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07 / OPP # 34143B

HED DOC. NO. 013580

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July, 20, 1999

MEMORANDUM

SUBJECT: ***DIMETHOATE: A COMPREHENSIVE REPORT OF THE TOXICOLOGY END POINT SELECTION*** **- Report of the Hazard Identification Assessment Review Committee.**

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

THROUGH: Jess Rowland, Co-Chair
And
Pauline Wagner, 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 June 29 and July 8, 1999, the Health Effects Division's Hazard Identification Assessment Review Committee (HIARC) re-evaluated the toxicology endpoints selected previously in 1996 for dietary and non-dietary risk assessments of dimethoate. On June 29, the HIARC re-examined the toxicology endpoint selected for acute dietary risk assessment and on July 8, the Committee evaluated a recently submitted 5-day dermal toxicity study in rats (MRID No. 44818902), its impact on dermal risk assessment, and also re-examined the toxicology endpoints selected previously selected for intermediate dermal as well as short and intermediate inhalation risk assessments. This comprehensive report presents the toxicology endpoints selected for the dietary and non-dietary exposure risk assessments during these Committee meetings. **THIS DOCUMENT SUPERSEDES THE PREVIOUS TES DOCUMENT DATED FEBRUARY 3, 1997 (HED Document No.013180).**

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Committee Members in Attendance

Members present June 29: William Burnam, Karen Hamernik, Pam Hurley, Mike Ioannou, Tina Levine, Susan Makris, Nicole Paquette, Kathleen Raffaele, David Anderson, Pauline Wagner, Jess Rowland, PV Shah, and Brenda Tarplee (Executive Secretary).

July 8 David Anderson, Viriginia Dobozy, Karen Hamernik, Pam Hurley, Mike Ioannou, Susan Makris, Nancy McCarroll, PV Shah, Jess Rowland, and Brenda Tarplee (Executive Secretary).

Also present at the July 8th meeting were: Robert Fricke, Paula Deschamp, and Al Nielsen.

Data was presented by Paul Chin of Reregistration Branch 1.

Data Presentation and Report Preparation: _____
Paul Chin, Ph.D.
Toxicologist

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I. INTRODUCTION

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. At this meeting, following a consistency review 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 10 x 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 study and evaluated its appropriateness for use in a short term dermal exposure risk assessment. Previously, the TES Committee selected an oral NOAEL of 2 mg/kg/day from the acute neurotoxicity study in rats for use a short term dermal risk assessment.

The conclusions reached at these meeting are presented in this report. This document supersedes the previous TES report .

II. HAZARD IDENTIFICATION

A. Acute Dietary (one day)

Study Selected: Acute Neurotoxicity Study in Rats (MRID No. 42865102) §81-8

Co-critical Studies: 90 - Day Feeding Study in Rats (MRID No. 00051675 & 00077532)
90 - Day Neurotoxicity Study in Rats (MRID No. 43128201)

MRID No. See Above

Acute Neurotoxicity Study: In an acute neurotoxicity study, four groups of Sprague-Dawley Crl:CD^{R}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 LEL for systemic effects was 200 mg/kg and the NOEL 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 or 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 LEL for neurotoxicity toxicity was 20 mg/kg/day based on pupil response and the NOEL was 2 mg/kg/day.**

90-Day Feeding Study: In the subchronic feeding study rats were dosed with 0, 2, 8 or 32 ppm (0, 0.1, 0.4, 1.6 mg/kg/bw) of dimethoate in the diet for 13 weeks. Plasma and RBC cholinesterase measurements were made at pre-exposure and weeks 1, 2, 6, 10, and 13 of exposure. At sacrifice brain cholinesterase was also measured. Plasma, RBC, and brain cholinesterase levels did not differ significantly from controls at any time period. **Thus for the one week time period, the NOAEL is 32 ppm (1.6 mg/kg/bw).** This study also included an additional segment where rats were dosed at 50 ppm (2.5 mg/kg/bw) for four weeks, sacrificed and plasma, RBC and brain cholinesterase measurements were taken. At the four week time period all three compartments were depressed from controls(plasma 80%, RBC 56% and brain 36% for males).

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90-day Neurotoxicity Study: In the subchronic neurotoxicity study rats were dosed at 0, 1, 50, 125 ppm(0, 0.06, 3.2, 8 mg/kg/bw) in the diet for 13 weeks. Plasma and RBC cholinesterase measurements were made at pre-exposure, and weeks 3, 7, and 13 of exposure. At sacrifice brain cholinesterase was also measured. **At the three week time point the NOAEL for cholinesterase inhibition was 50 ppm(3.2 mg/kg/bw) based on statistically significant plasma cholinesterase inhibition at 125 ppm(8 mg/kg/bw).** At 50 ppm (3.2 mg/kg/bw) the plasma cholinesterase measurement was minimally depressed (19%), not statistically significant and there was no inhibition of RBC cholinesterase. Given the fact that in the previously described study, the LOAEL for plasma cholinesterase inhibition at four weeks was 50 ppm(2.5 mg/kg/bw), the time dependency of this dose level vis-a-vis an effect level appears to be between three and four weeks for repeated dose studies.

These two studies, taken together, lend support to the choice of the acute neurotoxicity study for the acute dietary endpoint. Although there were no cholinesterase measurements in that study, the levels at which the NOAELs (50 ppm; 1.6 mg/kg and 3.2 mg/kg) occurred in the two subchronic studies at weeks 1 and 3, respectively,

Dose and Endpoint for establishing the acute RfD: NOAEL = 2 mg/kg based on the lack of pupil response (in the acute neurotoxicity study) and the NOAEL of 1.6 mg/kg and the 3.2 mg/kg in the 90-day feeding and the 90-day neurotoxicity study, respectively.

Uncertainty Factor: 100 (10 x for inter-species extrapolation and 10 x for intra-species variation.

$$\textbf{Acute RfD} = \frac{\textbf{2.0 mg/kg}}{\textbf{100 (UF)}} = \textbf{0.02 mg/kg}$$

Comments about Dose, Endpoint and UF: The acute neurotoxicity study is appropriate for use in establishing the acute dietary reference dose since the effects are a result of a single exposure to dimethoate. Although cholinesterase activities were not measured in this study, the endpoint selected (absent pupillary response) is indicative of cholinergic toxicity. This endpoint is supported by two subchronic studies (discussed above), both of which had interim cholinesterase measurements. The NOAEL of 2 mg/kg established in the acute neurotoxicity study is supported by the NOAELs established in the 90 day studies: In the 1958 study the NOAEL was 32 ppm (1.6 mg/kg) for lack of cholinesterase inhibition at the 1-week measurement and in the 1994 neurotoxicity, the NOAEL was also 50 ppm (3.2 mg/kg) for lack of cholinesterase inhibition at the 3-week measurement. Thus, the lack of cholinesterase inhibition in these studies increases confidence that the use of the NOAEL of 2 mg/kg reported in the acute study will not underestimate the toxicity of dimethoate in acute dietary assessments. It was presumed that cholinesterase inhibition would not have occurred at the 2 mg/kg (NOAEL) dose in this study since no cholinesterase inhibition was seen after repeated dosing (i.e., at 1 week and also at 3-weeks) in the subchronic studies.

This risk assessment is required.

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B. Chronic Dietary : (from TES HED Doc. No.013180)

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

MRID 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 NOEL 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 = 0.05 mg/kg based on RBC and brain cholinesterase inhibition at 0.25 mg/kg (LOAEL).

Uncertainty Factor (UF): An uncertainty factor of 100 was applied to account for both inter-species extrapolation and intra-species variation.

Chronic RfD - $\frac{0.05 \text{ mg/kg}}{100 \text{ (UF)}}$ = 0.0005 mg/kg

This risk assessment is required.

C. Occupational/Residential Exposure

1. Dermal Absorption (TES HED Doc #No. 013180)

Dermal absorption of dimethoate was 7.6-8.2%, 7.9-8.5%, and 9-11% of the administered dose from rats 1, 2, and 5 days after dermal treatment at 10 mg/kg, respectively. At 100 mg/kg, dermal absorption was 1-2% of the dose from rats 1, 2, and 5 days after dermal treatment. In terms of weight equivalent of dimethoate absorbed, dermal absorption was approximately 1 mg/kg at each dose level (MRID No. 43964001).
Dermal absorption was not measured 8 or 10 hours post treatment. Therefore, the Committee recommended the use of the highest percent dermal absorption value (11%) measured 5 days after treatment at the low dose.

A dermal absorption factor is required ONLY for the Intermediate-Term risk assessment. A dermal absorption factor is NOT required for Short-Term risk assessment since a dermal NOAEL was selected for this exposure period.

% absorbed: 11 % .

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2. Short-Term Dermal (1-7 days)

Study Selected: Five-Day Dermal Toxicity Study - Rats

MRID No.: 44818902

Executive Summary: In a 5-day dermal toxicity study dimethoate 4E (43.5% a.i.) was administered topically to the clipped dorsal region (intact skin) of Sprague Dawley [Crl:CD VAF/Plus] rats (16/sex/dose). Animals received daily dose of 0, 5, 10, 20, 40, or 100 mg a.i./kg/day) for 6 hours per day for 5 days. Plasma, red blood cell, cortex, hippocampus, and striatum cholinesterase determinations were performed on days 3 and 5 (at termination). None of the animals died during the study. Treatment and dose related effects on dermal reactions (desquamation) were found in males only. Other treatment related clinical signs of toxicity observed were ptosis (males) and excessive lacrimation (females). Tremors, shallow breathing, pale eyes, and exophthalmus were observed in the highest dose females (100 mg/kg/day) only. No treatment related effects on FOB measurements were noted during the study. In males, there was a statistical significant reduction ($p < 0.05$ or 0.01) in red blood cell (33-50% inhibition relative to controls), hippocampus (31%), striatum (22-23%) and cortex (20-30%) cholinesterase activity in 100 mg/kg/day group (days 3 or 5). In females treated at 20 mg/kg/day (days 3 or 5), there was a statistical significant reduction ($p < 0.05$ or 0.01)in plasma (33%), red blood cell (35%), and cortex (21%) cholinesterase activity. In females treated at 40 or 100 mg/kg/day (days 3 or 5), there was a statistical significant reduction ($p < 0.05$ or 0.01) in plasma (33-50%), red blood cell (50-75%), hippocampus (38-48%), striatum (40-46%) and cortex (21-51%) cholinesterase activity.

The LOAEL for ChE inhibition was 100 mg a.i./kg/day for males and 20 mg a.i./kg/day for females based on statistically significant inhibition of red blood cell cholinesterase and brain cholinesterase activity. The NOAEL was 40 mg/kg/day for males and 10 mg/kg/day for females.

Dose and Endpoint Selected: NOAEL = 10 mg/kg based on statistically significant inhibition of plasma, red blood cell and brain cholinesterase activity in female rats at 40 mg/kg (LOAEL).

Comments about Study/Endpoint: . The dose, endpoint and study is appropriate for the route (dermal) and exposure period (1-7 days) of concern. Although a 21-day dermal toxicity study in rabbits (MRID No. 00159759) is available in the data base, it was not used since the rabbits are not the appropriate species since they may under estimate the toxicity of this class of chemicals (organophosphates) and also the vehicle used (i.e, paraffin) was not appropriate (TES Document 013180).

This risk assessment is required.

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3. Intermediate Term Exposure (7 Days to Several Months)

Studies Selected: 90 - Day Feeding Study in Rats (MRID No. 00051675 & 00077532)
90 - Day Neurotoxicity Study in Rats (MRID No. 43128201)

MRID No(s). See Above

Executive Summary:

90-Day Feeding Study: In the subchronic feeding study rats were dosed with 0, 2, 8 or 32 ppm (0, 0.1, 0.4, 1.6 mg/kg/bw) of dimethoate in the diet for 13 weeks. Plasma and RBC cholinesterase measurements (titrimetric method) were made at pre-exposure and weeks 1, 2, 6, 10, and 13 of exposure. At sacrifice brain cholinesterase was also measured. Plasma, RBC, and brain cholinesterase levels did not differ significantly from controls at any time period. This study also included an additional group where rats were dosed at 50 ppm (2.5 mg/kg/bw) for four weeks, sacrificed and plasma, RBC and brain cholinesterase measurements were taken. At the four week time period all three compartments were depressed from controls (plasma 80%, RBC 56% and brain 36% for males).

90-Day Neurotoxicity Study: In the subchronic neurotoxicity study Sprague-Dawley rats (10/sex/dose) received dietary administration of dimethoate (99.1%) at dosed at 0, 1, 50, or 125 ppm (0, 0.06, 3.22 or 8.13 mg/kg/day in males and 0, 0.08, 3.78 or 9.88 mg/kg/day in females, respectively) in the diet for 13 weeks. Plasma and RBC cholinesterase measurements were made at pre-exposure, and weeks 3, 7, and 13 of exposure. At sacrifice brain cholinesterase was also measured. At 50 ppm (3.22 mg/kg/day) at the three week measurement plasma cholinesterase was minimally depressed (19%), not statistically significant and there was no inhibition of RBC cholinesterase. At the 7-week measurement statistically significant inhibition of plasma (25%) and RBC (48%) in males and RBC (35%) in females were observed.

Dose and Endpoint Selected: LOAEL = 50 ppm (3.2 mg/kg/day) based on the cholinesterase inhibition seen at 4 week in the 1958 study and at 7 week in the 1994 study at this dose (i.e., combined results of the two studies)..

Comments about Study: The oral LOAEL was selected for this exposure scenario for the following reasons: 1) A 21 dermal toxicity study is not available in the database; 2) The 5 day dermal toxicity study used for the Short-Term exposure is not adequate sine the treatment period (5 days) will underestimate the risk for the exposure period of concern (up to but no more than 30 days); 3) based on the results of the two subchronic studies, the true NOAEL lies somewhere between 32 ppm (1.6 mg/kg/day) and 50 ppm (2.5 mg/kg/day) at the 3 week measurement and the higher confidence in the LOAEL of 50 ppm; and 4) the concern for the occurrence of cholinesterase inhibition at approximately 3-4 weeks which is the exposure period of concern (exposure up to 30 days)

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The HIARC noted that the LOAEL is based on the dietary concentration of 50 ppm in both studies. However, when converted to mg/kg/day dose, there is a slight difference in the converted doses: in the 1958 study, the converted value of 2.5 mg/kg/day is based on the standard conversion factor of 0.05 for normal food consumption (50 ÷ 20 = 2.5 mg/kg/day), whereas in the 1994 study, the value of 3.2 mg/kg/day is based on actual food consumption value. The HIARC selected the higher value (3.2 mg/kg/day) because of higher overall confidence in the study (conducted in 1994) and also because its based on the actual food consumption value.

Since a LOAEL is used, a MOE of 300 is required for this exposure scenario.

Since an oral value was selected the 11% dermal absorption factor should be used for risk assessment.

This risk assessment is required.

4. Long Term Dermal (Several Months to Life Time)

The current use pattern does not indicate the potential for long term dermal exposure.

This risk assessment is NOT required.

5. Inhalation Exposure (Short and Intermediate Term)

Based on the LC50 of > 2 mg/L, (Tox.Cat. IV), the TES Committee determined that a separate inhalation exposure risk assessment is not required (HED Document No. 013180).

During the May 12-14, 1998 meeting the HIARC recommended the use of the oral NOAEL for inhalation exposure risk assessment (HIARC Report dated July 7, 1998).

At the July 8, 1999 meeting, the HIARC recommended the use of the oral NOAEL of 2.0 mg/kg for Short-Term and the oral LOAEL of 3.2 mg/kg/day for the Intermediate-Term inhalation exposure risk assessments. Since an oral dose is used, risk assessment should follow the route-to route extrapolation as below:

The inhalation exposure component (i.e. µg a.i /day) using 100% absorption rate (default value) and application rate should be converted to an **equivalent oral dose** (mg/kg/day). The equivalent oral dose should then be compared to the oral values shown below to calculate the MOE's.

Short-Term:	NOAEL 2 mg/kg/day	Acute Neurotoxicity -Rat
Intermediate Term	LOAEL 3.2 mg/kg/day	13-Week dietary -Rat
Long-Term	Not required based on the use pattern.	

This risk assessment is required.

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D. Margins of Exposure for Occupational/ Residential Exposures

A Margin of Exposure **(MOE) of 100** is adequate for **Short-Term** dermal and inhalation occupational and residential exposure risk assessments. A **MOE of 300** (for the use of a LOAEL) is required for **Intermediate-Term** dermal and inhalation occupational and residential exposure risk assessments.

E. Recommendation for Aggregate (Food + Water + Residential) Risk Assessments

For **acute** aggregate exposure risk assessment, combine the high end exposure values from food + water and compare it to the acute RfD.

For **short-and intermediate term** aggregate exposure risk assessment, the Aggregate Risk Index (ARI) should be used for due to differences in the MOEs required for these exposure scenarios; MOE of 100 for short term dermal and inhalation and a MOE of 300 for intermediate term dermal and inhalation exposure scenarios. The aggregate systemic (oral), dermal and inhalation exposure risk assessments are appropriate due to the common toxicological endpoint (cholinesterase inhibition) seen via the three routes.

$$\text{Aggregate MOE}_{(\text{total})} = \frac{1}{1/\text{MOE}_{(\text{oral})} + 1/\text{MOE}_{(\text{dermal})} + 1/\text{MOE}_{(\text{inhalation oral equivalent})}}$$

III. 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).

IV. FQPA CONSIDERATIONS

The FQPA assessment was made during the May 12- 14, 1998 HIARC meeting

1. Neurotoxicity

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.

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The acute neurotoxicity study is described in Section II. A. Acute Dietary. No treatment-related neuropathological effects were observed. The NOAEL was 2 mg/kg based on a absence of pupil response at 20 mg/kg (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 1 ppm and the LOAEL was 50 ppm 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).

2. Developmental Toxicity

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 8 mg/kg/day during gestation days 6 through 15. For maternal toxicity, the NOAEL was 3 mg/kg/day and the LOAEL was 6 mg/kg/day based on clinical signs of toxicity (small pellet like feces). For developmental toxicity, the NOAEL was 185 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 weigh 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).

3. Reproductive Toxicity

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 1.29 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).

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4. 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.

5. Determination of Need For Developmental Neurotoxicity Study

There are sufficient data available to adequately assess the potential for toxicity to young animals following pre-and/or post-natal exposure to dimethoate. These include acceptable developmental toxicity studies in rats and rabbits, as well as, a 2-generation reproduction studies in rats. In addition, no treatment-related neuropathology was seen after acute and subchronic exposure to rats. Additionally, there was no evidence of abnormalities to the fetus to the fetal nervous system in the pre- and post-natal studies. Based on the weight-of-evidence, the HIARC determined that a developmental neurotoxicity study in rats is not required for dimethoate

6. Recommendation of the FQPA Safety Factor

On **June 15 and 16, 1998**, the FQPA Safety Factor Committee (FQPA SFC) evaluated hazard and exposure data for dimethoate and determined that the 10 x 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).**

V. DATA GAPS

None

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VI. ACUTE TOXICITY ENDPOINTS

The table below summarizes the results of acute toxicity studies on dimethoate:

TEST	MRID No.	RESULT	TOXICITY CATEGORY
Acute Oral -Rat	Not Available	LD 50 = 250-325 mg/kg	II
Acute Dermal - Rabbit	Not Available	LD50 => 1555 mg/kg	II
Acute Inhalation -Rat	Not Available	LC50= >2 mg/L	IV
Eye Irritation- Rabbit	00027098	Corneal damage in one animal; Draize score = 28/110 at 72 hours.	I
Dermal Irritation- Rabbit	Not Available	Not irritating	IV
Dermal sensitization - Guinea pig	00254924	Not a sensitizer	N/A
Acute neurotoxicity - Hen	42884401	Does not produce delayed toxicity	N/A

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VII. SUMMARY OF TOXICOLOGY ENDPOINT SELECTION

Toxicological endpoints for risk assessments with dimethoate are tabulated below:

EXPOSURE SCENARIO	DOSE (mg/kg/day)	ENDPOINT	STUDY
Acute Dietary	NOAEL= 2.0 UF = 100	Absence of pupil response and lack of cholinesterase inhibition at 1-week and 3-week measurements	Acute Oral Neurotoxicity in Rats & 90-day studies
	Acute RfD = 0.02 mg/kg/day		
Chronic Dietary	NOAEL=0.05 UF = 100	RBC and brain cholinesterase inhibition	Chronic Toxicity/Carcinogenicity -Rat
		Chronic RfD = 0.0005 mg/kg/day	
Short-Term (Dermal) 1	Dermal NOAEL= 10.0	Plasma, RBC and Brain cholinesterase inhibition in female rats	5-Day Dermal Study in Female Rats
Intermediate-Term (Dermal) 2	Oral LOAEL=3.2	Plasma, RBC and Brain cholinesterase inhibition at 3 and 4 week intervals	90-Day Studies in Rats
Long-Term (Dermal)	None	The use pattern and exposure scenario do not indicate a need for long term risk assessment	
Short-Term (Inhalation) 3	Oral NOAEL= 2.0	Absence of pupil response and lack of cholinesterase inhibition at 1-week and 3-week measurements	Acute Oral Neurotoxicity in Rats & 90-day studies
Intermediate-Term (Inhalation) 4	Oral LOAEL =3.2	Plasma, RBC and Brain cholinesterase inhibition at 3 and 4 week intervals	90-Day Studies in Rats
Long Term (Inhalation)[1]	None	The use pattern and exposure scenario do not indicate a need for long term risk assessment.	

1. A MOE of 100 is adequate.

2. Oral value was selected therefore 11% dermal absorption factor should be used for route-to-route extrapolation Also, a MOE of 300 is required for use of a LOAEL.

3. Oral value was selected therefore 100% inhalation absorption factor should be used for route-to-route extrapolation. A MOE of 100 is adequate.

4. Oral value was selected therefore 100% inhalation absorption factor should be used for route-to-route extrapolation must be used. Also, a MOE of 300 is required for use of a LOAEL.

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