMENTAL TOXICITY STUDIES IN RABBITS

CHEMICAL	MATERNAL TOXICITY				DEVELOPMENTAL TOXICITY		
	(mg/kg/day)		ENDPOINT		(mg/kg/day)		ENDPOINT
	NOEL	LOEL			NOEL	LOEL	
1) ACEPHATE	3.0	10.0	Abortions and increased nasal discharge.		≥10.0	NA	No developmental toxicity at HDT.
2) AZINPHOS METHYL	1.0	2.5	Plasma & RBC ChEI		2.5	6.0	Increases in pre-and postimplantation losses.
3) BENSULIDE	20.0	80.0	Decreased body weight and body weight gain.		≥80.0	Not Achieved (NA)	No developmental toxicity at HDT.
4) CADUSAFOS	0.3	0.9	Increased mortality and cholinergic signs		0.3	0.9	Increase in total number of resorptions, decrease in total number of fetuses and fetal death.
5) CHLORETHOXYPHOS	0.76	1.38	Increased mortality associated with ChEI.		1.38	2.1	Increase in early resorptions/litter along with increase in the number of litters with at least one early resorption/total litter.
6) CHLORPYRIFOS	81.0	140.0	Decrease in body weight.		81.0	140.0	Decreases in fetal weight and length, increased incidence of skeletal variations and ossification delays in the sternbrae
7) CHLORPYRIFOS-METHYL	≥16.0	NA	STUDY UNACCEPTABLE		≥16.0	NA	STUDY UNACCEPTABLE
8) COUMAPHOS	2.0	18.0	Increased mortality and cholinergic signs.		≥18.0	NA	No developmental toxicity at HDT.
9) DDVP	0.1	2.5	Increased mortality, cholinergic signs and decreases in body weight and body weight gain.		≥7	NA	No developmental toxicity at HDT.

NOELs/LOELs & ENDPOINTS FOR DEVELOPMENTAL TOXICITY STUDIES IN RABBITS

CHEMICAL	MATERNAL TOXICITY			DEVELOPMENTAL TOXICITY		
	(mg/kg/day)		ENDPOINT	(mg/kg/day)		ENDPOINT
	NOEL	LOEL		NOEL	LOEL	
10) DIAZINON	25	100	Increased mortality.	≥100	NA	No developmental toxicity at HDT.
11) DICROTOPIOS	--	--	STUDY UNACCEPTABLE	--	--	STUDY UNACCEPTABLE
12) DIMETHOATE	10.0	20.0	Decreased body weight gain	20.0	40.0	Decreased fetal body weight.
13) DISULFOTON	1.0	1.5	Cholinergic signs (tremors, unsteadiness/ incoordination and increased respiration)	≥5	NA	No developmental toxicity at HDT.
14) ETHION	2.4	9.6	Clinical signs (orange color urine) and decreases in body weight gain and food consumption.	≥9.6	NA	No developmental toxicity at HDT.
15) ETHOPROP	≥2.5	NA	No maternal toxicity at HDT.	≥2.5	NA	No developmental toxicity at HDT.
16) ETHYL PARATHION	4.0	16.0	Mortality, increased morbidity and decreases in body weight and body weight gain.	4.0	16.0	Decreased litter size.
17) FENAMIPHOS	0.5	2.5	Cholinergic signs.	≥2.5	NA	No developmental toxicity at HDT.
18) FENTHION	1.0	2.75	Clinical signs (soft stools).	2.75	7.5	Increased resorptions, decreased fetal weight, decreased metacarpal ossification and decreased incidence of extra ribs in the number of fetuses but not in the number of litters.

NOELs/LOELs & ENDPOINTS FOR DEVELOPMENTAL TOXICITY STUDIES IN RABBITS

CHEMICAL	MATERNAL TOXICITY			DEVELOPMENTAL TOXICITY		
	(mg/kg/day)		ENDPOINT	(mg/kg/day)		ENDPOINT
	NOEL	LOEL		NOEL	LOEL	
19) FENITROTHION	10.0	30.0	Increased mortality, cholinergic signs and decreased body weight gains.	≥30.0	NA	No developmental toxicity at HDT.
20) FONOFOS	NO DATA AVAILABLE					
21) ISOFENPHOS	0.25	1.25	Plasma, RBC & Brain ChEI.	≥7.5	NA	No developmental toxicity at HDT.
	Sys. 1.25	Sys 7.5	Increased mortality and decreases in body weight and body weight gains.			
22) ISAZOPHOS	NO DATA AVAILABLE					
23) MALATHION	25.0	50.0	Decreased body weight gain.	25.0	50.0	Slight increase in mean resorption sites.
24) METHIDATHION	6.0	12.0	Cholinergic signs	≥12.0	NA	No developmental toxicity at HDT.
25) METHIDAMIDOPHOS	0.2	0.65	Decreased body weight gain and food consumption.	≥2.5	NA	No developmental toxicity at HDT.
26) METHYL PARATHION	≥3.0	NA	No maternal toxicity at HDT.	≥3.0	NA	No developmental toxicity at HDT.
27) NALED	≥8.0	NA	No maternal toxicity at HDT.	≥8.0	NA	No developmental toxicity at HDT.
28) ODM	0.2	0.8	Erythrocyte & Brain ChEI.	≥0.8	NA	No developmental toxicity at HDT.
29) PHORATE	0.15	0.5	Increased mortality and body weight loss.	≥1.2	NA	No developmental toxicity at HDT.

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NOELs/LOELs & ENDPOINTS FOR DEVELOPMENTAL TOXICITY STUDIES IN RABBITS

CHEMICAL	MATERNAL TOXICITY			DEVELOPMENTAL TOXICITY		
	(mg/kg/day)		ENDPOINT	(mg/kg/day)		ENDPOINT
	NOEL	LOEL		NOEL	LOEL	
30) PHOSMET	5	15	Clinical signs and decreased body weight.	5	15	Increased incidence of skeletal variations in fetuses.
31) PHOSTEBUPIRIM	0.1	0.3	Erythrocyte ChEI.	≥0.3	NA	No developmental toxicity at HDT.
32) PIRIMIPHOS METHYL	12.0	24.0	Plasma & RBC ChEI.	≥48.0	NA	No developmental toxicity at HDT.
33) PROFENOPHOS	30.0	60.0	Decreased body weight gain.	≥60.0	NA	No developmental toxicity at HDT.
34) PROPETAMPHOS	4	8	Decreased body weight gain	4	8	Increased resorption.
35) SULFOTEP	INADEQUATE DATA BASE					
36) TEMEPHOS	NO DATA/ NO STUDY					
37) TERBUFOS	0.1	0.25	Clinical signs (soft stools) and decreased body weight gain.	0.25	0.5	Increased resorptions and decreased fetal body weights.
38) TETRACHLORVINPHOS	375.0	750.0	Increased mortality and abortions and clinical signs (red vaginal fluid).	375.0	750.0	Increase in early resorptions/dam with a corresponding increase in postimplantation loss and a decrease in live fetuses/dam.
39) TRIBUFOS	NA	1.0	Plasma & RBC ChEI	≥9.0	NA	No developmental toxicity at HDT.
	Sys. 3.0	Sys. 9.0	Decreased body weight gain.			
40) TRICHLORFON	10.0	35.0	Abortions and RBC and Brain ChEI.	35.0	110.0	Increase in number of does with resorptions, decreased male fetal body weight and delayed ossification.

ATTACHMENT 3

NOELs/LOELs and ENDPOINTS FOR THE TWO-GENERATION REPRODUCTION STUDIES IN RATS

NOELs/LOELs & ENDPOINTS FOR THE 2-GENERATION REPRODUCTION TOXICITY STUDIES IN RATS

CHEMICAL	PARENTAL SYSTEMIC TOXICITY				OFF SPRING TOXICITY (mg/kg/day)		
	(mg/kg/day)		ENDPOINT		(mg/kg/day)		ENDPOINT
	NOEL	LOEL			NOEL	LOEL	
1) ACEPHATE	2.5	25	Decreased body weight gain and clinical signs (alopecia and soft stool).		2.5	25	Decreased viability index and decreased pup body weight gain.
2) AZINPHOS METHYL	0.75	2.25	Increased mortality, decreased body weight and clinical signs (poor coordination and convulsions).		0.25	0.75	Decrease in pup viability and lactation indices
	Not Achieved (NA)	0.55	Plasma & RBC ChEI.		0.55	1.54	Decrease in pup viability index and decreased pup body weights on post natal days (PD) 14 and 21.
			1-Generation Study				
3) BENSULIDE	2.6	15.4	RBC ChEI in F1		15.4	93.2	Decreased F2 pup survival.
4) CADUSAFOS	0.025	0.25	Plasma & RBC ChEI.		≥0.25	NA	No offspring toxicity at HDT.
5) CHLORFETHOXYFOS	0.296	0.607	Tremors during lactation.		0.607	NA	No offspring toxicity at HDT.
6) CHLORPYRIFOS	0.1	0.3	Plasma & RBC ChEI.		≥1.0	NA	No offspring toxicity at HDT.
	0.8	1.2	Decrease in body weight gains in males		≥1.2	NA	No offspring toxicity at HDT.
	≥3.58	NA	No parental systemic toxicity at HDT.		≥3.58	NA	No offspring toxicity at HDT.
	0.1	1.0	Plasma & RBC ChEI and adrenal gland lesions.		1.0	5.0	Increased postnatal mortality and reduced pup body weight.
7) CHLORPYRIFOS METHYL	--	--	STUDY UNACCEPTABLE		--	--	STUDY UNACCEPTABLE
8) COUMAPHOS	≥1.79	NA	No parental systemic toxicity at HDT.		≥1.79	NA	No offspring toxicity at HDT.
9) DDVP	2.3	8.3	Decreased % of females with estrous cycle and increased % of females cycling with abnormal cycle.		2.3	8.3	Reduced dams bearing litters, fertility index, pregnancy index, pup weight.

NOELs/LOELs & ENDPOINTS FOR THE 2-GENERATION REPRODUCTION TOXICITY STUDIES IN RATS

NOELs/LOELs & ENDPOINTS FOR THE 2-GENERATION REPRODUCTION TOXICITY STUDIES IN RATS						
CHEMICAL	PARENTAL SYSTEMIC TOXICITY			OFF SPRING TOXICITY (mg/kg/day)		
	(mg/kg/day)		ENDPOINT	(mg/kg/day)		ENDPOINT
	NOEL	LOEL		NOEL	LOEL	
10) DIAZINON	0.67	6.69	Decreased body weight gain.	0.67	6.69	Pup mortality, decreased pup weight gained during lactation.
11) DICROTOPHOS	0.025	0.25	Decreases in body weight and food utilization.	0.025	0.25	Reduced no. Of F2 pups/liter during lactation.
12) DIMETHOATE	0.08	1.2	ChEI in both sexes in all generations.	1.2	5.46	Decreases in number of live pups, pup body weights, and fertility in F1a, F1b, F2a and F2b matings.
13) DISULFOTON	0.025	0.1	Plasma and RBC ChEI.	0.1	0.45	Pup mortality and pup weight decrements
14) ETHION	0.2	1.25	Plasma ChEI	≥1.25	NA	No offspring toxicity at HDT.
15) ETHOPROP	2.3	13.0	Decrease in body weight gain.	2.3	13.0	Increased pup mortality PD 21& 28 and decreased pup body weight gain in both generations .
16) ETHYL PARATHION	0.05	0.5	Plasma, RBC & Brain ChEI.	≥1.0	NA	No offspring toxicity at HDT.
17) FENAMIPHOS	0.17	0.64	Plasma & RBC ChEI.	≥3.2	NA	No offspring toxicity at HDT.
18) FENTHION	0.1	0.7	Epididymal vacuolation and Plasma & RBC ChEI.	0.1	0.7	Plasma ChEI.
19) FENITROTHION	2.74	8.4	Decreases in body weight, body weight gains and food consumption.	2.74	8.4	Decreases in fertility, number of implantation sites, viability and lactation in one generation.
20) FONOFOS	NO DATA AVAILABLE					
21) ISOFENPHOS	0.08	0.44	Plasma, RBC and/or Brain ChEI.	0.08	0.44	Increased pup mortality (reductions in lactation indices and mean litter sizes) and clinical signs (small to very small emaciated pups).
22) ISAZOPHOS	NO DATA AVAILABLE					

NOELs/LOELs & ENDPOINTS FOR THE 2-GENERATION REPRODUCTION TOXICITY STUDIES IN RATS

NOELs/LOELs & ENDPOINTS FOR THE 2-GENERATION REPRODUCTION TOXICITY STUDIES IN RATS							
CHEMICAL	PARENTAL SYSTEMIC TOXICITY				OFFSPRING TOXICITY (mg/kg/day)		
	(mg/kg/day)		ENDPOINT	(mg/kg/day)		ENDPOINT	
	NOEL	LOEL		NOEL	LOEL		
23) MALATHION	394.0	612	Decreased body weights of F1 during gestation and lactation and decreased F1 pre-mating body weight.		131.0	394.0	Decreased F1a and F2b pup body weight during lactation Day 21.
24) METHIDATHION	0.25	1.25	Tremors, decreased food consumption during lactation and decreased ovarian weights.		0.25	1.25	Decreased pup body weight and clinical signs (hypothermia and appearance of starvation).
25) METHAMIDAPHOS	0.5	1.65	Decreased body weight.		0.5	1.65	Decreased pup viability and body weight during lactation Day 14.
26) METHYL PARATHION	0.44	2.3	Decreased pre-mating body weight for F1 females and decreased maternal body weight during lactation for both generations.		0.44	2.3	Decreased pup survival in early lactation and decreased body weight gain and increased food consumption immediately after weaning.
27) NAL-ED	6.0	18.0	Decreased body weight gains.		≥18.0	NA	No offspring toxicity at HDT.
28) ODM	0.05	0.5	Decreased body weight for both sexes for entire study and for females during gestation.		0.05	0.5	Decreased viability index and pup body weight during lactation at Day 5.
	0.38	2.1	Decreases in male and female fertility of unknown origin in P and F1 generations.		0.38	2.1	Decreased litter size at birth and decreased pup weight during lactation.
29) PHORATE	0.2	0.4	Tremors and Plasma and Brain ChEI		0.2	0.4	Decrease in pup survival during early lactation and decrease in pup weight during late lactation.
30) PHOSMET	≤1.5	6.1	RBC ChEI.		1.5	6.1	Decreased number of live pup/litter, pup weights, fertility index and lactation index.
31)-PHOSTEBUPIRIM	0.05	0.25	Plasma & RBC ChEI.		0.25	1.25	Tremors in neonates, decreased pup body weight gain, increase in pup mortality, and ChEI on PD 21 but not on PD 4.
32) PIRIMIPOS METHYL	NA	0.87	Plasma ChEI at LDT.		≥13.72	NA	No offspring toxicity at HDT.

NOELs/LOELs & ENDPOINTS FOR THE 2-GENERATION REPRODUCTION TOXICITY STUDIES IN RATS

CHEMICAL	PARENTAL SYSTEMIC TOXICITY			OFFSPRING TOXICITY (mg/kg/day)		
	(mg/kg/day)		ENDPOINT	(mg/kg/day)		ENDPOINT
	NOEL	LOEL		NOEL	LOEL	
33) PROFENOPHOS	7.3	29.0	Decreased body weight gain and food consumption.	7.3	29.0	Decreased pup body weight in both sexes of F1 and F2 and cumulative body weight gain on PD 14 and 21.
34) PROPETAMPHOS	0.3	2.1	RBC & Brain ChEI.	0.3	2.1	Plasma & RBC ChEI.
35) SULFOTEPP	NO DATA AVAILABLE					
36) TEMEPHOS	≥6.25	NA	No parental systemic toxicity at HDT. Study unacceptable since the high dose did not elicit any systemic toxicity in the parental animals.	≥6.25	NA	No toxicity to the offspring at HDT. However, doses for parental animals are inadequate since there were no systemic toxicity to the parental animals.
37) TERBUFOS	0.08	0.22	Decreased body weight gain during lactation.	0.07	0.17	Decrease in pregnancy rate and male fertility.
38) TETRACHLORVINPHOS	25.0	100.0	Decreased body weight gain in males in Fo and in both sexes in F1 and increased mean adrenal gland weights in Fo females.	≥100.0	NA	No offspring toxicity at HDT.
39) TRIBUFOS	NA	0.2	Plasma ChEI.	1.7	15.0	Increases in number of litters with still born pups and pup death throughout lactation, decreases in F1 and F2 pup body weights and increases in F1 gestation period.
40) TRICHLORFON	NA	15.0	Plasma and Brain ChEI in both generations.	50.0	175.0	Decreases in F1 pup body weights on PD 7 and 21 and presence of dilated renal pelvis.
	15.0	50.0	Decreased body weight gain.	15.0	50.0	Based on reduced fertility during F0 matings (lower litter size).

ATTACHMENT -4

TOXICOLOGY ENDPOINTS SELECTED FOR DIETARY & NON DIETARY EXPOSURE RISK ASSESSMENTS

TOXICOLOGY END POINTS SELECTION FOR DIETARY & NON-DIETARY EXPOSURE RISK ASSESSMENTS

CHEMICAL	ACUTE DIETARY	CHRONIC DIETARY	DERMAL EXPOSURE			INHALATION (ANY TIME PERIOD)
			SHORT-TERM	INTERMEDIATE-TERM	LONG-TERM	
1) ACEPHATE	Range Finding-Rat: Plasma & Brain ChEI.	90-Day Rat: Brain ChEI	21-Day Dermal Rat: Brain ChEI.	21-Day Dermal Rat: Brain ChEI.	21-Day Dermal Rat: Brain ChEI.	4-week inhalation- Rat: Plasma, RBC, Brain ChEI.
2) AZINPHOS METHYL	Acu. Neuro.-Rat: Plasma, RBC, Brain ChEI. UF 3 x applied for use of LOEL.	1-Year Dog: RBC ChEI	Dermal Absorption-Rat: RBC ChEI.	1-Year-Dog Oral: RBC ChEI.	Not required based on use pattern.	90-Day inhalation- Rat: Plasma and RBC ChEI.
3) BENSULIDE	Acu.Neuro.-Rat: Plasma ChEI.	1-Year Dog: Plasma ChEI	Developmental-Oral-Rat: Maternal Plasma ChEI.	1-Year Dog Oral: Plasma & Brain ChEI.	1-Year Dog Oral: Plasma & Brain ChEI.	Oral Studies/endpoints used for dermal exposures.
4) CADUSAFOS	14-Day-Dog: Plasma ChEI.	1-Year Dog: Tremors, RBC and Brain ChEI.	IMPORT TOLERANCE. OCCUPATIONAL/RESIDENTIAL RISK ASSESSMENTS NOT REQUIRED			
5) CHLORETHOXYFOS	6-Month Ocular Tox. Dog: Plasma ChEI.	90-Day , 6-Month & 1-Year Dog: Plasma ChEI.	6-Month Ocular Tox. Dog: Plasma ChEI.	6-Month Ocular Tox.. Dog Oral: Plasma ChEI.	90-Day , 6-Month & 1-Year Dog: Plasma ChEI.	Oral Studies/endpoints used for dermal exposures.
6) CHLORPYRIFOS	28 Day-Human: Plasma ChEI/ Signs.	28-Day Human: Plasma ChEI/Signs.	28 Day-Human: Plasma ChEI/ Signs.	28 Day-Human Oral: Plasma ChEI/ Signs.	28 Day-Human Oral: Plasma ChEI.	Oral Study/Endpoint used for derma exposures.
7) CHLORPYRIFOS METHYL	INADEQUATE DATA BASE - UNACCEPTABLE STUDIES FOR TOXICOLOGY ENDPOINT SELECTION					
8) COUMAPHOS	90-Day Rat: RBC ChEI	1-Year Dog: Plasma and RBC ChEI.	21-Day Dermal Rat: RBC ChEI	21-Day Dermal Rat: RBC ChEI	Not required based on use pattern.	Oral study -90-Day Rat: RBC ChEI

Toxicology End Points Selection for Dietary & Non-Dietary Exposure Risk Assessments

CHEMICAL	ACUTE DIETARY	CHRONIC DIETARY	DERMAL EXPOSURE			INHALATION (ANY TIME PERIOD)
			SHORT-TERM	INTERMEDIATE-TERM	LONG-TERM	
9) DDVP	Acute-Human: RBC ChEI.	1-Year Dog: Plasma, RBC and Brain ChEI.	Acute-Human: RBC ChEI.	21-Day Human Oral: RBC ChEI. UF 3 x applied for use of LOEL.	Not required based on use pattern.	2-year inhalation -Rat: Plasma, RBC & Brain ChEI.
10) DIAZINON	Acu.Neuro.-Rat: Plasma ChEI.	43-Day Human: Plasma ChEI. UF 3 x for closeness of NOEL/LOEL and use of one sex.	43-Day Oral Human: Plasma ChEI. UF 3 x for closeness of NOEL/LOEL and use of one sex.	43-Day Human Oral: Plasma ChEI. UF 3 x for closeness of NOEL/LOEL and use of one sex.	43-Day Oral Human: Plasma ChEI. UF 3 x for closeness of NOEL/LOEL and use of one sex.	21-Day inhalation-Rat: Plasma & RBC ChEI. UF 3 x for use of LOEL
INADEQUATE DATA BASE -- UNACCEPTABLE STUDIES FOR TOXICOLOGY ENDPOINT SELECTION						
11) DICROTOPHOS	90-Day Neuro. Rat Oral: Plasma and RBC ChEI.	2-Year Rat: RBC and Brain ChEI.	90-Day Neuro. Rat Oral: Plasma and RBC ChEI.	90-Day Neuro. Rat Oral: Plasma and RBC ChEI.	2-year Rat Oral: RBC & Brain ChEI.	Oral Studies/endpoints used for dermal exposures.
12) DIMETHOATE	Acute.Neuro.-Rat: Plasma, & RBC ChEI; Clinical Signs.	1-Year Dog Oral: Plasma & RBC ChEI and Corneal / Retinal ChEI.	21-Day Dermal Rabbit: Plasma ChEI.	6-Month Rat Oral: Plasma, Erythrocyte & Brain ChEI.	1-Year Dog Oral: Plasma & RBC ChEI and Corneal/ Retinal ChEI.	90-Day inhalation Rat: Plasma, Erythrocyte & Brain ChEI.
13) DISULFOTON	21-Day-Human: Clinical signs of ChEI. LOEL used but NO additional UF since effects were seen on Day 19.	21-Day Human: Clinical signs of ChEI. UF 10 x for use of a LOEL.	21-Day Human Oral: Clinical signs of ChEI. UF 10 x for use of a LOEL.	21-Day-Human: Clinical signs of ChEI. UF 10 x for use of a LOEL.	21-Day-Human: Clinical signs of ChEI. UF 10 x for use of a LOEL	Oral Studies/endpoints used for dermal exposures.

TOXICOLOGY END POINTS SELECTION FOR DIETARY & NON-DIETARY EXPOSURE RISK ASSESSMENTS

CHEMICAL	ACUTE DIETARY	CHRONIC DIETARY	DERMAL EXPOSURE			INHALATION (ANY TIME PERIOD)
			SHORT-TERM	INTERMEDIATE-TERM	LONG-TERM	
15) ETHOPROP	90-Day Dog: Plasma ChEI on day 2.	5-Month & 1-Year Dog: Plasma ChEI.	90-Day Dermal-Rabbit: Plasma, Erythrocyte & Brain ChEI.	90-Day Dermal Rabbit: Plasma, Erythrocyte & Brain ChEI.	90-Day Dermal-Rabbit: Plasma, Erythrocyte & Brain ChEI.	90-Day oral endpoint for short-term. 1-year dog oral endpoint for Intermediate & Long-Term.
16) ETHYL PARATHION	Acute.Neuro.-Rat: Plasma & RBC ChEI.	1-Year Dog: Plasma and RBC ChEI. UF 3 x applied for use of a LOEL.	Acu.Neuro.Rat Oral: Plasma & RBC ChEI.	6-month Dog Oral: Plasma ChEI.	Not required based on use pattern.	Use of oral Endpoints (same as dermal).
17) FENAMIPHOS	Acute.Neuro.-Rat: Plasma & RBC ChEI. UF 3 x applied (use of a LOEL).	1-Year Dog: Plasma ChEI.	21-Day Dermal Rabbit: Plasma & Brain ChEI.	21-Day Dermal Rabbit: Plasma & Brain ChEI.	1-Year Dog Oral: Plasma ChEI.	21-Day Inhalation Rat: Plasma ChEI.
18) FENITROTHION	Acute Neuro - Rat Decreases in FOB and motor activity	1-Year Dog: Plasma Chel & Histopathology.	IMPORT TOLERANCE; OCCUPATIONAL/RESIDENTIAL RISK ASSESSMENTS NOT REQUIRED.			
19) FENTHION	28-Day Human: Plasma ChEI.	2-Year Monkey/28-Day Human: Plasma ChEI. UF 3 x for threshold NOEL/LOEL.	28-Day Human Oral: Plasma ChEI.	28-Day Human Oral: Plasma ChEI.	21-Day Human Plasma ChEI	Oral Studies/endpoints used for dermal exposures.
20) FONOFOS	NO DATA AVAILABLE.					

TOXICOLOGY END POINTS SELECTION FOR DIETARY & NON-DIETARY EXPOSURE RISK ASSESSMENTS

CHEMICAL	ACUTE DIETARY	CHRONIC DIETARY	DERMAL EXPOSURE			INHALATION (ANY TIME PERIOD)
			SHORT-TERM	INTERMEDIATE-TERM	LONG-TERM	
21) ISOFPENPHOS	Acute.Neuro.-Rat: Plasma, RBC & Brain ChEI and clinical signs. UF 3 x for use of a LOEL.	2-Gen. Reproduction: Clinical signs and increased pup mortality.	Acu.Neuro.Rat Oral: Plasma, RBC & Brain ChEI and clinical signs. UF 3 x for use of a LOEL.	90-day Neuro. Rat Oral: Plasma, RBC & Brain ChEI.	90-day Neuro. Rat Oral: Plasma, RBC & Brain ChEI	Oral Studies/endpoints used for dermal exposures.
NO DATA AVAILABLE						
22) ISAZOPHOS						
23) MALATHION	Developmental-Rat: maternal toxicity	2-Year Rat: Plasma ChEI.	21-Day Dermal Rabbit: Plasma, RBC & Brain ChEI.	21-Day Dermal Rabbit: Plasma, RBC & Brain ChEI.	2-year Rat Oral: Plasma ChEI.	90-Day Inhalation-Rat: Plasma & RBC ChEI; respiratory pathology
24) METHAMIDAPHOS	Acute.Neuro.-Rat: Plasma, RBC & Brain ChEI.	8-Week Rat: Brain ChEI.	21-Day Dermal Rat Plasma, RBC & Brain ChEI.	21-Day Dermal Rat Plasma, RBC & Brain ChEI.	21-Day Dermal Rat Plasma, RBC & Brain ChEI.	90-day inhalation-Rat: Plasma, RBC & Brain ChEI.
25) METHIDATHION	90-Day Rat: Serum & Brain ChEI.	1-Year Dog: RBC ChEI and histopathology.	90-Day Rat Oral: Serum & Brain ChEI.	90-Day Rat Oral: Serum & Brain ChEI.	1-Year Dog Oral: RBC ChEI and liver lesions.	Oral Studies/endpoints used for dermal exposures.
26) METHYL PARATHION	Acute.Neuro.-Rat: ChEI, abnormal FOB, neuropathology.	2-Year Rat: RBC ChEI, systemic toxicity and neuropathology.	Acu.Neuro.Rat Oral: ChEI, abnormal FOB, neuropathology	2-year Rat Oral: RBC ChEI, neuropathology & systemic toxicity.	2-year Rat Oral :RBC ChEI, neuropathology & systemic toxicity.	Oral Studies/endpoints used for dermal exposures.
27) NALED	28-Day Rat: Plasma & Brain ChEI and cholinergic signs.	2-Year Rat: Brain ChEI.	28-Day Dermal Rat: Plasma, RBC & Brain ChEI.	28-Day Dermal Rat: Plasma, RBC & Brain ChEI.	2-year Rat Oral : Brain ChEI.	90-Day inhalation-Rat: Plasma & RBC ChEI.

TOXICOLOGY END POINTS SELECTION FOR DIETARY & NON-DIETARY EXPOSURE RISK ASSESSMENTS

CHEMICAL	ACUTE DIETARY	CHRONIC DIETARY	DERMAL EXPOSURE			INHALATION (ANY TIME PERIOD)
			SHORT-TERM	INTERMEDIATE-TERM	LONG-TERM	
28) ODM	Acute, Neuro. Rat: Plasma, RBC and Brain ChEI. UF 3 x for use of a LOEL	120-Days Human: Plasma and RBC ChEI.	7-Day Dermal-Rat: RBC & Brain ChEI.	14-Day Dermal Rat: Brain ChEI.	120-Day Human Oral: Plasma & RBC ChEI.	Acute Inhalation- Rat. UF 3 x for use of a LOEL
29) PHORATE	1-Year Dog: RBC & Brain ChEI.	1-Year Dog: RBC & Brain ChEI.	1-Year Dog Oral: RBC & Brain ChEI.	1-Year Dog Oral: RBC & Brain ChEI.	1-Year Dog Oral: RBC & Brain ChEI.	Oral Studies/endpoints used for dermal exposures.
30) PHOSMET	2-year Rat: Serum & Plasma ChEI at 2-4 weeks. Developmental- Rabbit: Maternal RBC ChEI.	2-year Rat: Serum & Plasma ChEI 1-Year Dog: Plasma, RBC & Brain ChEI.	2-year Rat Oral: Serum & Plasma ChEI at 2-4 weeks.	2-year Rat Oral: Serum & Plasma ChEI at 2-4 weeks.	Not required based on use pattern.	Oral Studies/endpoints used for dermal exposures.
31) PHOSTEBUPIRIM	28/56-Day Human: lack of ChEI up to day 7.	56-Day Human: Plasma ChEI. Total UF 30 x for use of LOEL (3 x) & data gaps for chronic studies (10x)	28/56-Day Human Oral: lack of ChEI up to day 7.	1-Year Dog Oral: Plasma, RBC & Brain ChEI.	1-Year Dog Oral: Plasma, RBC & Brain ChEI.	28-Day Inhalation-Rat: RBC ChEI.
32) PIRIMIPHOS METHYL	28/56-Day Human: lack of ChEI up to day 7.	56-Day Human: Plasma ChEI. Total UF 30 x for use of LOEL (3 x) & data gaps for chronic studies (10x)	28/56-Day Human Oral: lack of ChEI up to day 7.	56-Day Human Oral: Plasma ChEI. UF 3 x for use of LOEL.	56-Day Human Oral: Plasma ChEI. Total UF 30 x for use of LOEL (3 x) & data gaps for chronic studies (10x).	Oral Studies/endpoints used for dermal exposures.
33) PROFENOPHOS	Special Acute Study- Rat: Plasma & RBC ChEI.	6-Month Dog: Plasma & RBC ChEI.	21-Day Dermal Rabbit: Serum, RBC & Brain ChEI.	21-Day Dermal Rabbit: Serum, RBC & Brain ChEI.	6-Month-Dog Oral: Plasma & RBC ChEI.	21-Day Inhalation-Rat: Plasma, RBC & Brain ChEI.

TOXICOLOGY END POINTS SELECTION FOR DIETARY & NON-DIETARY EXPOSURE RISK ASSESSMENTS

CHEMICAL	ACUTE DIETARY	CHRONIC DIETARY	DERMAL EXPOSURE			INHALATION (ANY TIME PERIOD)
			SHORT-TERM	INTERMEDIATE-TERM	LONG-TERM	
34) PROPE/TAMPHOS	4-Week Mouse: Brain ChEI.	2-Year Mouse:	6-Month Dog & 4-Week Mouse: ChEI.	6-Month Dog & 4-Week Mouse: ChEI	6-Month Dog & 4-Week Mouse: ChEI	21-Day Inhalation-Rat:
35) SUI,FOTEPP	NO DATA AVAILABLE					
36) TEMEPHOS	Non-Food Use-Risk Assessment Not Required	Non-Food Use-Risk Assessment Not Required	90-Day Rat: Plasma ChEI.	90-Day Rat Oral: Plasma ChEI.	90-Day Rat Oral: Plasma ChEI.	Oral Studies/endpoints used for dermal exposures.
37) TERBUFOS	28-Day Dog: Plasma ChEI.	28-Day Dog: Plasma ChEI.	28-Day Dog Oral: Plasma ChEI.	28-Day Dog Oral: Plasma ChEI.	28-day Dog Oral: Plasma ChEI.	21-Day Inhalation-Rat: Plasma, RBC & Brain ChEI.
38)TETRACHLORVINPHOS	13-Week Rat: Plasma and RBC ChEI>.	2-Year Rat: Adrenal and histopathology.	13-Week Rat: Plasma and RBC ChEI>.	13-Week Rat: Plasma and RBC ChEI>.	2-Year Rat: Adrenal and histopathology	Oral Studies/endpoints used for dermal exposures.
39) TRIBUFOS	Developmental-Rat: Maternal Plasma & RBC ChEI.	1-Year Dog: Plasma ChEI.	21-Day Dermal Rabbit: Plasma, RBC & Brain ChEI. UF 10 for concern for severity of toxicity	21-Day Dermal Rabbit: Plasma, RBC & Brain ChEI. UF 10 for concern for severity of toxicity.	Not required based on use pattern.	Not required based on use pattern.
40) TRICHLORFON	Human: Plasma & RBC ChEI as well as clinical signs.	10-Year Monkey: Brain ChEI.	21-Day Dermal Rabbit: RBC ChEI.	21-Day Dermal Rabbit: RBC ChEI.	10-Year Monkey: Brain ChEI.	21-Day Inhalation Rat: ChEI.

ATTACHMENT - 5

DOSES SELECTED FOR DIETARY & NON DIETARY EXPOSURE RISK ASSESSMENTS

DOSES SELECTED FOR DIETARY & NON-DIETARY EXPOSURE RISK ASSESSMENTS

DOSES SELECTED FOR DIETARY & NON- DIETARY EXPOSURE							
CHEMICAL	ACUTE DIETARY NOEL (mg/kg/day)	CHRONIC DIETARY NOEL (mg/kg/day)	DERMAL ABSORPTION FACTOR FOR USE WITH ORAL DOSES FOR DERMAL EXPOSURE RISK ASSESSMENTS	DERMAL EXPOSURE			INHALATION EXPOSURE (ANY TIME' PERIOD)
				SHORT-TERM	INTERMEDIATE- TERM	LONG-TERM	
				NOEL (mg/kg/day)			
				The doses in these columns are ORAL values unless specified			
1) ACEPHATE	0.5	0.12	Not Required; dermal NOEL	Dermal: 12.0	Dermal: 12.0	Dermal: 12.0	>0.0005
2) AZINPHOS METHYL	LOEL=1.0	0.149	42% (Rat Study)	0.56	0.149	Not Required	0.0012
3) BENSULIDE	15.0	0.5	100% (Default)	5.5	0.5	0.5	Oral Equivalents
4) CADUSAFOS	0.02	0.001	Not Required	IMPORT TOLERANCE OCCUPATIONAL/RESIDENTIAL NOT REQUIRED			
5) CHLORETHOXYPHOS	0.06	0.06	100% (Default)	0.06	0.06	0.06	Oral Equivalents
6) CHLORPYRIFOS	0.1	0.03	1% (-Human Study)	0.1	0.03	0.03	Oral Equivalents
IN ADEQUATE DATA BASE - UNACCEPTABLE STUDIES FOR TES							
7) CHLORPYRIFOS METHYL				Dermal: 0.5	Dermal: 0.5	Not Required	Oral Equivalents
8) COUMAPHOS	0.2	0.025	Not Required; dermal NOEL				
9) DDVP	0.5	0.05	11% (Estimated-Rat Study)	0.5	LOEL=0.1	0.05	0.00005
10) DIAZINON	0.25	0.02	100% (Default)	0.02	0.02	0.02	LOEL =0.0001
IN ADEQUATE DATA BASE - UNACCEPTABLE STUDIES FOR TES							
11) DICROTOPHOS							
12) DIMETHOATE	0.06	0.05	11% (Rat Study)	0.06	0.06	0.05	Oral Equivalents
13) DISULFOTON	0.25	0.013	36% (Rat Study)	Dermal: 0.4	0.03	0.013	0.00016

DOSES SELECTED FOR DIETARY & NON-DIETARY EXPOSURE RISK ASSESSMENTS

CHEMICAL	ACUTE DIETARY NOEL (mg/kg/day)	CHRONIC DIETARY NOEL (mg/kg/day)	DERMAL ABSORPTION FACTOR FOR USE WITH ORAL DOSES FOR DERMAL EXPOSURE RISK ASSESSMENTS	DERMAL EXPOSURE			INHALATION EXPOSURE (ANY 'TIME' PERIOD) NOEL (mg/L)
				SHORT-TERM	INTERMEDIATE- TERM	LONG-TERM	
The doses in these columns are ORAL values unless specified							
14) ETHION	LOEL=0.05	LOEL =0.05	3.3% (Human Study)	LOEL= 0.05	LOEL =0.05	LOEL=0.05	Oral Equivalents
15) ETHOPROP	0.025	0.01	Not Required; dermal NOEL	Dermal: 0.1	Dermal: 0.1	Dermal: 0.1	Oral Equivalents
16) ETHYL PARATHION	0.025	LOEL=0.01	100% (Default)	0.025	0.025	Not Required	Oral Equivalents
17) FENAMIPHOS	LOEL=0.37	0.01	100% (Default)	Dermal: 2.5	Dermal: 2.5	Oral: 0.01	0.00025
18) FENITROTHION	12.5	0.125	Not Required	IMPORT TOLERANCE; OCCUPATIONAL/RESIDENTIAL NOT REQUIRED			
19) FENTHION	0.07	NOEL/ LOEL=0.02	20% (Estimated)	0.07	0.02	0.02	Oral Equivalents
20) FONOFOS	NO DATA AVAILABLE						
21) ISOFPENPHOS	LOEL=2.0	0.08	100% (Default)	LOEL=2.0	0.06	0.06	Oral Equivalents
22) ISAZOPHOS	NO DATA AVAILABLE						
23) MALATHION	50.0	4.0	10% (Human Study)	50.0	50.0	4.0	LOEL=0.1
24) METHAMIDAPHOS	0.3	0.03	Not Required; dermal NOEL	1.0	1.0	1.03	0.001
25) METHIDATHION	0.2	0.15	100% (Default)	0.2	0.2	0.15	Oral Equivalents
26) METHYL PARATHION	0.025	0.02	100% (Default)	0.025	0.02	0.02	Oral Equivalents

DOSES SELECTED FOR DIETARY & NON-DIETARY EXPOSURE RISK ASSESSMENTS							
CHEMICAL	ACUTE DIETARY NOEL (mg/kg/day)	CHRONIC DIETARY NOEL (mg/kg/day)	DERMAL ABSORPTION FACTOR FOR USE WITH ORAL DOSES FOR DERMAL EXPOSURE RISK ASSESSMENTS	DERMAL EXPOSURE			INHALATION EXPOSURE (ANY TIME' PERIOD) NOEL (mg/L)
				SHORT-TERM	INTERMEDIATE- TERM	LONG-TERM	
The doses in these columns are ORAL values unless specified							
27) NALED	1.0	0.2	100% (Default)	1.0	1.0	0.2	0.00023
28) ODM	LOEL=2.5	0.05	Not Required; dermal NOEL	Dermal: 5.0	Dermal: 0.3	Not Required	LOEL=0.177
29) PHORATE	0.05	0.05	100% (Default)	0.05	0.05	0.05	Oral Equivalents
30) PHOSMET	1.1	1.1	10% (Rat Study)	1.1	1.1	Not Required	Oral Equivalents
31) PHOSTEBUPIRIM	0.1	0.02	100% (Default)	0.1	0.02	0.02	0.00016
32) PIRIMIPHOS METHYL	0.25	LOEL=0.25	100% (Default)	0.25	LOEL=0.25	LOEL=0.25	Oral Equivalents
33) PROFENOPHOS	0.5	0.005	100% (Default)	Dermal: 1.0	Dermal: 1.0	0.005	LOEL=0.068
34) PROPETAMPHOS	0.05	0.05	100% (Default)	0.05	0.05	0.05	LOEL=0.027
35) SULFOTEPP	NO DATA AVAILABLE						
36) TEMEPHOS	Non food-use; Not required		100% (Default)	0.3	0.3	0.3	Oral Equivalents
37) TERBUFOS	0.005	0.005	100% (Default)	0.005	0.005	0.005	0.00001
38) TETRACHLORVINPHOS	5.0	4.23	9.57% (Rat Study)	5.0	5.0	4.23	Oral Equivalents
39) TRIBUFOS	1.0	0.1	Not Required; dermal LOEL	Dermal LOEL: 2.0	Dermal LOEL: 2.0	Not Required	Not Required

DOSES SELECTED FOR DIETARY & NON-DIETARY EXPOSURE RISK ASSESSMENTS							
CHEMICAL	ACUTE DIETARY	CHRONIC DIETARY	DERMAL ABSORPTION FACTOR FOR USE WITH ORAL DOSES FOR DERMAL EXPOSURE RISK ASSESSMENTS	DERMAL EXPOSURE			INHALATION EXPOSURE (ANY TIME' PERIOD)
	NOEL (mg/kg/day)	NOEL (mg/kg/day)		SHORT-TERM	INTERMEDIATE- TERM	LONG-TERM	
				NOEL (mg/kg/day) The doses in these columns are ORAL values unless specified			
40) TRICHLORFON	2.5	0.2	10 % (Estimated)	Dermal: 100.0	Dermal: 100.0	0.2	0.0127