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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
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MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: Methamidophos (Monitor): Review of Lab Audit Report on Two Studies, Rat Chronic Feeding/Oncogenic Study and Rat Teratogenic Study

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The full identification of the above studies is as follows:

1. Chronic Feeding/Oncogenicity Study of Technical Methamidophos (Monitor) to Rats; Mobay Chemical Corporation; No. 81-271-01; November 13, 1984. MRID/Accession Nos.: 257630 and 257631.

2. Embryotoxic and Teratogenic Effects of Methamidophos (Monitor) in Rats; Mobay Chemical Corporation; No. 82-611-01; October 15, 1984. MRID/Accession No.: 257632.

Both studies were evaluated for Toxicology Branch by Dynamac Corporation, chronic feeding/oncogenic study in 1985 and teratogenic study in 1986, and were classified as follows:

1. Chronic feeding/oncogenic study: Core-Minimum for chronic toxicity (because urinalysis data were not provided) and Core-Guideline for oncogenicity.

2. Teratogenic study: Core-Minimum

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Toxicology Branch also concluded in 1985 that the chronic feeding study did not meet the regulatory requirements because a NOEL was not determined (cholinesterase activity was inhibited in brain, plasma and erythrocytes at 2 ppm, lowest level fed). This conclusion is still valid. Monitor was not oncogenic in this study.

Monitor was not maternally toxic or fetotoxic at 1 mg/kg and not teratogenic at 3 mg/kg (highest level tested).

The above studies were audited by EPA at Mobay Corporation during September 22-26, 1986 and a detailed report was submitted to Toxicology Branch. The lab audit report (see attached summary) does not change the existing reviews of these studies.

Findings listed in the audit report included mostly deviations from the study protocol, inaccuracies and/or deficiencies in recording of data, missing information, imprecise terminology used for gross observations, and lack of correlation between gross and microscopic pathology. However, none of these findings was extensive or serious enough to warrant changing the existing evaluations of these studies. Furthermore, as was indicated in the audit report, the rat chronic feeding/oncogenic study was conducted before GLP was published (in 1983). At that time, testing laboratories had their own record keeping procedures and these were generally inadequate by comparison with those of GLP.

Toxicology Branch responses to some of the comments in the audit report are as follows:

Rat chronic feeding/oncogenic study

1. Tissues were not examined microscopically at the interim (12-month) sacrifice. This was a deviation from Mobay's Standard Procedure. No reason for the lack of this histopathology was given in the report submitted to EPA.

   Since few neoplasms generally appear in rats during the first year of feeding a test material and since this study was negative for oncogenicity, histopathology on the interim sacrifice animals was not regarded as vital to the assessment of toxicity/oncogenicity of Monitor in this case.

2. Two male rats in the 18 ppm group were listed as "found dead" on one of Mobay's forms and "sacrificed in extremis" on another. A third male rat in the same group was first listed in the Mortality Log and then crossed out and listed as "Terminal Sacrifice".

   These discrepancies are minor and will not affect the

initial review of the study. (Levels of Monitor tested were 0, 2, 6, 18 and 54 ppm).

3. For a total of 10 males (1 control and 9 treated) and 7 females (all treated), there was no correlation between gross observations and microscopic diagnosis. For example, in a pathology report a mass in the subcutis noted at necropsy was not accompanied by microscopic diagnosis; or a mammary mass noted at necropsy was diagnosed as skin fibroma, without microscopic diagnosis for mammary gland. There were 17 masses in all dose groups without direct correlating microscopic diagnosis.

Based on the evaluation of many long-term feeding studies with rodents, it has been the experience of this reviewer that a mass noted at necropsy does not always show histopathological changes. In the pre-GLP era, if nothing remarkable was seen microscopically, sometimes nothing was recorded. Apparently the auditors did not attempt to find out if this was the case with masses lacking microscopic diagnosis. Nine masses had no microscopic diagnosis.

Regarding the discrepancies/noncorrelations (8 masses), comments were made in the audit report that these were probably not true noncorrelations. Rather, they may have been due to imprecise terminology used for gross examinations or to entry of gross examinations under two organ systems. Toxicology Branch agrees with these comments.

Considering also that, with one exception*, the above masses were single incidences (occurred one per animal) and were observed at all dose levels and in a variety of organs/tissues, Toxicology Branch concluded that the original evaluation of this study-negative for oncogenicity-should remain unchanged.

*(One rat in the 18 ppm group had a lung mass and a testicular mass, each without microscopic diagnosis in the pathology report).

4. According to the audit report, it could not be ascertained that the EPA received a copy of the amended study final report. The final report should indicate the location of the animal supplier and the disposition of all animals in the study.

The audit report gives neither the ID number nor the date of the amended study final report. The report evaluated by Dynamac Corporation/Toxicology Branch (two volumes) was numbered 554/#88637 (Study No. 81-271-01), dated November 13, 1984 and authored by R. H. Hayes. The name of the

animal supplier was reported, but not his location. The disposition of all of the reserve/satellite animals was missing.

5. The auditors recommended that Mobay exclude excessive feed spillage from statistical analyses. Pelletizing feed after treatment would also have been a very useful recommendation.

Rat teratogenic study

1. According to the audit report, animals were assigned to groups before mating and without regard to weight, and not after mating and on the basis of body weight, as was stated in Mobay's Standard Procedure and reported to EPA.

   No reference is made to the randomization time in the EPA 1982 Guidelines. On gestation day (gd) 0, the mean body weights and (standard deviations) of the dams in the control, positive control, and the 0.3, 1.0 and 3.0 mg/kg groups were 241(19), 239(23), 232(16), 236(23) and 237(16)g, respectively. Although incorrect reporting is regrettable, the intra- and intergroup weight variations at the start of the study are acceptable.

2. Animals were dosed on gd 6-20 and not 6-15 as reported. They were killed on gd 21.

   Again, the incorrect reporting is regrettable, but longer dosing does not make the study unacceptable. According to the EPA 1982 Guidelines, "Alternatively, the period of dosing may be extended to approximately one day before the expected delivery date."

3. Three crossouts on Mobay's toxicology forms were either not initialed or reasons for them were not given.

   The crossouts represent only poor laboratory practices, as no data (values and/or verbal statements) were involved.

4. According to the auditors, skeletal findings listed in the study report included observations of 13, 14 and extra ribs. Since rats normally have 13 pairs of ribs, the distinction between 14 and extra ribs was not clear. Subsequent examination of the visceral and skeletal specimens indicated that "13" and "14" referred to the rudimentary ribs, whereas "extra" referred to a full-length 14th rib. However, some ambiguities still remained.

   Toxicology Branch appreciates the above information.

5. In one instance, reported litter and fetal weights were 74 g

and 4.9 g, respectively, but should have been, according to an auditor's calculations, 79.6 g and 5.3 g, respectively. In another instance, a dose for one dam was 1.2 (units unspecified, but apparently mL), but should have been 1.3 (mL?).

It is not clear how the auditors happened to have selected this one animal or if other litter and fetal weights were also checked.

In summary, the auditors concluded that, although inconsistencies, deficiencies and inaccuracies between the raw data and the reported procedures and results were noted in the rat teratogenic study, they were minor and did not appear to affect the overall assessment of the study results. Toxicology Branch agrees with this conclusion.

The data audit findings are summarized below:

I. Methamidophos Technical (Monitor): Chronic feeding/Oncogenicity Study to Rats.

1. Histopathology was not performed on the interm sacrifice animals as required by the protocol.

2. Discrepancies were found on the type of death of a few animals between the Mortality log and Tox Form 33.

3. A number of gross lesions were apparently not examined microscopically.

4. The staining quality of sections of decalcified bones was considered to be fair to poor. Although it did not affect the interpretation of sections of the tail, it would not be optimal for evaluation of decalcified nasal sections.

5. Serological tests for common viral and mycoplasmal infections should be routinely performed on animals (sentinel) to determine the presence or absence of infection in a study.

6. The wet tissue review revealed that:

   a. Tissue identifiers (ears or toes) were not present.

   b. Examination of all orifices (mouth and pharynx) was apparently not preformed.

   c. The majority of tissues, such as gastrointestinal tract and liver were not retained with the residual wet tissues.

   d. One wet tissue bag contained 2 heads.

7. The slide/block match revealed that discrepancies were found on the identification of some slides.

8. It could not be ascertained that the EPA has received a copy of the amended study final report.

9. The final report should indicate the location of the animal supplier and the disposition of all animals in the study.

10. The laboratory has a tendency to do more than is required by the study protocol. Although this is better than doing less, the study protocol should precede the SOPs and the personnel should read and follow the protocol.

11. The statistically significant difference in body weight at the start of the study should be avoided.

12. It was recommended to exclude exessive feed spillage from statistical analyses.

13. Organ weight of animals that died during the study and questionable organ weights should not be included in the statistical analyses.

14. The chromatograms for stability analyses of the test article were missing and apparently discarded.

15. There were no records on the control feed (Purina) analyses reports.

16. The homogeneity of feed was analyzed 5 months after the start of the study. A protocol deviation was noted on the lowest dose level used for the homogeneity analysis.

17. Data on the storage stability tests were not available. It was noted that feed samples were frequently analyzed after the confirmed stability timeframe (16 days) had elapsed.

18. There was a discrepancy on the color of the test chemical between the final report and the archived sample.

II. Methamidophos Technical: Teratological Effects on Rats.

1. There were several inconsistencies between the final report and the raw data on the randomization of animals and the duration and amount of test chemical administered.

2. There were several calculation errors.

3. Deficiencies were found in the recording of data.

4. Discrepancies were found between the auditor and the laboratory on the reading of fetal visceral and skeletal specimens.