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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

SEP 24 1986

MEMORANDUM

SUBJECT: Laboratory Audit Report - Miles Laboratories, Inc., Elkhart, Indiana 46515

TO: William Nelson, Investigator
Food and Drug Administration
105 East Jefferson, Suite 222
South Bend, Indiana 46601

John A. McCann, Manager
National Lab Audit Program
Benefits and Use Division (TS-768C)

FROM: Quang Q. Bui, Ph.D. Quang Bui
Toxicologist, Section V
Toxicology Branch
Hazard Evaluation Division (TS-769C)

An on-site audit of several studies conducted at the Toxicology Department, Miles Laboratories Inc., Elkhart, Indiana was performed by investigators from the Food and Drug Administration (Mr. William Nelson) and the Environmental Protection Agency (Dr. Quang Bui) from September 15-19, 1986.

Attached is our report relative to data auditing of five toxicology studies:

1. Teratology study with Metasystox R in rabbits
2. Teratology study with Dasanit in rats
3. 21-day dermal with Cutter Insect Repellent in rabbits
4. Primary eye irritation with Cutter Insect Repellent in rabbits
5. Primary dermal irritation with Cutter Insect Repellent in rabbits

cc. Dr. Ted Farber, Tox. Branch Chief (TS-769C)
Laurence D. Chitlik, Section Head (TS-769C)
Dr. Ken Kanagalingam (EN-342)
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AUDIT REPORT SUMMARY

An inter-agency on-site audit of 5 toxicology studies conducted by the Department of Toxicology, Miles Laboratories, Elkhart, Indiana 46515 was performed by the Food and Drug Administration (Mr. William Nelson, FDA investigator stationed at South Bend, Indiana) and the Environmental Protection Agency (Dr. Quang Bui, Toxicology Branch, Hazard Evaluation Division, Arlington, Virginia). The on-site audit was broadly divided into 2 phases: GLP compliance and data auditing. The GLP compliance was conducted by the FDA investigator whereas the data auditing was performed by this auditor.

With respect to data auditing, this auditor confirmed that all raw data as well as specimens (maternal and fetal) were properly archived at the testing facility. The testing facility's Standard Operating Procedures were available and were properly referred to in final reports submitted to the Agency. A re-examination of the raw data and fetal speciments was conducted and, in general, the re-examined data confirmed the reported findings. Several discrepancies were noted by this auditor and are described in detail in the attached respective study audit reports. However, this auditor believes that these errors did not have any significant impact on the validity of the studies audited.

AUDIT REPORT # 1

Study type: Teratology study in rabbits
Compound: Metasystox-R
Registrant: Mobay Chemical Corporation
Report No.: M-146989
Mobay 86391
Report Date: 4/10/84
Study Directors: G. Clemens and R. Hartnagel Jr.

A re-examination of the raw data was performed by this auditor and included:

1. Standard Operation Procedures for rabbit teratology study
2. Dose preparation data
3. Clinical observation data
4. Body weight data
5. Food consumption data
6. Compound dosing data
7. Necropsy data
8. Fetal examination data
9. Statistical data
10. Quality assurance data

Remarkably, no discrepancies between the raw data and the final report were noted by this auditor.

In addition, preserved maternal and fetal specimens were counted with the following findings:

a. All data were properly archived and were accounted for at the testing facility.

b. All specimens were prepared and stored according to the testing facility's Standard Operating Procedures.

A re-examination of randomly selected fetal specimens was performed by this auditor with the assistance of Kim Hilbish, Head Technician of the Teratology and Reproduction Section at Miles Laboratories, with the following findings:

a. Re-examination of the fetal specimens supported the findings in the final report.

In conclusion, the raw data available at the testing facility supported the reported findings. It should be noted, however, that the dose levels used in this study were not adjusted to 100% purity. Therefore, the dose levels indicated in the final report as 0.1, 0.4, and 1.6 mg/kg should be corrected to, respectively, 0.05, 0.2, and 0.8 mg/kg since the test material had a purity of only 50%.

AUDIT REPORT No. 2

Study Type: Teratology study in rats
Compound: Dasanit (Fensulfothion)
Registrant: Mobay Chemical Corporation
Report No.: M-149185
Mobay 88916
Report Date: 1/25/85
Study Authors: G. Clemens, J. Bare, and R. Hartnagel Jr.

A re-examination of the raw data was performed by this auditor and included:

1. Standard Operating Procedures for teratology study in rats
2. Dose preparation data
3. Body weight data
4. Compound administration data
5. Food consumption data
6. Clinical observation data
7. Necropsy data
8. Fetal examination data
9. Statistical data
10. Quality Assurance data

No discrepancies between the raw data and the final report were found by this auditor. In addition, a re-examination of maternal and fetal specimens was conducted by this auditor with the assistance of Mr. Kim Hilbish, Head Technician, with the following findings:

a. All specimens and raw data are properly archived
b. All specimens were stored, prepared, and identified according to the testing facility's Standard Operating Procedures
c. All specimens were available to verify the reported findings
d. All findings were supported by re-examination of the specimens

In conclusion, supporting raw data and specimens were available to verify and confirm the reported findings in this study.

AUDIT REPORT # 3

Study Type: 21-day dermal in rabbits
Compound: Cutter Insect Repellent
Report No.: M-151648
Report Date: 4/17/85
Study Authors: R. Kowaslski, V. Jasty, J. Bare, and R. Hartnagel Jr.

A re-examination of the raw data was performed by this auditor and included:

1. Animal request order
2. Quarantine data
3. Body weight data
4. Clinical observation data
5. Dosing preparation data
6. Necropsy data
7. Histopathology data
8. Standard Operating Procedures for 21-day dermal study
9. Quality assurance data

In general, the raw data supported the scientific findings in the final report. All dermal scores were accurately reported. Necropsy and histopathology data were performed on all animals and were available for audit. However, the following dificiencies were noted by this auditor and have been discussed with the study director (R. Kowalski), department of toxicology director (R. Hartnagel) and the quality assurance officer (J. Thain) for rectification:

a. Dose levels

Page 1 of the final report (Appendix 1) indicated that dose levels of 0.2, 0.6, and 2.0 ml/kg were used. However, dose levels of 0.2, 0.6, and 2.0 mg/kg were mentioned throughout the final report. Since the % by weight of the active ingredients used (Appendix 2) was 40% of the dosing solution, it is unlikely that these volumes would be equalled to these weights.

b. Reporting Differences

The dose levels indicated in table VIII were: 0.2, 0.6, and 2.0 ml/kg/day (Appendix 3) whereas those in table X were 0.02, 0.06, and 0.20 mg/kg (Appendix 4) and those in table XI were 0.2, 0.06, and 0.20 mg/kg (Appendix 5).

c. Data recording

Control animal # 2471 was sacrificed on 11/19/84 (Appendix 6) but was described as normal on 11/26/84 (Appendix 7). An examination of the necropsy and histopathology data by this auditor confirmed that animal #2471 was sacrificed on 11/19/84 and the above discrepancy apparently was an oversight of the technician and/or study director. The testing facility is requested to rectify this difference.

d. Data archiving

Apparently all raw data of studies conducted at Miles Laboratories were microfilmed. A discrepancy in this procedure was noted by this auditor.

This 21-day dermal study with Cutter Repellent in rabbits was conducted from November to December 1984. However, all raw data were stamped as being microfilmed on June 10, 1982. A re-examinination of all pertinent data (animal request, clinical chemistry, pathology data, etc.) confirmed that this study was indeed conducted in 1984. This auditor believes that the "June 10, 1982" stamped on the raw data apparently was a technical error and does not affect the validity of the study.

This auditor concludes that the above differences did not have any significant impact on the validity and integrity of the study. The study was scientifically conducted and all supporting raw data are available at the testing facility. However, the testing facility is requested to rectify these differences.

AUDIT REPORT No. 4

Study Type: Primary Eye Irritation in rabbits
Compound: Cutter Insect Repellent
Report No. M-151644
Report Date: 3/11/85
Study Authors: R. Kowalski and R. Hartnagel Jr.

An audit of the raw data was conducted and no discrepancies and/or differences with the final report were noted.

AUDIT REPORT # 5

Study Type: Primary dermal irritation in rabbits
Compound: Cutter Insect Repellent
Report No.: M-151646
Report Date: 3/18/85
Study Authors: R. Kowalski and R. Hartnagel Jr.

An audit of the raw data was conducted and no discrepancies and/or differences with the final report were noted.