MEMORANDUM


FROM:  Paul Chin, Ph.D.
Reregistration Branch I
Health Effects Division (7509C)

THROUGH:  Jess Rowland, Co-Chair
and
Elizabeth Doyle, Co-Chair
Hazard Identification Assessment Review Committee
Health Effects Division (7509C)

TO:  Diana Locke, Risk Assessor
Reregistration Branch II
Health Effects Division (7509C)

PC Code: 035001

On March 14, 2002, the Health Effects Division’s Hazard Identification Assessment Review Committee (HIARC) re-evaluated the toxicology data because the registrant recently submitted a developmental neurotoxicity study in rats (MRID 45529703), a comparative cholinesterase inhibition study in the adult and juvenile rats (MRID 45529702), a dose-finding developmental neurotoxicity study (MRID No. 45529701), and a dermal absorption study in male rats (MRID 45530501). The HIARC considered the results of these studies in determining the acute and chronic Reference Doses (RfDs) and the toxicological endpoints for use in occupational/residential exposure risk assessments. The potential for increased susceptibility of infants and children from exposure to dimethoate was also evaluated as required by the Food Quality Protection Act (FQPA) of 1996. The conclusions drawn at this meeting are presented in this report.

THIS DOCUMENT SUPERSEDES THE PREVIOUS HIARC DOCUMENT DATED JULY 19, 1999 (TXR No. 013580).
Committee Members in Attendance

Members present were: William Burnam, Pam Hurley, Jess Rowland, John Liccione, David Nixon, Elizabeth Doyle, Jonathan Chen, Elizabeth Mendez Ayaad Assaad, and Virginia Fornillo (Executive Secretary).

Members in absentia: Paula Deschamp

Data evaluation prepared by: Paul Chin of Reregistration Branch 1.

Also in attendance were: Whang Phang, Mike Metzger, Kathleen Raffaele, Bill Sette, Bonnie Cropp-Kohlligian, Diana Locke, Pauline Wagner, Al Nielsen, Anna Lowit, Susan Makris, and Brian Dementi, HED and Patrick Dobak, SRRD.

Data evaluation / Report Presentation

Paul Chin, Ph.D.
Toxicologist

Report Concurrence

Brenda Tarplee, B.S.S.
Science Info. Management Branch
INTRODUCTION

The HIARC has evaluated dimethoate on several occasions as summarized below:

On January 28, 1997 the Health Effects Division's Toxicology Endpoint Selection Committee (TES) evaluated the toxicology database for dimethoate and selected doses and endpoints for acute and chronic dietary as well as occupational exposure risk assessments. The Committee also assessed the potential enhanced susceptibility of infants and children from exposure to dimethoate as required by the Food Quality Protection Act of 1996 (TES Document dated February 3, 1998; HED Doc. No. 013180)

During May 12 through 14, 1998, the HIARC conducted a comprehensive review of 40 organophosphates, including dimethoate, for consistency of the doses and endpoints selected for dietary and non-dietary exposures. At this meeting the HIARC recommended the oral NOAEL of 0.06 mg/kg/day from the subchronic neurotoxicity in rats as the dose for inhalation exposure risk assessments since a dose and endpoint were not identified previously by the TES Committee (Hazard Assessment of the Organophosphates: Report of the Hazard Identification Assessment Review Committee dated July 7, 1998).

On June 15 and 16, 1998, the FQPA Safety Factor Committee (FQPA SFC) evaluated hazard and exposure data for dimethoate and determined that the 10x to account for enhanced sensitivity of infants and children (as required by FQPA) should be removed (FQPA Safety Factor Recommendations for the Organophosphates: A Combined Report of the Hazard Identification Assessment Review Committee and the FQPA Safety Factor Committee dated August 6, 1998).

On June 29 and July 8, 1999, HIARC re-examined the previously selected doses and endpoints by the TES Committee and also reviewed a recently submitted a dermal toxicity in rats (MRID No. 44818902) and the NOAEL of 10 mg/kg/day was selected as the dose for short term dermal exposure risk assessment. The LOAEL of 20 mg/kg/day was based on a statistically significant reduction in plasma, RBC, and brain (cortex) ChE activity on days 3 or 5. Previously, the TES Committee selected an oral NOAEL of 2 mg/kg/day from the acute neurotoxicity study in rats for use in a short term dermal risk assessment.

On Sept. 28, 1999 dimethoate was returned to the HIARC for re-evaluation of acceptability of the 5-day dermal toxicity study on dimethoate and for reconsideration of the short term dermal endpoint selection. HIARC accepted the 5-day dermal toxicity study with 4E (43.5% a.i.) formulation, but it made no changes on the previously determined short- and intermediate-term dermal endpoints.

On March 14, 2002, the Health Effects Division’s Hazard Identification Assessment Review Committee (HIARC) re-evaluated the toxicology data because the registrant recently submitted a developmental neurotoxicity study in rats (MRID 45529703), a comparative cholinesterase
inhibition study in the adult and juvenile rats (MRID 45529702), a dose-finding developmental neurotoxicity study (MRID No. 45529701), and a dermal absorption study in male rats (MRID 45530501). The HIARC considered the results of these studies in determining the acute and chronic Reference Doses (RfDs) and the toxicological endpoints for use in occupational/residential exposure risk assessments. The potential for increased susceptibility of infants and children from exposure to dimethoate was also evaluated as required by the Food Quality Protection Act (FQPA) of 1996. The conclusions drawn at this meeting are presented in this report.

1 [NOTE: A cover letter from the registrant (MRID 45529700) recently submitted with three studies (the developmental neurotoxicity, comparative ChE inhibition study, and range-finding developmental neurotoxicity) lists a series of preliminary data submissions and additional information provided to EPA on these studies. The final reports supersede the preliminary data submissions. A number of arguments related to the interpretation of the pup deaths, motor activity data, and the FQPA implications of these data were provided and were considered in the previous reports (HED Doc. Nos. 014502, 014522) or in the current DERs.]
I. FQPA HAZARD CONSIDERATIONS

1. Adequacy of the Toxicity Data Base
The HIARC concluded that the toxicology database for dimethoate is adequate. There are sufficient data available to adequately assess the potential for toxicity to young animals following pre- and/or postnatal exposure to dimethoate. These include acceptable developmental toxicity studies in rats and rabbits, a developmental neurotoxicity study in rats, as well as a 2-generation reproduction studies in rats.

2. Evidence of Neurotoxicity
The data indicated that dimethoate inhibited ChE activity and produced clinical signs associated with ChE inhibition in acute neurotoxicity studies. The executive summaries from neurotoxicity study DERs are presented below:

In an acute delayed neurotoxicity study, no delayed neurotoxicity was seen in hens given a single oral dose (via gelatin capsule) of dimethoate at 50 mg/kg (MRID No. 42884401). The Committee noted that this study did not assess for the potential of dimethoate to inhibit neurotoxic esterase (NTE) in hens.

In an acute neurotoxicity study, four groups of Sprague-Dawley Crl:CD\(^8\)BR strain rats (Charles River, Portage Michigan) were dosed as control, 2, 20 or 200 mg/kg of dimethoate in water by gavage and assessed for reactions in FOB assessments and motor activity measurements at the predetermined estimated peak effect time of 2 hours post dosing and on days 7 and 14. Systemic toxicity manifested as decreased body weight gain at 20 mg/kg (38%, males only, particularly in the first 7 days). The LOAEL for systemic effects was 200 mg/kg and the NOAEL was 20 mg/kg based on decrease in body weight. Neurotoxicity was characterized as behavioral reactions at the initial observation only. At 20 mg/kg the critical effect was an absence of pupil response (an autonomic domain response with 5/12 males and 6/12 females affected vs only 1 or 2 in the controls). At 200 mg/kg the most obvious reactions were tremors (all animals affected, none in other groups), decreased motor activity (total: 40% males, 54% females and ambulatory: 56% both sexes), decreased body temperature (about 4.4 degrees both sexes), increased catalepsy time (0.6 seconds in males and 3.6 seconds in females) and eleven other parameters which indicated that coordination, sensory and motor systems were affected (see table 1 of DER for listing). These effects were noted immediately following treatment and were reversed by day 7, but based on cage side observations some symptoms persisted for up to day 5. There were no neurohistopathological effects in either the central or peripheral nervous systems. **The LOAEL for neurotoxicity toxicity was 20 mg/kg/day based on absence of pupillary response and the NOAEL was 2 mg/kg/day.** (MRID No. 42865102).

In the subchronic neurotoxicity study, male and female Sprague-Dawley rats received diets containing dimethoate (99.1% a.i.) in the diet at doses of 1, 50, and 125 ppm (0.06, 3.22 and 8.13 mg/kg/day for males and 0.08, 3.78, and 9.88 mg/kg/day for females, respectively) for 13 weeks. Dimethoate treatment did not result in differences between
the control and treated animals in the functional observational battery or in the locomotor activity evaluations. The NOAEL was 0.06 mg/kg and the LOAEL was 3.22 mg/kg based on reduction of in plasma (24-48%) and red blood cell (RBC) (34-60%) ChE activity at mid and high dose levels and brain ChE activity (12-20%) at the high dose level. The reductions in olfactory and cortex ChE activity in the high dose males were 12-18% (MRID No. 43128201). No treatment-related neurohistopathology was seen in this study.

In a developmental neurotoxicity study (MRID 45529703), Dimethoate (99.1% a.i., batch # 20522-00) was administered to 24 parent female Crl:CD®BR rats per dose by gavage at dose levels of 0, 0.1, 0.5, or 3.0 mg/kg/day from gestation day 6 through postnatal day 10, and to the offspring from postnatal day 11 to postnatal day 21 inclusive. A Functional Operational Battery was performed on 10 dams/dose on gestation days 12 and 18 and lactation days 4 and 10. Offspring were evaluated as follows: age-appropriate functional observation battery on days 4, 11, 21, 35, 45, and 60, automated motor activity on days 13, 17, 22, and 60; assessment of auditory startle response days 23/24 and 60/61, assessment of learning and memory (Morris Water Maze) at postnatal days 23/24, and at postnatal day 61/62 (separate groups), brain weights on days 11, 21, and 65, and brain histopathology and morphometrics on days 21 and 65. Pup physical development was assessed by body weight, and sexual maturation of females was assessed by age at vaginal opening. Maturation of males was assessed by age at completion of balanopreputial separation. There were no treatment-related effects for maternal animals. The maternal LOAEL for Dimethoate in rats is not identified. The maternal NOAEL is 3 mg/kg/day (HDT).

For offspring, there were no effects on body weight, food consumption, clinical signs, auditory startle parameters, learning and memory evaluations, brain weight, or histopathological evaluations at any time point. There was no effect on litter size or pup weight at birth, but there was an increase in pup death during early lactation. The number of pup deaths was similar in control and low dose groups (15 deaths in 10 litters for controls, 11 deaths in 6 litters at 0.1 mg/kg/day), but was increased at 0.5 mg/kg/day (43 deaths in 10 litters, including 1 total litter loss) and at 3.0 mg/kg/day (89 deaths in 14 litters, including 3 total litter losses). There were also decreased activity levels, as measured in the FOB, at 3.0 mg/kg/day, and changes in automated motor activity measures (decreased rearing in females at 3.0 mg/kg/day on PND17; dose-related increases in horizontal activity in males at 0.5 mg/kg/day [65%] and 3.0 mg/kg/day [122%] on PND17). The offspring LOAEL is 0.5 mg/kg/day, based on increased pup death and increases in motor activity. The offspring NOAEL is 0.1 mg/kg/day.

In a special study that compared ChE inhibitory effects of dimethoate in adults and pups rats (MRID 45529702), the results indicated that dimethoate significantly inhibited plasma, RBC, and brain ChE in both adults and pups at similar dose levels.

3. Developmental Toxicity Study Conclusions
The developmental toxicity studies in rats and rabbits showed no evidence of additional sensitivity to young rats or rabbits following pre- or postnatal exposure to dimethoate and comparable NOAELs were established for adults and offspring.

In a developmental toxicity study pregnant Crl:COBS-CD(SD) rats received oral doses of dimethoate (97.3%) at doses of 0, 3, 6 or 18 mg/kg/day during gestation days 6 through 15. For maternal toxicity, the NOAEL was 6 mg/kg/day and the LOAEL was 18 mg/kg/day based on clinical signs of toxicity (small pellet like feces). For developmental toxicity, the NOAEL was 18 mg/kg/day (HDT); a LOAEL was not established. There was no evidence of developmental toxicity (MRID No. 00141142, 00150130).

In a developmental toxicity study, pregnant New Zealand White rabbits were given single oral dose of dimethoate (97.3%) at 0, 10, 20, or 40 mg/kg/day during gestation days 7 through 19. For maternal toxicity, the NOAEL was 10 mg/kg/day and the LOAEL was 20 mg/kg/day based on decreased body weight gain. For developmental toxicity, the NOAEL was 20 mg/kg/day and the LOAEL was 40 mg/kg/day based on decreased fetal body weight. There was no evidence of developmental toxicity (MRID No.00149126).

4. Reproductive Toxicity Study Conclusions

In a two-generation reproduction study, Crl:CD BR rats were fed diets containing dimethoate (96.4%) at 0, 1, 15 or 65 ppm (0, 0.08, 1.2 or 5.46 mg/kg/day in males and 0.09, 1.3 or 6.04 mg/kg/day in females). There was no increased sensitivity to pups over the adults. For parental/systemic toxicity, the NOAEL was 0.08 mg/kg/day and the LOAEL was 1.2 mg/kg/day based on cholinesterase inhibition in both sexes in all generation. For reproductive toxicity, the NOAEL was 1.2 mg/kg/day) and the LOAEL was 5.46 mg/kg/day based on decreases in the number of live pups, pup body weights, and fertility in the F1a, F1b, F2a and F2b matings (MRID No. 42251501).

5. Additional Information from Literature Sources

A literature search did not find additional neurotoxicity studies or developmental neurotoxicity studies.

6. Pre-and/or Postnatal Toxicity

A. Determination of Susceptibility

Prenatal developmental toxicity studies in rats and rabbits provided no indication of increased susceptibility of rat or rabbit fetuses to in utero exposure to dimethoate. There was no indication of increased susceptibility in the offspring as compared to parental animals in the 2-generation reproduction study. There was evidence of quantitative/qualitative susceptibility in the developmental neurotoxicity study.
B. Degree of Concern Analysis and Residual Uncertainties

Since there is evidence of increased susceptibility of the young following exposure to dimethoate in the rat developmental neurotoxicity study, HIARC performed a Degree of Concern Analysis to: 1) determine the level of concern for the effects observed when considered in the context of all available toxicity data; and 2) identify any residual uncertainties after establishing toxicity endpoints and traditional uncertainty factors to be used in the risk assessment of this chemical. When residual uncertainties are identified, HIARC examines whether these residual uncertainties can be addressed by a special FQPA safety factor and, if so, the size of the factor needed. The results of the HIARC Degree of Concern analyses for dimethoate follow.

In the developmental neurotoxicity study (DNT) conducted with dimethoate, quantitative/qualitative evidence of increased susceptibility in the young is manifested as an increase in pup mortality seen in the absence of maternal toxicity. In determining the degree of concern for these findings in the DNT, HIARC considered the overall quality of the study; the dose levels at which the pup effects were observed; the dose response of the pup effects; and the comparative severity of the effects. The majority of the HIARC agreed that there is a low degree of concern for the susceptibility since: 1) the study was well conducted; 2) the dose-response in the offspring is well characterized; 3) clear NOAEL and LOAEL were established for the effects on the offspring; 4) the apparent “steepness” of the dose response is misleading since there is a five-fold difference between the NOAEL and LOAEL for offspring effects; and 5) although the pup effects seen at the LOAEL (0.5 mg/kg/day) are severe (pup death), since they occurred during early lactation, it is possible that the actual dose causing the effects was much higher - increasing the protection level at the NOAEL.

C. Hazard-based Special FQPA Safety Factor

After selecting toxicity endpoints and traditional uncertainty factors to be used in the risk assessments for dimethoate, the HIARC concluded that there are no residual uncertainties resulting from the effects seen in the DNT. Therefore, the default Special FQPA Safety Factor could be removed (1X) when assessing the dietary and residential non-dietary risks posed by the use of dimethoate.

The HIARC determined that a special FQPA safety factor of 1X is adequate because: 1) there is low concern for the effects seen in the DNT (see previous discussion in Section B.); 2) no mortality was observed at the same dose levels in a comparative ChE study in adults and pups, indicating no concern for increased sensitivity; and 3) in a range-finding developmental neurotoxicity study and the
2-generation reproduction study, pup deaths were seen at a much higher dose (5.46-6 mg/kg/day) - indicating that the offspring NOAEL in the DNT is already protective by at least 10X.

II. HAZARD IDENTIFICATION

1. Acute Reference Dose (aRfD) - Females 13+ years

Study Selected: Developmental neurotoxicity study §83-6

MRID No.: 45529703

Executive Summary: See section I.2 above.

Dose and Endpoint for Establishing aRfD: Offspring NOAEL of 0.1 mg/kg/day based on increased pup death and increases in motor activity at 0.5 mg/kg/day (LOAEL).

Uncertainty Factor(s): 100 to account for inter-species extrapolation (10x) and intra-species variability (10x).

Comments about Study/Endpoint/Uncertainty Factor(s): The increased pup death could be attributed to a single dose in utero exposure to dimethoate and/or early lactation effect. This subgroup is appropriate for regulating pup exposure during early lactation because offspring exposure will be modulated by maternal intake.

$$\text{Acute RfD (females 13+ years)} = \frac{0.1 \text{ (NOAEL) mg/kg}}{100 \text{ (UF)}} = 0.001 \text{ mg/kg}$$

2. Acute Reference Dose (aRfD) - general population

Study Selected: Comparative ChE inhibition study in the adult and juvenile rats

MRID No.: 45529702

Executive Summary: In a special neurotoxicity study (MRID 45529702), dimethoate (99.1% a.i., batch/lot # 20522-00) was administered to groups of Crl:CD® (SD) IGS BR rats by gavage at dose levels of 0.0, 0.1, 0.5 or 3.0 mg/kg/day. Treatment groups consisted of 9 pregnant dams treated from GD 6 through GD 20 and terminated; 10 pregnant dams treated from GD 6 through PND 10 followed by treatment of 1 male and 1 female offspring/litter on PND 11 through PND 21; groups of 8 untreated dams whose offspring were treated on PND 11. In addition, groups of 16 adult male and female rats were treated with dimethoate for 11 days. Although the study investigated the effect of
the test material on developmental criteria such as reproductive performance, gestation, fetal viability, etc., the primary purpose was to determine the effect of dimethoate on blood and brain cholinesterase activities in adult male and female rats, pregnant dams, fetuses, and offspring following both acute and repeated exposures.

No significant treatment-related effects were found on any reproductive or developmental parameters. In addition, the test material did not increase mortality, or cause clinical signs of toxicity in adult male and female rats, fetuses or offspring at any dose. No histopathology of the nervous system was seen in five offspring examined after PND 60.

For almost all groups of adult animals, pregnant dams, fetuses, and pups, dimethoate doses of 3.0 mg/kg/day significantly decreased the activities of plasma, red blood cell (RBC), and brain cholinesterase following acute or multiple daily doses of dimethoate. Acute doses of 0.5 mg/kg caused no significant effects. Repeated exposure to 0.5 mg/kg caused significant inhibition in brain ChEs in dams, fetuses, and nursing pups. By day 60, all ChE levels had recovered. No consistent difference in sensitivity to ChEI was found following acute or repeated exposures.

**For acute exposures:**
- the LOAEL for brain ChEI is 3 mg/kg (adults and pups of both sexes);
- the LOAEL for red blood cell ChEI is 3 mg/kg (adults of both sexes); and
- the LOAEL for plasma ChEI is 3 mg/kg (male pups and male adults).

*The acute NOAEL for ChEI in all compartments is 0.5 mg/kg for both adults and offspring.*

**For repeated exposures:**
- the LOAEL for plasma ChEI is 3 mg/kg/day (adults and offspring of both sexes);
- the NOAEL for plasma ChEI is 0.5 mg/kg/day;
- the LOAEL for red blood cell ChEI is 3 mg/kg/day (adults and offspring of both sexes);
- the NOAEL for red blood cell ChEI is 0.5 mg/kg/day;
- the LOAEL for brain ChEI is 0.5 mg/kg/day (adults and offspring of both sexes); and
- the NOAEL for brain ChEI is 0.1 mg/kg/day.

*The repeated exposure NOAEL for ChEI is 0.1 mg/kg/day based on brain ChEI in adults and offspring.*

Dose and Endpoint for Establishing an RfD: NOAEL of 0.5 mg/kg/day based on RBC and brain ChE inhibition in adults and pups following single exposure at 3 mg/kg/day (LOAEL).

Uncertainty Factor(s): 100 to account for inter-species extrapolation (10 x) and intra-species variability (10 x).

Comments about Study/Endpoint/Uncertainty Factor(s): The endpoint of concern (ChEI)
was seen after a single oral dose in adults and offsprings and thus appropriate for this population and duration of concern.

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\text{Acute RfD (general population)} = \frac{0.5 \textit{(NOAEL)} \text{mg/kg}}{100 \textit{(UF)}} = 0.005 \text{mg/kg}
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3. Chronic Reference Dose (cRfD)

Selected Study: Chronic toxicity/Carcinogenicity study - Rat §83-1

MRID No.: 00164177; Accession No.: 00265610

Executive Summary: In a chronic/carcinogenicity feeding study, Wistar rats (65/sex/group) were fed diets containing 0, 5, 25 or 100 ppm dimethoate (equivalent to 0, 0.25, 1.25 or 5 mg/kg/day) for 2 years. An additional 20 animals/sex were given 1 ppm in order to determine a NOAEL for ChE inhibition. For systemic toxicity, the NOAEL was 1.25 mg/kg/day and the LOAEL was 5 mg/kg/day based on increased mortality (females), decreased body weight gain (males), anemia (males) and increased leukocytes (males and females). For cholinesterase inhibition, the NOAEL was 0.05 mg/kg/day and the LOAEL was 0.25 mg/kg/day based on red blood cell and brain inhibition.

Dose and Endpoint for Establishing the RfD: NOAEL of 0.05 mg/kg based on RBC and brain cholinesterase inhibition at 0.25 mg/kg (LOAEL).

Uncertainty Factor (UF): 100 to account for both inter-species extrapolation and intra-species variation.

Comments about Study/Endpoint/Uncertainty Factor: This endpoint is appropriate for the route and duration of exposure.

\[
\text{Chronic RfD} = \frac{0.05 \textit{(NOAEL)} \text{mg/kg}}{100 \textit{(UF)}} = 0.0005 \text{mg/kg}
\]

4. Incidental Oral Exposure: Short-Term (1-30 days)

Study Selected: Comparative ChE inhibition study in the adult and juvenile rats

MRID No(s). 45529702

Executive Summary: see \textbf{Acute Reference Dose (aRfD)} - general population

Dose and Endpoint for Risk Assessment: NOAEL of 0.1 mg/kg/day based on brain ChE
inhibition in adults and pups following repeated exposure at 0.5 mg/kg/day (LOAEL).

Comments about Study/Endpoint: This endpoint was selected from the comparative ChE inhibition study in the adult and juvenile rats because route and duration of exposure is appropriate for intermediate term (1 to 30 days) exposure scenario and population (toddlers). This endpoint is also supported by the similar LOAEL found in the developmental neurotoxicity study.

5. Incidental Oral Exposure: Intermediate-Term (1 - 6 Months)

Selected Study: Chronic toxicity/Carcinogenicity study - Rat §83-1

MRID No.: 00164177; Accession No.: 00265610

Executive Summary: see 3. Chronic Reference Dose (cRfD)

Dose and Endpoint for Establishing the RfD: NOAEL of 0.05 mg/kg based on RBC and brain cholinesterase inhibition at 0.25 mg/kg (LOAEL).

Uncertainty Factor (UF): 100 to account for both inter-species extrapolation and intra-species variation.

Comments about Study/Endpoint/Uncertainty Factor: This endpoint is appropriate for the route and duration of exposure.

6. Dermal Absorption

Dermal Absorption Factor: 28%

Proposed Study: A dermal absorption study in rats (MRID 45530501) #: 85-2

MRID No.: 43964001

EXECUTIVE SUMMARY: The study investigated dermal absorption (MRID 45530501) in male rats following a single dermal administration of $^{14}$C-Dimethoate (98% radiochemical purity) in formulation concentrate and in 10% and 0.5% aqueous dilutions thereof. The nominal dose preparations equated to doses of 0.02, 0.4 and 4.0 mg/cm². A total of 64 animals (16 per dose/4 per time group) were exposed for 1, 10, and 24 hour periods and sacrificed 1,10, 24 or 72 hours after exposure began. The 72-hour group underwent skin wash at 24 hours and were carried to 72 hours before termination.

Mean recoveries of applied radioactivity from all dose groups ranged from 94 to 107%. The following table summarizes mean percent absorption at each time period for the low
and intermediate dose groups. Results from the high dose group are not presented because an excessive amount of the applied material was found on the application site cover and surrounding skin at all exposure periods for this dose group. Material on the cover and the skin around the application site is not available for absorption. Therefore data from the high dose group is unusable for determining the dermally absorbed portion of the applied dose. Material retention in the protective cover and surrounding skin was within expected ranges for all other doses/exposures.

<table>
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<tr>
<th>Dose Level</th>
<th>Mean Percentage of Dose Absorbed</th>
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<tr>
<td></td>
<td>1 hour</td>
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<tr>
<td>0.02 mg/cm² (0.2 mg/animal)</td>
<td>5.68</td>
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<tr>
<td>0.4 mg/cm² (4.0 mg/animal)</td>
<td>5.68</td>
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* 72 hour value washed at 24 hours carried to 72 hours

Total radioactivity absorbed increased with increasing exposure time but decreased with increasing dose indicating saturation of penetration with increasing dose. The largest amount of radioactivity was found in the 10- and 24-hr skin washes from each dose (i.e., 50-60% recovered radioactivity). For both dose groups, the second skin wash (after the 72-hr exposure/observation period) contained significantly less applied radioactivity (1-4%) and proportionately more radioactivity was absorbed. The absorbed radioactivity was excreted rapidly and almost exclusively via the urine.

Comments about Dermal Absorption: Previously, the HIARC recommended the use of the highest percent dermal absorption value (11%) measured 5 days after treatment at the low dose (10 mg/kg; 0.2 mg/cm²; 2 mg/animal; MRID No. 43964001) because dermal absorption was not measured 8 or 10 hours post treatment. The new dermal absorption study (MRID 45530501) used 14C-Dimethoate dissolved in formulation concentrate, the most widely used product, instead of 14C-Dimethoate. This new study also has dermal absorption value (28%) measured at 10 hours post treatment.

7. Dermal Exposure: Short-Term (1-30 days) Exposure

Study Selected: Developmental neurotoxicity study §83-6

MRID No(s). 45529703

Executive Summary: see Acute Reference Dose (aRfD) - females 13+ years

Dose and Endpoint for Establishing aRfD: Offspring NOAEL of 0.1 mg/kg/day based on increased pup death and increases in motor activity at 0.5 mg/kg/day (LOAEL).

Uncertainty Factor(s): 100 to account for inter-species extrapolation (10x) and intra-species variability (10x).
Comments about Study/Endpoint/Uncertainty Factor(s): It is noted that although 5-day dermal toxicity study in rats (MRID No. 44818902) is available in the database, it was not used since 5-day is not appropriate for the exposure period (1-30 days) of concern. An oral NOAEL from the developmental neurotoxicity was selected because it is based upon effects not measured in the dermal study. Since an oral NOAEL was used, a 28% dermal absorption factor should be used in route-to-route extrapolation.

8. Dermal Exposure: Intermediate-Term (1 - 6 Months)

Selected Study: Chronic toxicity/Carcinogenicity study - Rat §83-1

MRID No.: 00164177; Accession No.: 00265610

Executive Summary: see 3. Chronic Reference Dose (cRfD)

Dose and Endpoint for Establishing the RfD: NOAEL of 0.05 mg/kg based on RBC and brain cholinesterase inhibition at 0.25 mg/kg (LOAEL).

Uncertainty Factor (UF): 100 to account for both inter-species extrapolation and intra-species variation.

Comments about Study/Endpoint/Uncertainty Factor: An oral NOAEL was selected due to lack of an appropriate dermal toxicity study. A 28% dermal absorption factor should be used.

9. Dermal Exposure Long-Term (> 6 Months)

Selected Study: Chronic toxicity/Carcinogenicity study - Rat §83-1

MRID No.: 00164177; Accession No.: 00265610

Executive Summary: see 3. Chronic Reference Dose (cRfD)

Dose and Endpoint for Establishing the RfD: NOAEL of 0.05 mg/kg based on RBC and brain cholinesterase inhibition at 0.25 mg/kg (LOAEL).

Uncertainty Factor (UF): 100 to account for both inter-species extrapolation and intra-species variation.

Comments about Study/Endpoint/Uncertainty Factor: An oral NOAEL was selected due to lack of an appropriate dermal toxicity study. A 28% dermal absorption factor should be used.

10. Inhalation Exposure: Short -Term (1- 30 days)
Study Selected: Developmental neurotoxicity study §83-6

MRID No(s): 45529703

Executive Summary: see Acute Reference Dose (aRfD) - females 13+ years

Dose and Endpoint for Establishing aRfD: Offspring NOAEL of 0.1 mg/kg/day based on increased pup death and increases in motor activity at 0.5 mg/kg/day (LOAEL).

Uncertainty Factor(s): 100 to account for inter-species extrapolation (10x) and intra-species variability (10x).

Comments about Study/Endpoint/Uncertainty Factor(s): In the absence of an inhalation study, an oral NOAEL was selected. Absorption via inhalation should be assumed to be equal to oral absorption.

11. Inhalation Exposure: Intermediate-Term (1-6 Months)

Selected Study: Chronic toxicity/Carcinogenicity study - Rat §83-1

MRID No.: 00164177; Accession No.: 00265610

Executive Summary: see 3. Chronic Reference Dose (cRfD)

Dose and Endpoint for Establishing the RfD: NOAEL of 0.05 mg/kg based on RBC and brain cholinesterase inhibition at 0.25 mg/kg (LOAEL).

Uncertainty Factor (UF): 100 to account for both inter-species extrapolation and intra-species variation.

Comments about Study/Endpoint/Uncertainty Factor: In the absence of an inhalation study, an oral NOAEL was selected. Absorption via inhalation should be assumed to be equal to oral absorption.

12. Inhalation Exposure: Long-Term (>6 Months)

Selected Study: Chronic toxicity/Carcinogenicity study - Rat §83-1

MRID No.: 00164177; Accession No.: 00265610

Executive Summary: see 3. Chronic Reference Dose (cRfD)

Dose and Endpoint for Establishing the RfD: NOAEL of 0.05 mg/kg based on RBC and brain cholinesterase inhibition at 0.25 mg/kg (LOAEL).
Uncertainty Factor (UF): 100 to account for both inter-species extrapolation and intra-species variation.

Comments about Study/Endpoint/Uncertainty Factor: In the absence of an inhalation study, an oral NOAEL was selected. Absorption via inhalation should be assumed to be equal to oral absorption.

13. Margins of Exposure

The target Margins of Exposure (MOEs) for occupational exposure risk assessments are as follows:

<table>
<thead>
<tr>
<th>Route</th>
<th>Short-Term (1-30 Days)</th>
<th>Intermediate-Term (1 - 6 Months)</th>
<th>Long-Term (&gt; 6 Months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dermal</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Inhalation</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>

The MOEs for dermal and inhalation exposures may be combined for occupational exposure risk assessment because the toxicity endpoints for these routes of exposure are the same.

The target MOEs for residential exposure risk assessments will be determined by the FQPA Safety Factor Committee.

14. Recommendation for Aggregate Exposure Risk Assessments

An aggregate exposure risk assessments is not required since there are no residential uses at the present time.

III. CLASSIFICATION OF CARCINOGENIC POTENTIAL

1. Combined Chronic Toxicity/Carcinogenicity Study in Rats

MRID No.: 00164177; Accession No.: 00265610

Executive Summary: In a chronic/carcinogenicity feeding study, Wistar rats (65/sex/group) were fed diets containing 0, 5, 25, or 100 ppm Dimethoate (0, 0.25, 1.25 or 5 mg/kg/day) for 2 years. An additional 20 animals/sex were given 1 ppm in order to determine a NOAEL for ChE inhibition. The NOAEL for systemic toxicity was 1.25 mg/kg/day and the LOAEL was 5 mg/kg/day based on increased mortality (females),
decreased body weight gain (males), anemia (males) and increased leukocytes (males and females). The ChE activity NOAEL was 0.05 mg/kg/day and the LOAEL was 0.25 mg/kg/day based on brain and red blood cell ChE inhibition.

Discussion of Tumor Data

Administration of Dimethoate was associated with dose-related trends for:

(I) spleen hemangiosarcoma;
(ii) combined spleen hemangioma and hemangiosarcoma, and;
(iii) combined spleen hemangioma, hemangiosarcoma and skin hemangiosarcoma.

Furthermore, there were significant differences in pair-wise comparisons between controls and the low dose (0.25 mg/kg) or high dose (5 mg/kg) for spleen (hemangioma/hemangiosarcoma) and in the combined tumors of spleen and skin hemangiosarcoma and lymph angioma/angiosarcoma. Although there was no dose response, there were significant pair-wise comparisons at the low and high doses for all tumors combined. The HED Peer Review Committee agreed that despite no dose response, these tumors were compound-related but that the tumor incidences did not indicate much more than a weak effect (MRID # 00164177).

Adequacy of the Dose Levels Tested

The HED Peer Review Committee considered the dosing levels in this study adequate for assessment of carcinogenic potential. This was based on several parameters:
(I) There was significantly decreased plasma, RBC and brain ChE activity in both sexes (decreases at doses of 25 ppm and above); and
(ii) Body weight and body weight gain were significantly decreased in high dose males during the first year of the study (body weight gain decrease of 19% after first week; 7% decrease at week 51 compared to control). Body weight gain was depressed in high dose females during the first eight months of the study (29% after first week; 9% decrease at week 39).

Male rats had no significant mortality with incremental doses of dimethoate. Female rats had a significant dose-related trend, but no significant differences in the pair-wise comparisons between the controls and any dose level. There were no differences in food consumption between the control and treated animals.

2. Carcinogenicity Study in Mice

MRID No: 00163800; Accession No.: 265362-265364

Executive Summary: In a chronic/carcinogenicity feeding study, B6C3F1 mice (60/sex/group) were fed diets containing 0, 25, 100 or 200 ppm Dimethoate (0, 3.75, 15 and 30 mg/kg/day) for 78 weeks. Ten animals of the 60 per sex were used as satellite
animals and were sacrificed at 52 weeks. The NOAEL/LOAEL for the systemic toxicity were less than 3.75 mg/kg/d (the lowest dose tested) based on:

(I) the increased incidence of hepatic vacuolation in females at all levels;
(ii) decrease in the relative weights of brain, heart, kidney, and spleen in all treated animals;
(iii) decrease in the absolute and relative weight of the ovaries in all treated animals, and;
(iv) a significant decrease in body weight gain in all males and in high dose females (during the first five weeks of the study).

Absolute liver weights were significantly increased in both sexes of the mid and high dose groups, while relative liver weights were significantly decreased in mid and high dose females. The ChE activity NOAEL/LOAEL were less than 3.75 mg/kg/day based on significant depression (p<0.01) of plasma and RBC ChE activities at all dosage levels. Brain ChE was not measured.

Discussion of Tumor Data

Administration of Dimethoate in the males was associated with a significant dose-related increase in:
(I) combined lung adenoma and/or adenocarcinoma;
(ii) for lymphoma, and;
(iii) for the combined group of lymphoma, reticular sarcoma, and leukemia.
A significant difference in the pair-wise comparison of control and the highest dose level (30 mg/kg/d) was found for the combined tumor group of lymphoma, reticular sarcoma, and leukemia. The HED Peer Review Committee agreed that the increased incidence for the combined tumors compared to concurrent controls appeared to be compound-related, but could only classify this incidence as equivocal. Administration of Dimethoate in females was associated with a significant dose-related increase in liver carcinoma and for combined liver adenoma and/or carcinoma. However, the Committee agreed that not much weight should be put on the combined tumor incidence in female mice because there were no significant pair-wise comparisons. There also was no evidence of precursor lesions to carcinogenicity (MRID # 00163800; Accession # 265362-265364).

Adequacy of the Dose Levels Tested

The HED Peer Review Committee considered the dosing levels in this study adequate for assessment of carcinogenic potential. This was based on several parameters:
(I) There was significantly decreased plasma and RBC ChE activity in both sexes (decreases at all doses up to 77-88% at the highest dose)
(ii) A significant decrease in body weight gain in males (37, 31, and 51% in low, mid, and high dose groups, respectively) and in high dose females (19%) during the first five weeks of the study was observed. The body weight differences persisted in the high dose males up to week 50;
(iii) Organ weight changes were prevalent in dosed females, especially lower relative
liver weights, ovary weights and other organ weights.

Male mice had no statistically significant mortality with incremental doses of dimethoate. Female mice had a statistically significant difference between control and the mid-dose group (100 ppm). Food consumption was similar between control and treated animals of both sexes throughout the study.

**Classification of Carcinogenic Potential**

The Cancer Peer Review Committee has classified dimethoate as a **Group C** carcinogen (possible human carcinogen) based on equivocal hemolymphoreticular tumors in male B6C3F1 mice, the compound-related (no dose response) weak effect of combined spleen (hemangioma and hemangiosarcoma), skin (hemangiosarcoma), and lymph (angioma and angiosarcoma) tumors in male Wistar rats, and positive mutagenic activity associated with dimethoate (CPRC Document dated 8/29/91). A RfD approach was considered more appropriate for quantification of potential human risk. The reasons are as follows:

1) The mouse study showed an equivocal response in tumor incidence (hemolymphoreticular tumors).
2) The rat study showed a compound-related, weak effect of combined spleen (hemangioma and hemangiosarcoma), skin (hemangiosarcoma), and lymph (angioma and angiosarcoma) tumors, but there was no dose response.
3) In addition, the chronic RfD is considered protective enough of any potential cancer risk since the NOAEL from which it is derived (0.05 mg/kg/day) is at least an order of magnitude lower than the NOAELs or LOAELs derived from the systemic effects seen in the rat and mouse carcinogenicity studies.

**IV. MUTAGENICITY**

The HIARC concluded that there is a concern for mutagenicity resulting from exposure.

In the Ames test, Dimethoate was not mutagenic when tested in *S. typhimurium* strains TA1535, 1537, 98 and 100 at non-cytotoxic doses (MRID # 00063996).

Equivocal results were obtained from a Chinese hamster ovary (CHO)/HGPRT gene mutation assay. In this assay, Dimethoate was tested at 0, 1000, 1500, 2000, 2700 or 2500 ug/mL. A statistically significant increase in mutation frequency was observed at 2700 (with and without S-9 activation) and 3500 ug/mL (without S-9 activation). Because some of the results were not reproducible, it could not be determined if increases were biologically significant or were due to inherent technical problems with the assay (Accession # 256594).

Dimethoate was not mutagenic in a dominant lethal assay. In this assay, Dimethoate was administered orally by gavage at 5, 10 or 20 mg/kg to 5 male mice/group for 5 consecutive days. Dimethoate did not elicit a dominant lethal effect in the offspring of male mice which were sequentially mated (2 females/mating) for 8 weeks (Accession #
Dimethoate was not mutagenic in a cytogenetic assay in bone marrow of rat. Dimethoate at intraperitoneal doses of 15, 75, or 150 mg/kg, a clastogenic response was not observed in bone marrow of male or female rats harvested 6, 16 and 24 hours after treatment (Accession # 259921).

Dimethoate was not mutagenic in a mouse micronucleus assay. Dimethoate did not induce any significant increase in the number of PCE (polychromatic erythrocytes) containing micronuclei from animals (5/sex/group) administered single or multiple intraperitoneal doses of 55 mg/kg (Accession # 257603).

Dimethoate was positive for inducing unscheduled DNA synthesis (UDS) in rat hepatocytes. Dimethoate at the highest dose tested (763.33 ug/mL) and 229.0 ug/mL caused an increase in grain counts (i.e. evidence of UDS) in autoradiographically treated slide cultures. Dimethoate was cytotoxic at concentrations of 763.33 ug/mL and above (MRID # 43151801).

Dimethoate was positive in a dose-related trend for inducing UDS in rat hepatocyte cultures exposed to doses from 229 to 2290 ug/mL as measured by uptake of radiothymidine by liquid scintillation counting. Dimethoate was cytotoxic at concentrations of 2290 ug/mL (MRID # 43151801, 43151802).

V. HAZARD CHARACTERIZATION

The toxicity data indicate that dimethoate is very toxic by acute oral exposure (Toxicity Category II) and moderately toxic by acute dermal exposure (Toxicity Category III). Dimethoate did not appear to be acutely toxic by the inhalation route (Toxicity Category IV). It is not a skin sensitizer, nor a dermal irritant. An acute delayed neurotoxicity study in hens showed that brain ChE was greatly decreased and brain neuropathy target esterase (NTE) was slightly decreased relative to controls. The toxicity endpoints selected for the risk assessment for dimethoate are based on neurotoxic effects, primarily but not exclusively, ChE inhibition of the plasma, RBC, and brain, as well as absence of pupil response.

In an acute oral neurotoxicity screen study in rats, the most notable responses were tremors, decreased motor activity, decreased body temperature, and increased catalepsy time, as well as eleven other parameters which indicated that coordination and, sensory and motor systems were affected. These effects were noted immediately following treatment and were reversed by day 7.

The 5-day dermal toxicity study showed that dimethoate 4E produced dermal reactions (desquamation), ptosis, excessive lacrimation, tremors, shallow breathing, pale eyes, and exophthalmus. The 90-day toxicity study showed decreased growth and food
consumption in rats and dogs and increased kidney and liver weight ratios in rats.

In a one year feeding study in dogs, the systemic toxicity observed were decreased liver weights and the presence of a brown, granular pigment in the liver.

In a chronic/carcinogenicity feeding study in rats, dimethoate produced increased mortality, decreased body weight gain, anemia and increased leukocytes. Administration of dimethoate in the male rats was associated with the compound-related (no dose response) weak effect of combined spleen (hemangioma and hemangiosarcoma), skin (hemangiosarcoma), and lymph (angioma and angiosarcoma) tumors.

In a chronic/carcinogenicity feeding study in mice, major toxicity observed were the increased incidence of hepatic vacuolation; increase in absolute liver weights; decrease in the relative weights of liver, brain, heart, kidney, and spleen in all treated animals; decrease in the absolute and relative weight of the ovaries; a significant decrease in body weight gain. Administration of dimethoate in the male mice was associated with the equivocal increase in the incidence of hemolymphoreticular tumors.

Dimethoate produced developmental toxicity in rabbits (reduction in fetal weight) but not in rats. Dimethoate affected reproductive parameters in rats including slight, but dose-related decreases in the number of live pups at birth and pup weight at birth in the F1a and F2b pups, and decreased fertility for the F1a & b and F2a & b matings. These developmental toxicity studies provided no indication of increased susceptibility of rat or rabbit fetuses to in utero exposure to dimethoate. In a developmental neurotoxicity study, an increase in the incidence of pup death and increase in motor activity was seen at 0.5 mg/kg. At this dose, brain ChE inhibition in offspring and adults was also seen following a repeated dosing in the comparative ChE inhibition study.

The Cancer Peer Review Committee has classified dimethoate as a Group C carcinogen (possible human carcinogen); based on equivocal hemolymphoreticular tumors in male B6C3F1 mice, the compound-related (no dose response) weak effect of combined spleen (hemangioma and hemangiosarcoma), skin (hemangiosarcoma), and lymph (angioma and angiosarcoma) tumors in male Wistar rats, and positive mutagenic activity associated with dimethoate. For the purposes of cancer risk assessment a dose-response approach ($Q_1^*$) was not indicated for this chemical, but a RfD approach was considered more appropriate for quantification of potential human risk. The reasons are as follows:
1) The mouse study showed an equivocal response in tumor incidence (hemolymphoreticular tumors).
2) The rat study showed a compound-related, weak effect of combined spleen (hemangioma and hemangiosarcoma), skin (hemangiosarcoma), and lymph (angioma and angiosarcoma) tumors, but there was no dose response.
3) In addition, the chronic RfD is considered protective enough of any potential cancer risk since the NOAEL from which it is derived (0.05 mg/kg/day) is at least and order of magnitude lower than the NOAEs or LOAEs derived from the systemic effects seen in
the rat and mouse carcinogenicity studies.

VI. DATA GAPS / REQUIREMENTS

Twenty eight (28)-day inhalation study in rats (abbreviated 90-day protocol). The registrant is recommended to follow all the procedures stipulated in the Subdivision F Guidelines for the 90-day inhalation toxicity study (870.3465) except that the exposure duration can be reduced to 28 days. The HIARC request this study due to the potential occupational exposure via this route and there are no studies available at the present time.
## VII. **ACUTE TOXICITY**

**Acute Toxicity of Dimethoate (PC 035001)**

<table>
<thead>
<tr>
<th>Guideline No.</th>
<th>Study Type</th>
<th>MRID No.</th>
<th>Results</th>
<th>Toxicity Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>870.1100</td>
<td>Acute Oral - Rat</td>
<td>00164219</td>
<td>LD&lt;sub&gt;50&lt;/sub&gt; = 387 mg/kg</td>
<td>II</td>
</tr>
<tr>
<td>870.1200</td>
<td>Acute Dermal - Rabbit</td>
<td>00164220</td>
<td>LD&lt;sub&gt;50&lt;/sub&gt; &gt; 2.0 g/kg</td>
<td>III</td>
</tr>
<tr>
<td>870.1300</td>
<td>Acute Inhalation - Rat</td>
<td>00060719</td>
<td>LC&lt;sub&gt;50&lt;/sub&gt; &gt; 2 mg/L</td>
<td>IV</td>
</tr>
<tr>
<td>870.2400</td>
<td>Acute Eye Irritation - Rabbit</td>
<td>00164222</td>
<td>Corneal opacities, iritis, and conjunctivitis; reversible within 7 days.</td>
<td>III</td>
</tr>
<tr>
<td>870.2500</td>
<td>Acute Dermal Irritation - Rabbit</td>
<td>00164221</td>
<td>Not a dermal irritant</td>
<td>IV</td>
</tr>
<tr>
<td>870.2600</td>
<td>Skin Sensitization - Guinea Pig</td>
<td>254924</td>
<td>Not a skin sensitizer</td>
<td>N/A</td>
</tr>
<tr>
<td>870.6100</td>
<td>Acute Delayed Neurotoxicity - Hen</td>
<td>42884401</td>
<td>No clinical signs of acute delayed neurotoxicity and no compound-related histological changes in nerve tissue.</td>
<td>N/A</td>
</tr>
</tbody>
</table>
### VIII. SUMMARY OF TOXICOLOGY ENDPOINT SELECTION

Summary of Toxicology Endpoint Selection for dimethoate (PC 035001)

<table>
<thead>
<tr>
<th>Exposure Scenario</th>
<th>Dose (mg/kg/day)</th>
<th>Hazard-Based Special FQPA Safety Factor*</th>
<th>Endpoint for Risk Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dietary Risk Assessments</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute Dietary females 13-50 years of age</td>
<td>NOAEL=0.1 UF = 100</td>
<td>1X</td>
<td>LOAEL = 0.5 mg/kg/day based on Increased pup death and increases in motor activity (during lactation period)</td>
</tr>
<tr>
<td></td>
<td>Acute RfD = 0.001 mg/kg/day</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute Dietary general population including infants and children</td>
<td>NOAEL = 0.5 UF = 100</td>
<td>1X</td>
<td>LOAEL = 3 mg/kg/day based on RBC and brain ChE inhibition in adults and pups following single exposure.</td>
</tr>
<tr>
<td></td>
<td>Acute RfD = 0.005 mg/kg/day</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic Dietary all populations</td>
<td>NOAEL= 0.05 UF = 100</td>
<td>1X</td>
<td>LOAEL = 0.25 mg/kg/day based on RBC and brain cholinesterase inhibition</td>
</tr>
<tr>
<td></td>
<td>Chronic RfD = 0.0005 mg/kg/day</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Incidental Oral</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Short-Term (1 - 30 Days)</td>
<td>NOAEL= 0.1 MOE= 100</td>
<td>1X</td>
<td>LOAEL = 0.5 mg/kg/day based on brain ChE inhibition in adults and pups following repeated exposure.</td>
</tr>
<tr>
<td>Residential Only</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Incidental Oral</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intermediate-Term (1 - 6 Months) Residential Only</td>
<td>NOAEL= 0.05 MOE = 100</td>
<td>1X</td>
<td>LOAEL = 0.25 mg/kg/day based on RBC and brain cholinesterase inhibition</td>
</tr>
<tr>
<td><strong>Non-Dietary Risk Assessments</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exposure Scenario</td>
<td>Dose (mg/kg/day) UF /MOE</td>
<td>Hazard-Based Special FQPA Safety Factor*</td>
<td>Endpoint for Risk Assessment</td>
</tr>
<tr>
<td>-------------------------</td>
<td>--------------------------</td>
<td>----------------------------------------</td>
<td>------------------------------------------------------------------</td>
</tr>
<tr>
<td>Dermal Short-Term a, b</td>
<td>Oral NOAEL= 0.1</td>
<td>1X</td>
<td>LOAEL = 0.5 mg/kg/day based on Increased pup death and increases in motor activity (during lactation period)</td>
</tr>
<tr>
<td>(1 - 30 days)</td>
<td>MOE = 100</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dermal Intermediate-Term a, b</td>
<td>Oral NOAEL= 0.05</td>
<td>1X</td>
<td>LOAEL = 0.25 mg/kg/day based on RBC and brain cholinesterase inhibition</td>
</tr>
<tr>
<td>(1 - 6 Months)</td>
<td>MOE = 100</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dermal Long-Term a, b</td>
<td>Oral NOAEL= 0.05</td>
<td>1X</td>
<td>LOAEL = 0.25 mg/kg/day based on RBC and brain cholinesterase inhibition</td>
</tr>
<tr>
<td>(&gt; 6 Months)</td>
<td>MOE = 100</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inhalation Short-Term a, b</td>
<td>Oral NOAEL= 0.1</td>
<td>1X</td>
<td>LOAEL = 0.5 mg/kg/day based on Increased pup death and increases in motor activity (during lactation period)</td>
</tr>
<tr>
<td>(1 - 30 days)</td>
<td>MOE = 100</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inhalation Intermediate-Term a, b</td>
<td>Oral NOAEL= 0.05</td>
<td>1X</td>
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</tr>
<tr>
<td>(1 - 6 Months)</td>
<td>MOE = 100</td>
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<td></td>
</tr>
<tr>
<td>Inhalation Long-Term a, b</td>
<td>Oral NOAEL= 0.05</td>
<td>1X</td>
<td>LOAEL = 0.25 mg/kg/day based on RBC and brain cholinesterase inhibition</td>
</tr>
<tr>
<td>(&gt; 6 Months)</td>
<td>MOE = 100</td>
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<td></td>
</tr>
<tr>
<td>Cancer</td>
<td>Classification: Group C</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Quantification: RfD approach</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Refer to Section I.6 for complete details regarding the Hazard-based Special FQPA Safety Factor for this chemical.

a = Since an oral NOAEL was selected, a dermal absorption factor of 28% should be used in route-to-route extrapolation.

b = Since an oral NOAEL was selected, an inhalation absorption factor of 100% (default value) should be used in route-to-route extrapolation.