UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

JUN 14 1995

MEMORANDUM

SUBJECT: RfD/Peer Review Report of Dimethoate [O,O-dimethyl-S-(N-methylcarbamoylmethyl)phosphorodithioate].

CASRN. 60-51-5
EPA Chem. Code: 035001
Caswell No. 358

FROM: George Z. Ghali, Ph.D. G. Ghali 6.12.95
Manager, RfD/QA Peer Review Committee
Health Effects Division (7509C)

THRU: William Burnam
Chairman, RfD/QA Peer Review Committee
Health Effects Division (7509C)

TO: Robert Forrest, PM 14
Insecticide-Rodenticide Branch
Registration Division (7505C)

Chief, Reregistration Branch
Special Review and Reregistration Division (7508W)

The Health Effects Division-RfD/Peer Review Committee met on March 27, 1995 to discuss and evaluate the existing and recently submitted toxicology data in support of Dimethoate reregistration and to reassess the Reference Dose (RfD) for this chemical.

Material available for review consisted of data evaluation records (DERs) for a combined chronic toxicity/carcinogenicity study in rats **(83-1a and -2a or 83-5)**, a carcinogenicity study in mice **(83-2b)**, a one-year oral toxicity study in dogs **(83-1b)**, a two-generation reproductive toxicity study in rats **(83-4)**, developmental toxicity studies in rats and rabbits **(83-3a and -3b)**, an acute neurotoxicity study in rats **(81-8)**, and a delayed neurotoxicity study in hens **(81-8)**.

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A. Chronic and Subchronic Toxicity:

The Committee considered the chronic toxicity phase of the combined chronic toxicity/carcinogenicity study in rats (83-1a, MRID No. 00164177, 40545501) to be acceptable and the data evaluation record (HED Doc. No. 006398, 008457) to be adequate. The NOEL/LOEL were considered to be 1 and 5 ppm (0.05 and 0.25 mg/kg/day, respectively) based on decreased activity of brain and red blood cell cholinesterase. Systemic NOEL/LOEL were considered to be 25 and 100 ppm (1.25 and 5 mg/kg/day, respectively) based on slight increase in mortality in females and growth retardation in males during the first half of the study. Also in rats receiving 100 ppm there was a slight anemia which was predominant in males and an increase in leukocytes in both sexes during the second half of the study. The Committee generally agreed with the evaluation and interpretation of data and classification of the chronic toxicity phase of the study.

The Committee considered the chronic toxicity study in dogs (83-1b, MRID No. 41939801) to be acceptable and the data evaluation record of this study (HED Doc. No. 008551) to be adequate. Brain cholinesterase inhibition and systemic toxicity were observed at all dose levels. The LOEL for brain cholinesterase inhibition and for systemic toxicity was considered to be 5 ppm (0.18 mg/kg/day in males and 0.19 mg/kg/day in females), the lowest dose level tested. The Committee generally agreed with the evaluation and interpretation of data and classification the study.

There were no subchronic toxicity studies in rats, mice (82-1a) or dogs (82-1b) for review by the Committee.

B. Carcinogenicity:

The Committee did not discuss the carcinogenicity phase (83-2a) of the combined chronic toxicity/carcinogenicity study in rats or the mouse carcinogenicity study (83-2b). Dimethoate has already been classified by the Health Effects Division-Carcinogenicity Peer Review Committee (HED-CPRC) as a "Group C", possible human carcinogen.

C. Reproductive and Developmental Toxicity:

The Committee considered the reproductive toxicity study in rats (83-4, MRID No. 42255101) to be acceptable and the data evaluation record (HED Doc. No. 010065) to be adequate. However, the Committee noted that body weight gain decrements occurred in dams at 65 ppm (5.46 mg/kg/day in males and 6.04 mg/kg/day in females), the highest dose tested.

Parental (systemic) toxicity NOEL/LOEL were considered to be 1 (0.08 mg/kg/day in males, and 0.09 mg/kg/day in females) and 15 ppm (1.2 mg/kg/day in males and 1.3 mg/kg/day in females),

respectively, based on cholinesterase inhibition of both sexes in all generations. There was no effect on premating body weight gain or food consumption. Body weight changes occurred in dams during gestation and lactation in the 65 ppm group. Reproductive toxicity NOEL/LOEL were considered to be 15 and 65 ppm (5.46 mg/kg/day in males and 6.0 mg/kg/day in females), respectively, based on slight, but dose related decreases in the number of live pups at birth and pup weight at birth and/or at days 8 and 21 in the F1a and F2b pups, and decreased fertility for the F1a, F1b, F2a and F2b matings. Startle reflex occurred at an increased age in F1 (34.8 days at 65 ppm vs. 34.3 days in controls, $p \leq 0.05$) and F2 (35.2 at 65 ppm vs. 34.5 days in controls) pups.

The Committee considered the developmental toxicity study in rats (83-3a, MRID No. 00141142, 00150130) to be acceptable. The Committee recommended that additional data tables (including fetal and litter incidence of the most common developmental effects noted, Tables 4(p22), 5(p23), 6(p24) and 7(p25) of the study report, MRID No. 141142) be included in the data evaluation record of this study (HED Doc. No. 003913). Maternal toxicity NOEL/LOEL were set at 3 and 6 mg/kg/day based on small pellet like feces at 6 and 18 mg/kg/day and body weight decrement at the high dose level. Developmental toxicity NOEL was considered to be ≥18 mg/kg/day, the highest dose level tested. Although there was a nominal dose related increased trend in skeletal anomalies, they were within historical control range.

The Committee considered the developmental toxicity study in rabbits (MRID No. 00149126, 00159760) to be acceptable. The Committee recommended that additional data tables (Table 3, p 23) be included in the data evaluation record of this study (HED Doc. No. 004756). Maternal toxicity NOEL/LOEL were set at 10 and 20 mg/kg/day, respectively, based on body weight gain decrement of 33% and 78% at the mid- and high-dose levels, tremors and unsteady gait at the high dose tested. Developmental toxicity NOEL/LOEL were set at 20 and 40 mg/kg/day, respectively, based on statistically significant decreases in fetal weight.

The Committee recommended that a developmental neurotoxicity study be conducted to better define whether the increased age to startle reflex observed in the two-generation study is a developmental or a systemic effect.

D. Acute and Subchronic Neurotoxicity

The Committee considered the subchronic neurotoxicity study in rats (82-7, MRID No. 43128201) to be acceptable and the data evaluation record (HED Doc. No. 011164) to be adequate. There was no difference between the treated groups and the control animals in the functional observational battery or in the locomotor activity evaluations. There was a statistically significant reduction in plasma (24-48%) and red blood cell (34-60%) cholinesterase activity

at the mid- and high-dose levels. Brain cholinesterase activity were reduced 15 to 20% in high dose males and females. The reduction in olfactory and cortex cholinesterase activity in the high dose males were 12-18%. The NOEL was 1 ppm (0.06 mg/kg/day in males and 0.08 mg/kg/day in females) based on reduction of cholinesterase activity in the 50 ppm dose animals.

The Committee considered the acute neurotoxicity study in rats (81-8, MRID No. 42865102) to be acceptable. However, it was noted that no acute cholinesterase measurements were included in the data evaluation record (HED Doc. No. 010797) of this study. These data were deemed necessary and should be included in the data evaluation record, if available, or should be requested from the registrant if not included in the original study report. The Committee recommended that summary data tables for motor activity, histopathology and hind limb grip strength be included in the data evaluation record of this study. The NOEL/LOEL were considered to be 2 and 20 mg/kg/day, respectively, based on pupil response.

The acute delayed neurotoxicity study in hens (81-7, MRID No. 428844-01) was considered to be acceptable and the data evaluation record (HED Doc. No. 010684) was considered to be adequate, but it was recommended that further study to fully characterize the time course of NTE inhibition following an acute exposure be conducted. The treatment was not associated with delayed neurotoxicity up to 200 mg/kg/day, the highest dose tested.

E. Reference Dose (RfD):

The Committee recommended that the basis for the existing RfD remain unchanged, except for the additional Uncertainty Factor (UF) which was used earlier to compensate for the lack of chronic toxicology data in a non-rodent species.

The RfD for this chemical was established by the RfD Committee in their meeting of March 4, 1988 and was verified by the Agency RfD Work Group on March 23, 1988. The RfD was based on the chronic toxicity feeding study in rats with a NOEL of 0.05 mg/kg/day. Brain and red blood cell cholinesterase inhibition was observed at the next higher dose level of 0.25 mg/kg/day. At that time an uncertainty factor (UF) of 100 was applied to account for the interspecies extrapolation and intraspecies variability and an additional UF of 3 to compensate for the lack of chronic toxicity data in a non-rodent species.

In the meeting of March 27, 1995, since the missing chronic toxicity study was made available, the additional UF of 3 was eliminated. **On this basis the RfD was calculated to be 0.0005 mg/kg/day.**

It should be noted that this chemical has been reviewed by the FAO/WHO joint committee on pesticide residues (JMPR) and an

Acceptable Daily Intake (ADI) of 0.02 mg/kg/day was established in 1985.

F. Individuals in Attendance:

Peer Review Committee members and associates present were William Burnam (Chief, SAB; Chairman, RfD/Peer Review Committee), George Ghali (Manager, RfD/Peer Review Committee), Karl Baetcke (Chief, TB I), Marcia Van Gemert (Chief, TB II), David Anderson, Kerry Dearfield, Susan Makris, Henry Spencer, William Sette, and Melba Morrow.

Scientific reviewer (Committee or non-committee member(s) responsible for data presentation; signature(s) indicate technical accuracy of panel report):

Paul Chin — JCS for P Chin

Joycelyn Stewart — Joycelyn Stewart

Respective branch chief (Committee member; Signature indicates concurrence with the peer review unless otherwise stated)

Karl Baetcke — Karl Baetcke

CC: Stephanie Irene
Karl Baetcke
Joycelyn Stewart
Paul Chin
Debra Edwards
Albin Kocialski
Beth Doyle
Kerry Dearfield
RfD File
Caswell File

G. Material Reviewed:

1. Hellwig, J. et al. (1986). Report on the study of the toxicity of dimethoate in rats after 24-month administration in the diet. MRID No. 00164177, 40545501, HED Doc. No. 006398, 008457. Classification: Guideline data. This study satisfies data requirements 83-1a and -2a (or 83-5) of Subpart F of the Pesticide Assessment Guideline for chronic toxicity/ carcinogenicity testing in rats.

2. Burford, P. et al. (1990). Dimethoate: 12-Month dietary study in beagle dogs (repeated daily dosage for 52 weeks). MRID No. 41939801, HED Doc. No. 008551, 009638. Classification: Core-minimum data. This study satisfies data requirement 83-1b of Subpart F of the Pesticide Assessment Guideline for chronic toxicity testing in dogs.

3. Brooker, A. J. et al. (1992). The effect of dimethoate on reproductive function of two-generation reproductions in the rat. MRID No. 42251501, HED Doc. No. 010065. Classification: Core-minimum data. This study satisfies data requirement 83-4 of Subpart F of the Pesticide Assessment Guideline for reproductive toxicity testing in rats.

4. Edwards, J. et al. (1984). Effects of dimethoate on pregnancy of the rat. MRID No. 00141142, 00150130, HED Doc. No. 003913. Classification: Core-minimum data. This study satisfies data requirement 83-3a of Subpart F of the Pesticide Assessment Guideline for developmental toxicity testing in rats.

5. Edwards, J. et al. (1984). Effects of dimethoate on pregnancy of the New Zealand rabbit. MRID 00149126, 00159760, HED Doc. No. 0047576, 000000. Classification: Core-minimum data. This study satisfies data requirement 83-3b of Subpart F of the Pesticide Assessment Guideline for developmental toxicity testing in rabbits.

6. Lamb, I. C. (1994). A subchronic (13-week) neurotoxicity study of dimethoate in rats. MRID No. 43128201, HED Doc. No. 011146. Classification: Guideline data. This study satisfies data requirement 82-7 of Subpart F of the Pesticide Assessment Guideline for subchronic neurotoxicity testing in rats.

7. Lamb, I. C. (1993). An acute neurotoxicity study of dimethoate in rats. MRID No. 42865102, HED Doc. No. 010797. Classification: Guideline data. This study satisfies data requirement 81-8 of Subpart F of the Pesticide Assessment Guideline for acute neurotoxicity testing in rats.

8. Redgrave, V. A. et al. (1991). Dimethoate: Acute delayed neurotoxicity in the domestic hen. MRID No. 42884401, HED Doc. No. 010684. Classification: Core-minimum data. This

study satisfies data requirement 81-7 of Subpart F of the Pesticide Assessment Guideline for delayed neurotoxicity testing in hens.

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