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

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

February 20, 1998

MEMORANDUM

SUBJECT: Methamidophos (Monitor) Technical: Additional Data for the Carcinogenicity Study in Mice (MRID No. 43248101) and Rats (MRID No. 43248102), requested by the California EPA.

DP Barcode No. D235731 Submission No. S523073
Rereg. Case No. 0043 P.C. Code No. 101201
CAS Registry No. 10265-92-6 Tox. Chem. No. 378 A

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BACKGROUND

In 1984, Chevron Chemical Company and Mobay Chemical Corporation submitted the following studies to the Agency in support of Methamidophos (Monitor) reregistration:

83-2 Hayes, R.H. (1984) Oncogenicity Study of Methamidophos Technical on Mice. Mobay Chemical Corporation; Mobay Study No. 80-332-01; Study Date: August 6, 1984. MRID No. 00145579

83-5 Hayes, R.H. (1984) Chronic Feeding/Oncogenicity Study of Technical Methamidophos (Monitor) to Rats. Mobay Chemical Corporation; Mobay Study No. 81-271-01; Study Study Date: November 13, 1984. MRID No. 00148452

In 1985/86, the above studies were reviewed by Dynamac Corporation (a contractor) for Toxicology Branch/HED and each study was classified as Acceptable-Guideline. No additional data

were requested then and in 1995 when these studies were discussed by the HED Reference Dose (RfD)/Peer Review Committee. No additional data were also requested for these studies by the HED Toxicology Science Advisory Council (SAC) in December, 1997.

According to the memorandum (dated May 26, 1994; MRID No. 43248100) from Miles Inc., the registrant of Methamidophos since January 1, 1992 (Valent is also a registrant), the above studies were also submitted to California EPA in 1984, in support of their registration of Methamidophos. However, in 1993, California requested additional data relating to each of these studies. The specific requests were:

For the mouse study:

(1) Provide the analytical report No. 84054.

(2) A rationale for the doses used in this study.

(3) Clarification of the fact that 10 mice were replaced by extra mice maintained on identical diets.

For the rat study:

(1) Provide the analytical methodology utilized in evaluating the dietary admixtures in this study.

(2) A rationale for the doses used in the study.

(3) The availability of urinalysis and opththalmology data.

(4) Clarification of the fact that 3 female rats were replaced by extra rats maintained on identical diets.

(5) Submission of individual clinical observational data.

RESPONSES FROM MILES INC.

The requested information was submitted in 1994 to California EPA by Miles Inc. as Miles Reports No. 87479-2 (mouse study) and No. 88687-2 (rat study), as follows:

For the mouse study:

(1) A detailed procedure (37 pages) for the gas chromatographic determination of Methamidophos in rodent feed was provided. It was also stated that the requested report No. 84054 *in reality refers to analytical assessment of dietary admixtures of*

methamidophos in ***canine*** *ration.*

(2) The doses used in the mouse carcinogenicity study (1, 5 and 25 ppm) were based on the inhibitions of cholinesterase (ChE) activities observed in a 6-week preliminary study. In that study, entitled **A Pilot Study Using Technical Methamidophos in Mice** (Stanley Research Center, Mobay Chemical Corporation; No 79CCM01 (P); dated August 22, 1980 - revised report), dietary concentrations of 2, 10, 50 and 100 ppm of Methamidophos were tested. Relative to the control values, the following inhibitions of ChE activities were observed in the 10 ppm group after 5 weeks of dosing (♂/♀): 66/62% in plasma; 62/58% in erythrocytes; and 58/63% in brain.

(3) Ten mice found dead or sacrificed moribund during the first month of the study were replaced with new mice, maintained on identical diets, in order to have 50 animals/dose/sex (a guideline requirement). These substitutes were sacrificed one month after termination of the study. No dose-related effects were responsible for mortalities.

For the rat study:

(1) A detailed procedure for the gas chromatographic determination of Methamidophos in rodent feed was provided. It is the same procedure as that used in the mouse carcinogenicity study.

(2) The doses used in the rat feeding/carcinogenicity study (2, 6, 18 and 54 ppm) were based on the inhibition of cholinesterase (ChE) activities observed in a 5-week preliminary study. In that study, entitled **A Pilot Study Using Technical Methamidophos in Rats** (Stanley Research Center, Mobay Chemical Corporation; No. 80-971-01; dated July 29, 1980 - revised report), dietary concentrations of 1, 2, 4, 8, 16, 32 and 64 ppm of Methamidophos were tested. Relative to the control values, brain ChE activity was inhibited 57% in males and 60% in females, in the 16 ppm group, after 5 weeks of dosing. Relative to the control values, plasma and erythrocyte ChE ctivities were inhibited 55% and 93%, respectively, in ales, and 78% and 92%, respectively, in females - both n the 32 ppm group after 5 weeks of dosing.

(3) Urinalysis and ophthalmology data were not collected in this study.

(4) The three female rats died during the first month of the study and were replaced with new rats, maintained on identical diets, in order to have 50 animals/dose/sex (a guideline requirement).

(5) Individual clinical observational data were included in the current submission (MRID No. 43248102).

RESPONSE FROM TOX. BRANCH II/HED

The above data, submitted to California EPA, were also submitted to the Agency (U.S. EPA). A comment was made by Miles Inc. that these data were not new, would not affect the interpretation of the results of the studies (which is true) and were submitted for the Agency's information only. The Agency did not ask for these additional data for the following reasons:

Mouse Study:

(1) Our guidelines for the reporting of a mouse carcinogenicity study do not require the inclusion of a detailed, step-by-step procedure for the anlyses of rodent diets. The procedure used for the determination of Methamidophos in the rodent diet was referenced and also briefly described.

(2) Since significant decreases in food consumption and body weight gain were observed in both sexes at the highest level of Methamidophos tested (25 ppm; or 3.6 mg/kg/day), dosing was considered adequate and no inquiries were made how doses were selected. The 6-week preliminary study that was apparently used for dose selection was not submitted to the Agency for review.

(3) It was reported in the original submission that 10 mice died during the first month of the study and were replaced with new mice that were fed identical diets, and how the substitutes were treated during the study. The explanations were clear, detailed and adequate. The registrant's response to California EPA was simply a repetition of what was written in the origial report.

Rat Study:

(1) See answer given for the mouse study.

(2) The doses used in this study were based on the results of a 5-week pilot study (No. 80-971-01) and this was noted in the main report. Both studies were reviewed at the same time by the Dynamac Corporation. The rationale for dose

selection was, therefore, known to the Agency.

(3) Since urinalysis and ophthalmology data were not reported, it was assumed that these data were not available. Since no gross or histopathological changes were observed in the eyes of the rats and there was no indication of renal toxicity (e.g. blood urea nitrogen, creatinine and glucose were not affected by Methamidophos), the absence of these data were not regarded as serious gaps.

(4) See responses from Miles Inc., the registrant.

(5) According to the available DER, this study was adequately reported and summary data were supported by individual animal data.

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