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

OCT 06 1997

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: RfD/Peer Review Report of Methamidophos.

CASRN: 10265-92-6
EPA Chem. Code: 101201
Caswell No.: 378A

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

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

TO: William Jacobs, PM 14
Insecticide-Rodenticide Branch
Registration Division (7505C)

The Health Effects Division-RfD/Peer Review Committee met on June 15, 1995 to discuss and evaluate recently submitted toxicology data in support of methamidophos (Monitor) registration with particular emphasis on developmental and reproductive toxicity, neurotoxicity, delayed neurotoxicity and carcinogenicity; 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 **(83-5)**, a chronic toxicity study in dogs **(83-1b)**, a carcinogenicity study in mice **(83-2b)**, a reproductive toxicity study in rats **(83-4)**, developmental toxicity studies in rats and rabbits **(83-3a and -3b)**, a non-guideline subchronic (8-weeks) cholinesterase inhibition study in rats, subchronic oral and inhalation toxicity studies in rats **(82-1a and -2)**, a non-guideline subchronic cholinesterase inhibition study in human volunteers, acute and subchronic neurotoxicity studies in rats **(81-8ss, and 82-5b)**, subchronic delayed neurotoxicity study in hens **(82-5a)**, and a battery of mutagenicity studies **(84-2)**.

A. Reproductive and Developmental Toxicity:

1. Reproductive Toxicity:

The Committee considered the reproductive toxicity study in rats (83-4, MRID No. 00148455, 41234301, HED Doc. No. 005313, 007891) to be acceptable and the data evaluation record to be adequate.

The systemic toxicity NOEL/LOEL were established at 10 and 33 ppm (0.5 and 1.65 mg/kg/day), respectively, based on premating body weight decrements in P0 males, decreased body weight gain in P0 females during gestation and lactation, and decreased body weight in F1 males and females.

The reproductive toxicity NOEL/LOEL were established at 10 and 33 ppm, respectively, based on decreased number of sperm-positive females delivering litters and decreased pup viability and body weights during lactation.

2. Developmental Toxicity:

The Committee considered the developmental toxicity study in rats (83-3a, MRID No. 00148454, HED Doc. No. 005313) to be acceptable and the data evaluation record to be adequate.

The maternal toxicity NOEL/LOEL were established at 1.0 and 3.0 mg/kg/day, respectively, based on decreased weight gain and food consumption during pregnancy and signs indicative of cholinesterase inhibition (fasciculation, hyperactivity, salivation, and lacrimation).

The developmental toxicity NOEL/LOEL were established at 1.0 and 3.0 mg/kg/day, respectively, based on decreased fetal weight. Variations and malformations were reported to be similar to controls, but tables were not available for verification.

The Committee considered the developmental toxicity study in rabbits (83-3b, MRID No. 00041315, HED Doc. No. 003968) to be acceptable and the data evaluation record to be adequate.

The maternal toxicity LOEL was considered to be <0.1 mg/kg/day (LDT), based on body weight gain decrement during gestation. Although the body weight gain reduced at all dose levels, the decrement was marginal.

The developmental toxicity NOEL was 2.5 mg/kg/day, the highest dose level tested. Although skeletal retardation in the treated animals were reported to be similar to the control incidence, the data tables provided were not adequate to verify this conclusion.

3. Developmental Neurotoxicity:

No developmental neurotoxicity data were available for review by the Committee. However, the Committee did not recommend a developmental neurotoxicity study at this time.

B. Carcinogenicity:

Based on the data available, the Committee determined that methamidophos did not alter the spontaneous tumor profile in rats and mice under the testing conditions. Therefore, it was recommended that methamidophos be classified as a **"Group E"**, indicating evidence of non-carcinogenicity for humans; i.e., the chemical is characterized as **"Not Likely"** to be carcinogenic in humans via relevant routes of exposure.

This weight of the evidence judgement is largely based on the absence of significant tumor increases in two adequate carcinogenicity studies in rats (MRID Nos.: 00148452, 43248102) and mice (MRID Nos.: 00145579, 43248101).

C. Neurotoxicity:

The Committee considered the acute (81-8ss, MRID No. 42770301, 43025001; 43345801, HED Doc. No. 011470) and subchronic (82-5b, MRID No. 43197901, HED Doc. 011530) neurotoxicity studies, and the subchronic delayed neurotoxicity study (82-5, MRID No. 40985202, HED Doc. No. 007386) to be acceptable, and the data evaluation records to be adequate.

In the first acute neurotoxicity study in rats the NOEL for neurotoxicity was not established. Based on the findings of the two acute neurotoxicity studies, the NOEL/LOEL for neurotoxicity were established at 0.7 and 1.0 mg/kg/day, respectively. The NOEL/LOEL for the inhibition of cholinesterase activities in plasma, RBC and brain were established at 0.3 mg/kg/day and 0.7 mg/kg/day, respectively.

In the subchronic neurotoxicity study, the NOEL for neurotoxicity was established at 1 ppm (0.067 and 0.074 mg/kg/day for males and females, respectively). The neurotoxicity LOEL was 12 ppm (0.787 and 0.899 mg/kg/day for males and females, respectively). The NOEL for the inhibition of plasma cholinesterase was 1 ppm (LDT). However, slight inhibition of plasma and brain cholinesterase was observed at this level.

In the subchronic delayed neurotoxicity study with hens, the NOEL for inhibition of plasma butyryl cholinesterase and neurotoxic esterase (NTE) activities was 0.3 mg/kg/day, and the LOEL was 1 mg/kg/day. This study was negative for neurotoxicity at 3 mg/kg/day (HDT).

D. Reference Dose (RfD):

The Committee reaffirmed its position on the Reference Dose and recommended that the Reference Dose remain unchanged as assessed by the HED-RfD Committee on May 29, 1992.

F. Individuals in Attendance:

Peer Review Committee members and associates present were William Burnam (chief, SAB; Chairman), David Anderson, Karl Baetcke (Chief, TB I), Stephen Dapson, Melba Morrow, William Sette, Henry Spencer and Rick Whiting.

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

Krystyna Locke Krystyna L. Locke 4/4/97

Roger Gardner _____

Respective Branch Chief (Committee member; signature indicates concurrence with peer review unless otherwise stated)

Karl Baetcke Karl Baetcke

cc: Krystyna Locke
RfD File
Caswell File