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 made 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
## *H*AZARD *I*DENTIFICATION *A*SSESSMENT *R*EVIEW *C*OMMITTEE

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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ATTACHMENTS

## 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 the 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* exposures, 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, in 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 as compared to maternal animals (i.e., cholinesterase inhibition occurred at the same doses in the pups and parental animals).

**1. <u>Prenatal Developmental Toxicity Study in Rats</u>**

(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 organophosphates 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 HIARC 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. <u>Prenatal Developmental Toxicity Study in Rabbits</u>**

(a) The NOELs, LOELs and endpoints selected for the maternal and developmental toxicity in the prenatal developmental toxicity study in rabbits are provided in **Attachment 2.** No evidence of enhanced susceptibility was observed for 34 of 40 organophosphates following *in utero* exposure to pregnant rabbits. 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 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 HIARC 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 decreases 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 in skeletal variations observed in the fetuses . |
| PROPETAMPHOS | The increased resorptions were not accompanied by decreases in litter size. |

**3. <u>Two-Generation Reproduction Study in Rats</u>**

(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 organophosphates 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 systemic 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. |

## 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<br><br>Neuropathology: Negative<br><br>NTE: Negative<br><br><u>Literature Data</u><br>NTE: Positive | Neuropathology: Negative<br><br>Cholinesterase activity measured (ChEI):Yes | Neuropathology: Negative<br><br>ChEI measured: Yes | No increased Susceptibility | No increased Susceptibility | Not Required | None |
| **2) AZINPHOS METHYL** | OPIDN: Negative<br><br>Neuropathology: Negative<br><br>Confirmatory NTE Study Required | Neuropathology: Negative<br><br>ChEI measured: Yes | Neuropathology: Negative<br><br>ChEI measured: Yes | No increased Susceptibility | No increased Susceptibility | Not Required | None |
| **3) BENSULIDE** | OPIDN: Negative<br><br>NTE: Negative | Neuropathology: Negative<br><br>ChEI measured: Yes | Study Waived | No increased Susceptibility | No increased Susceptibility | Not Required | None |

| 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<br><br>(No histopathology or NTE data)<br><br>Confirmatory NTE Study Required | Not available | Not available | No increased Susceptibility | No increased Susceptibility | **Reserved**<br><br>Pending<br><br>Acute Hen,<br><br>Acute & 90-day rat neurotoxicity studies | Acute-Hen<br><br>Acute -Rat Neurotoxicity<br><br>90-Day -Rat Neurotoxicity |
| | | No data to assess neurotoxicity, cholinesterase inhibition, behavioral effects, or neuropathology | | | | | |
| **5) CHLOR-ETHOXYFOS** | OPIDN: Negative<br><br>Neuropathology: Negative | Neuropathology: Negative<br><br>ChEI measured: Yes | Waived since other studies showed no evidence of neuropathology | No increased Susceptibility | No increased Susceptibility | Not Required | None |
| **6) CHLORPYRIFOS** | OPIDN: Negative<br><br><u>Literature Data</u><br><br>OPIDN: Positive<br><br>NTE: Positive | Neuropathology: Negative<br><br>ChEI measured: Yes | Neuropathology: Negative<br><br>ChEI measured: Yes | No increased Susceptibility<br><br><u>Literature Data</u><br>Enhanced susceptibility seen in young rats (ChEI, behavioral and other developmental neurotoxic effects). | No increased Susceptibility | **Required**<br><br>Literature Data<br><br>OPIDN: Positive | Develop-mental Neurotoxicity Study in Rats |

| 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<br><br>90-Day Rat Neurotoxicity<br><br>Develop-mental -Rat & Rabbit<br><br>2-Generation Reproduction |
| | | No data to assess neurotoxicity, cholinesterase inhibition, behavioral effects, or neuropathology | | | | | |
| **8) COUMAPHOS** | OPIDN: Negative<br><br>Neuropathology: Negative<br><br>Confirmatory NTE Study Required | Not available | Not available | No increased Susceptibility | No increased Susceptibility | **Reserved**<br><br>Pending Acute & 90-day neurotoxicity studies | Acute - Rat<br><br>90-Day-Rat |

| 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) DDVP** | Acute<br>OPIDN: Equivocal<br>28-day<br>Neuropathology: Negative<br>NTE: Negative | Neuropathology Negative<br>ChEI measured: Yes | Neuropathology Negative<br>ChEI measured: Yes | No increased Susceptibility | No increased Susceptibility | **Reserved**<br>Pending results of developmental toxicity study in Guinea Pigs requested by HIARC. See HIARC Report. | None |
| **10) DIAZINON** | OPIDN: Negative<br>Neuropathology: Negative<br>NTE: Negative | Neuropathology Negative<br>ChEI measured: Yes | Neuropathology Negative<br>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 | | | |

| 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<br><br>Neuropathology: Negative<br><br>NTE: Equivocal<br><br>Confirmatory NTE study Required | Neuropathology: Negative<br><br>ChEI measured: No. | Neuropathology: Negative<br><br>ChEI measured: Yes | No increased Susceptibility | No increased Susceptibility | Not Required | None |
| **13) DISULFOTON** | Unacceptable Study | Neuropathology: Negative<br><br>ChEI measured: Yes | Neuropathology: Equivocal<br><br>ChEI measured: Yes | No increased Susceptibility | No increased Susceptibility | **Reserved**<br><br>Pending Acute Hen study | Acute Hen |
| **14) ETHION** | OPIDN: Negative<br><br>Neuropathology: Negative<br><br>Confirmatory NTE Study Required | Neuropathology: Negative<br><br>ChEI measured: No | Equivocal neuropathology at high dose<br><br>ChEI measured: No | No increased Susceptibility | No increased Susceptibility | Not required | None |

| 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<br><br>Neuropathology: Negative<br><br>NTE requested by RfD Committee 5/96 | Neuropathology: Negative<br><br>ChEI measured: Yes | Neuropathology: Negative<br><br>ChEI measured: Yes | No increased Susceptibility | No increased Susceptibility | Not Required | None |
| **16) ETHYL PARATHION** | OPIDN: Negative<br><br>NTE : Negative<br><br>Neuropathology: Negative | Neuropathology: Negative<br><br>ChEI measured: Yes | Neuropathology: Negative<br><br>ChEI measured: Yes | No increased Susceptibility | No increased Susceptibility | Not Required | None |
| **17) FENAMIPHOS** | OPIDN: Negative<br><br>Neuropathology: Negative<br><br>Confirmatory NTE Study Required | Neuropathology: Negative<br><br>ChEI measured: Yes | Neuropathology: Negative<br><br>ChEI measured: Yes | No increased Susceptibility | No increased Susceptibility | Not required | None |

| 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) FENITROTHION** | OPIDN: Negative<br><br>Neuropathology: Negative<br><br>Confirmatory NTE Study Required | Neuropathology: Negative<br><br>ChEI measured: No | Neuropathology: Negative<br><br>ChEI measured: Yes | No increased Susceptibility | No increased Susceptibility | Not required | None |
| **19) FENTHION** | <u>Acute (Oral & Dermal)</u><br><br>OPIDN: Negative<br><br>Neuropathology: Negative<br><br>NTE: Negative<br><br><u>Subchronic</u><br><br>OPIDN: Negative<br><br>Neuropathology: Negative | Neuropathology: Negative<br><br>ChEI measured: Yes | Neuropathology: Negative<br><br>ChEI measured: Yes | No increased Susceptibility | No increased Susceptibility | No Required | None |
| **20) FONOFOS** | NO DATA AVAILABLE | | | | | | |

| 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><br><br>OPIDN: Negative<br><br>Neuropathology: Negative<br><br>Confirmatory NTE Study Required<br><br><u>Subchronic</u><br><br>OPIDN: Negative<br><br>Neuropathology: Negative | Neuropathology: Negative<br><br>ChEI measured: Yes | Neuropathology: Negative<br><br>ChEI measured: Yes | No increased Susceptibility | No increased Susceptibility | Not Required | None |
| **22) TRIUMPH (ISAZOPHOS)** | **NO DATA AVAILABLE** | | | | | | |

| 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<br><br>Neuropathology: Negative<br><br>**<u>Literature Data</u>**<br><br>NTE:-Negative | Neuropathology: Negative<br><br>ChEI measured: Yes | Neuropathology: Negative<br><br>ChEI measured: Yes | No increased Susceptibility | No increased Susceptibility | Not required | None |

| 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** | Acute & Subchronic<br><br>OPIDN: Negative<br><br>Neuropathology: Negative<br><br>NTE: Negative (Acute)<br>Positive (subchronic)<br><br>*Racemate & Enantiomers*<br><br>**Positive** for OPIDN at extremely high levels<br><br>**Literature Data**<br><br>Polyneuropathy & peripheral neuropathy in humans at high doses.<br><br>Polyneuropathy in adult hens at high | Neuropathology: Negative<br><br>ChEI measured: Yes | Neuropathology: Negative<br><br>ChEI measured: Yes | No increased Susceptibility | No increased Susceptibility | **Required**<br><br>Positive NTE<br><br>Polyneuropathy in hens and Delayed peripheral neuropathy in humans in published studies | Develop-mental Neurotoxicity Study in Rats |

| 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<br><br>Neuropathology: Negative<br><br>Confirmatory NTE Study Required | Neuropathology: Negative<br><br>ChEI measured: Yes | Negative for neuropathology<br><br>ChEI measured: Yes | No increased Susceptibility | No increased Susceptibility | Not required | None |
| **26) METHYL PARATHION** | OPIDN: Negative<br><br>Neuropathology: Negative<br><br>Confirmatory NTE Study Required | **Positive** for neuropathology<br><br>ChEI measured: Yes | **Equivocal** for neuropathology<br><br>ChEI measured: Yes | No increased Susceptibility in Subdivision F studies.<br><br>**<u>Literature Data</u>**<br><br>**Qualitative evidence of increased Susceptibility seen in open literature rat studies via subcutaneous. & intraperitoneal routes at high doses.** | No increased Susceptibility | **Required**<br><br>Positive neuropathology in acute rat<br><br>Equivocal neuropathology in subchronic rat<br><br>Positive Neuropathology in Chronic Rat and 1-Year Rat | Develop-mental Neurotoxicity Study in Rats |

| 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** | <u>Acute</u><br><br>OPIDN: Positive<br><br>Neuropathology: Positive<br><br>NTE: Negative<br><br><u>Subchronic</u><br><br>OPIDN: Negative | Neuropathology: Negative<br><br>ChEI measured: No | Neuropathology: Negative<br><br>ChEI measured: No | No increased Susceptibility | No increased Susceptibility | Not Required | None |

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

| 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<br><br>Neuropathology: Negative<br><br>NTE: Negative<br><br>Need re-review | Not available | Not available | No increased Susceptibility | No increased Susceptibility | **Reserved**<br><br>Pending Acute & 90-day rat neurotoxicity studies & Confirmation of results of hen studies | Acute-Rat Neurotoxicity<br><br>90-day Rat Neurotoxicity |
| | | No data to assess neurotoxicity, cholinesterase inhibition, behavioral effects, or neuropathology | | | | | |
| **31) PHOSTE-BUPIRIM** | OPIDN: Negative<br><br>Neuropathology: Negative<br><br>Confirmatory NTE Study Required | Not available | Not available | No increased Susceptibility | No increased Susceptibility | **Reserved**<br><br>Pending Acute & 90-day rat neurotoxicity studies | Acute-Rat Neurotoxicity<br><br>90-day Rat Neurotoxicity |
| | | No data to assess neurotoxicity, cholinesterase inhibition, behavioral effects, or neuropathology | | | | | |
| **32) PIRIMIPHOS-METHYL** | No Acute study<br><br>Subchronic: Unacceptable | Neuropathology: Negative<br><br>ChEI measured: Yes | Neuropathology: Negative<br><br>ChEI measured: Yes | No increased Susceptibility | No increased Susceptibility | **Reserved**<br><br>Pending Acute Hen & Chronic Dog/Rat | Acute-Hen<br><br>Chronic Toxicity-Dog<br><br>Chronic Toxicity-Rat |

| 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 | | | | |
| **33) PROFENFOS** | OPIDN: Negative<br><br>Neuropathology: Negative<br><br>Confirmatory NTE Study Required | Neuropathology: Negative<br><br>ChEI measured: Yes | Neuropathology: Negative<br><br>ChEI measured: Yes | No increased Susceptibility | No increased Susceptibility | Not Required | None |
| **34) PROPETAMPHOS** | OPIDN: Negative Neuropathology: Negative<br><br>Confirmatory NTE Study Required | Neuropathology: Negative<br><br>ChEI measured: No | Neuropathology: Negative<br><br>ChEI measured: No | No increased Susceptibility | No increased Susceptibility | Not Required | None |
| **35) SULFOTEPP** | **NO DATA AVAILABLE - INADEQUATE DATA BASE** | | | | | | |
| **36) TEMEPHOS** | Study Unacceptable<br><br>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. | | | |

| 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<br><br>Neuropathology: Negative<br><br>Confirmatory NTE Study Required | Not available | Not available | No increased Susceptibility | No increased Susceptibility | **Reserved**<br><br>Pending Acute & 90-day rat neurotoxicity studies | Acute-Rat Neurotoxicity<br><br>90-day Rat Neurotoxicity |
| | | No data to assess neurotoxicity, cholinesterase inhibition, behavioral effects, or neuropathology | | | | | |
| **38) TETRACHLOR-VINPHOS** | OPIDN: Negative<br><br>Neuropathology: Negative<br><br>Confirmatory NTE Study Required | Neuropathology: Negative<br><br>ChEI measured: No | Neuropathology: Negative<br><br>ChEI measured: No | No increased Susceptibility | No increased Susceptibility | Not required | None |

| 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<br><br>OPIDN: Positive<br><br>Neuropathology: Positive<br><br>Confirmatory NTE Study Required | Not available | Not available | No increased Susceptibility | No increased Susceptibility | **Required**<br><br>Evidence of neuropathology in the subchronic hen study | Acute -Hen (subchronic is via the dermal route).<br><br>Acute - Rat Neurotoxicity<br><br>90-day - Rat Neurotoxicity<br><br>Develop-mental Neurotoxicity Study in Rats |
| | | No data to assess neurotoxicity, cholinesterase inhibition, behavioral effects, or neuropathology | | | | | |

| CHEMICAL | ACUTE DELAYED NEUROTOXICITY HEN | MAMMALIAN NEUROTOXICITY - RAT | | EVIDENCE OF ENHANCED SUSCEPTIBILITY IN DEVELOPMENTAL STUDIES<br><br>RAT & RABBIT | EVIDENCE OF ENHANCED SUSCEPTIBILITY IN THE<br><br>2-GENERATION REPRODUCTION RAT | REQUIREMENT OF A DEVELOPMENTAL NEUROTOXICITY STUDY IN RATS | DATA GAPS |
|---|---|---|---|---|---|---|---|
| | | ACUTE | SUBCHRONIC | | | | |
| **40) TRICHLORFON** | <u>Acute</u><br><br>OPIDN: Positive<br><br>Neuropathology: Positive<br><br>Confirmatory NTE Study Required<br><br><u>Subchronic</u><br><br>OPIDN: Negative<br><br>Neuropathology: Positive | Not available | In Review | No increased Susceptibility (Rabbit)<br><br>**Rat (unacceptable)** | No increased Susceptibility | **Reserved**<br><br>1)Pending results of the developmental toxicity study in Guinea Pig required by HIARC.<br><br>2) Receipt and review of the Developmental toxicity study in rats | Acute-Rat Neurotoxicity<br><br>90-day Rat Neurotoxicity<br><br>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 Committe 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 subchonic 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 Committe 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 Safet 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 developmetnatl 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.<br><br>2) No evidence of neuropathology in rats following single or repeated exposures.<br><br>3) The requirement for a Developmental Neurotoxicity Study in Rats placed in *Reserve* status pending receipt of acute delayed neurotoxicity study in hens. |
| DISULFOTON | 1) Data gap for Acute Delayed Neurotoxicity Study in Hen<br><br>2) Equivocal evidence of neuropathology in the Subchronic Neurotoxicity Study in Rats.<br><br>3) The requirement for a Developmental Neurotoxicity Study in Rats placed in *Reserve* 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.<br><br>2) Data gap for Acute and Subchronic Neurotoxicity Studies in Rats.<br><br>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 Coumophos.<br><br>4) The requirement for a Developmental Neurotoxicity Study in Rats placed in *Reserve* 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.<br><br>2) Data gap for Acute and Subchronic Neurotoxicity Studies in Rats.<br><br>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.<br><br>4) The requirement for a Developmental Neurotoxicity Study in Rats placed in *Reserve* 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.<br><br>2) Data gap for Acute and Subchronic Neurotoxicity Studies in Rats.<br><br>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.<br><br>4) The requirement for a Developmental Neurotoxicity Study in Rats placed in *Reserve* 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.<br><br>2) Data gap for Acute and Subchronic Neurotoxicity Studies in Rats.<br><br>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.<br><br>4) The requirement for a Developmental Neurotoxicity Study in Rats placed in *Reserve* 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.<br><br>2) Data gap for Acute and Subchronic Neurotoxicity Studies in Rats.<br><br>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.<br><br>4) The requirement for a Developmental Neurotoxicity Study in Rats placed in *Reserve* 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..<br><br>2)In studies from *open literature*, 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 $LD_{50}$.<br><br>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.<br><br>4) Based on this evidence, a Developmental Neurotoxicity Study in Rats is **required** |

### 3. Recommendation to the FQPA Safety Committe for *RETAINING* 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 **retained** for the organophosphates listed below. The rational 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.<br><br>2) Therefore, data on organophosphate induced delayed neurotoxicity (OPIDN), NTE 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 Cadusofos.<br><br>3) The requirement for a Developmental Neurotoxicity Study in Rats placed in *Reserve* 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.<br><br>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.<br><br>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.<br><br>2) In studies (published) conducted in various reputable scientific research laboratories and reported in the open literature, qualitative evidence of enhanced susceptibility to perinatal rats has been identified following subcutaneous and intraperitoneal administration at high doses.<br><br>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.<br><br>4) Even though these routes of exposure (i.e., subcutaneous and intraperitoneal) are not the 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 *in vivo* 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 *in vitro* alkaline elution assay (not confirmed *in vivo*). Based on this, HIARC recommended a mouse specific locus test. |
| TRIBUFOS | 1) Evidence of OPIDN and neuropathology in hens following repeated dermal applications in a Subchronic Delayed Neurotoxicity Study.<br><br>2) Data gap for Acute Delayed Neurotoxicity Study in Hen Acute and Subchronic Neurotoxicity Studies in Rats.<br><br>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.<br><br>4) Ocular effects and neuropathology at low doses in various other studies.<br><br>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.<br><br>2) Evidence of neuropathology in hens in the Subchronic Delayed Neurotoxicity Study..<br><br>3) Data gap for Acute and Subchronic Neurotoxicity Studies in Rats.<br><br>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.<br><br>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.<br><br>6) Open literature identified a developmental toxicity in Guinea Pigs in which oral administration of Triclorfon resulted in decreases in brain weights.<br><br>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 provide 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 ADDITOINAL 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<br><br>Residential, Short, Intermediate and Long-Term Dermal | 10 | Use of a LOEL for in the critical (human) study.<br><br>Use of the human study with a LOEL and results of a 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/LOE 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<br><br>Inhalation (any time period) | 3 | Use of a LOEL in the critical (acute neurotoxicity) study.<br><br>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 this meeting for 15 organophosphates are summarized below:

| MODIFICATIONS MADE IN THE TOXICOLOGY ENDPOINT SELECION | | | | | | |
|---|---|---|---|---|---|---|
| **CHEMICAL NAME** | **CHANGED PARAMETER** | **DOSES** | | **END POINT** | | **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><br><br>Short-Term: Oral NOEL=5.5 mg/kg/day<br><br>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><br><br>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. |

| MODIFICATIONS MADE IN THE TOXICOLOGY ENDPOINT SELECION | | | | | | |
|---|---|---|---|---|---|---|
| **CHEMICAL NAME** | **CHANGED PARAMETER** | **DOSES** | | **END POINT** | | **RATIONALE FOR CHANGE** |
| | | **PREVIOUS SELECTION** | **CHANGED TO** | **PREVIOUS SELECTION** | **CHANGED TO** | |
| **COUMOPHOS** | Inhalation (Any Time Period) | None selected | Oral Equivalents<br><br>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<br><br>Short-and Intermediate Term: Oral NOEL=0.06 mg/kg/day<br><br>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. |

| MODIFICATIONS MADE IN THE TOXICOLOGY ENDPOINT SELECION | | | | | | |
|---|---|---|---|---|---|---|
| **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 | Oral Equivalents<br><br>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 | Oral Equivalents<br><br>Short Term: Oral NOEL = 0.025 mg/kg/day<br><br>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 SELECION | | | | | | |
|---|---|---|---|---|---|---|
| **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<br><br>Short Term: Oral NOEL = 0.07 mg/kg/day<br><br>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. |
| **ISOFENPHOS** | 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<br><br>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 SELECION | | | | | | |
|---|---|---|---|---|---|---|
| **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<br><br>Short-and Intermediate Term: Oral NOEL=0.2 mg/kg/day<br><br>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 SELECION | | | | | | |
|---|---|---|---|---|---|---|
| **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<br><br>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 | <u>Oral Equivalents</u><br><br>Short-and Intermediate Term: Oral NOEL=5.0 mg/kg/day<br><br>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 SELECION | | | | | | |
|---|---|---|---|---|---|---|
| **CHEMICAL NAME** | **CHANGED PARAMETER** | **DOSES** | | **END POINT** | | **RATIONALE FOR CHANGE** |
| | | **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<br><br>None selected | Dermal NOEL=100 mg/kg/day<br><br>Oral NOEL = 0.2 mg/kg/day with 10% dermal absorption. | None<br><br>None | ChEI<br><br>ChEI | A dose and endpoint for dermal risk assessment was not selected previously by TESC. |
| | Inhalation (Any Time Period) | None selected | Inhalation NOEL = 0.0127 mg/L | None | ChEI | 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 enhances 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

## NOELs/LOELs and 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 |
| | NOEL | LOEL | | NOEL | LOEL | |
| **1) ACEPHATE** | 5.0 | 20.0 | Decreases in body weight, 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, exothalomus, fasciculation). | 6 | 18 | Decreased fetal body weight. |
| **5) CHLORETHOXYFOS** | 0.25 | 0.25 | Decrease body weight. | NA | 50 | Delayed ossification of sternebrae. |
| **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) DICROTOPHOS** | 0.5 | 1.0 | Clinical signs (Fasiculations) | ≥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 sternebrae |
| **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) ETHYL 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<br><br><1.0 (CheI) | 18.0 | Clinical signs (hypoactivity, urine stains) and decreased body weight gain.<br><br>Plasma, RBC and Brain ChEI. | 4.2 | 18.0 | Increase in post implantation loss and increase in fetal Brain ChEI. |
| **19) FENITROTHION** | 8.0 | 25.0 | Clinical signs (tremors) and decreased body weight and body weight gains. | 8.0 | 25.0 | Increased incidence (fetal and litter) fetuses with one full and one rudimentary 13th ribs. |
| **20) FONOFOS** | NO DATA AVAILABLE | | | | | |
| **21) ISOFENPHOS** | 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). |
| **30) PHOSMET** | 10 | 15 | Decreased body weight gain and food consumption and clinical signs. | ≥15 | 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 | |
| **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 wight 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) SULFOTEPP** | **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. |
| **40) TRICHLORFON** | NA | ≥45 | Plasma and Brain ChEI. | NA | ≥45.0 | Increases in delayed ossification of skulls, vertebrae and sternebrae 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 sternebrae |
| **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 weigh gain. | ≥7 | NA | No developmental toxicity at HDT. |
| **10) DIAZINON** | 25 | 100 | Increased mortality. | ≥100 | 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** | |
| **11) DICROTOPHOS** | -- | -- | **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 moribundity 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. |
| **19) FENNITROTHION** | 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 | | | | | |

| 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** | |
| **21) ISOFENPHOS** | 0.25<br><br>Sys.<br>1.25 | 1.25<br><br>Sys<br>7.5 | Plasma, RBC & Brain ChEI.<br><br>Increased mortality and decreases in body weight and body weight gains. | ≥7.5 | NA | No developmental toxicity at HDT. |
| **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. |
| **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. |

| 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** | |
| **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) SULFOTEPP** | **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<br><br>Sys. 3.0 | 1.0<br><br>Sys. 9.0 | Plasma & RBC ChEI<br><br>Decreased body weight gain. | ≥9.0 | NA | No developmental toxicity at HDT. |
| **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.<br><br>1-Generation Study | 0.55 | 1.54 | Decrease in pup viability index and decreased pup body weights on post natal days (PD) 14 and 21. |
| **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) CHLORETHOXYFOS** | 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 | | | | | | |
|---|---|---|---|---|---|---|
| **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 | $\geq$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. | $\geq$1.0 | NA | No offspring toxicity at HDT. |
| **17) FENAMIPHOS** | 0.17 | 0.64 | Plasma & RBC ChEI. | $\geq$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 | | | | | | |
|---|---|---|---|---|---|---|
| CHEMICAL | PARENTAL SYSTEMIC TOXICITY | | | OFF SPRING 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 premating 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) NALED** | 6.0 | 18.0 | Decreased body weight gains. | $\geq$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** | $\leq$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. |

| 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** | |
| **32) PIRIMIPHOS METHYL** | NA | 0.87 | Plasma ChEI at LDT. | ≥13.72 | NA | No offspring toxicity at HDT. |
| **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

## *T*OXICOLOGY *E*ND POINTS *S*ELECTION 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: Brian 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** |
| **11) DICROTOPHOS** | **INADEQUATE DATA BASE -- UNACCEPTABLE STUDIES FOR TOXICOLOGY ENDPOINT SELECTION** | | | | | |
| **12) DIMETHOATE** | 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. |
| **13) DISULFOTON** | 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. |
| **14) ETHION** | 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.<br><br>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 CheI & 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** | | | | | |

| ***T*OXICOLOGY *E*ND POINTS *S*ELECTION 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) ISOFENPHOS** | 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. |
| **22) ISAZOPHOS** | **NO DATA AVAILABLE** | | | | | |
| **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. | 2-year Rat: Serum & Plasma 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** | Developmental-Rabbit: Maternal RBC ChEI. | 1-Year Dog: Plasma, RBC & Brain ChEI. | Developmental-Rabbit: Maternal RBC CheI. | 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) PROPETAMPHOS** | 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) SULFOTEPP** | **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

| 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 | |
| | | | | 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 |
| **7) CHLORPYRIFOS METHYL** | **IN ADEQUATE DATA BASE - UNACCEPTABLE STUDIES FOR TES** | | | | | | |
| **8) COUMAPHOS** | 0.2 | 0.025 | Not Required; dermal NOEL | Dermal: 0.5 | Dermal: 0.5 | Not Required | Oral Equivalents |
| **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 |
| **11) DICROTOPHOS** | **IN ADEQUATE DATA BASE - UNACCEPTABLE STUDIES FOR TES** | | | | | | |
| **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** | |
| | | | | **NOEL (mg/kg/day) 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) ISOFENPHOS** | **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** | |
| | | | | **NOEL (mg/kg/day) 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 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** | |
| | | | | **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 |