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OPP OFFICIAL RECORD
HEALTH EFFECTS DIVISION
SCIENTIFIC DATA REVIEWS
EPA SERIES 361

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MEMORANDUM

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

SUBJECT: Methiocarb (Mesurol): Evaluation of Toxicity Studies Performed with Mesurol Technical (Three Mutagenicity, One Acute Inhalation, and One 21-day Dermal Studies), Performed with Mesurol 75% Concentrate (One Acute Inhalation Study), or Performed with Mesurol Phenol (One Metabolism Study)

Barcode: D176010
Submission: S414546
PC Code: 100501
Tox Chem No.: 578B
MRID Nos.: 405081-01
405081-02
00159042
404042-01
405181-03
407008-01
409223-01

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PM #73
Reregistration Division

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CONCLUSIONS

The studies listed below were submitted by Miles, Inc. (formerly Mobay Corp.) in support of the reregistration of the carbamate pesticide Methiocarb (Mesurol). Provided are a brief summary of the results of each study (taken from the DERs) and their Core Classifications, or other appropriate information. Other synonyms for the technical material are Mercaptodimethur and H 321.

Test Material- Methiocarb Technical

1. MRID 405081-01. H 321 c.n. Mercaptodimethur. Salmonella/Microsome Test to Evaluate for Point Mutagenic Effect. Study performed by Bayer AG, Wuppertal-Elberfeld, Germany, Report number 91775, issued 1/10/86.

In three independently performed Salmonella typhimurium/mammalian microsome plate incorporation assays with tester strains TA1535, TA1537, TA98, and TA100, doses of H 321 ranging from 62.5 µg/plate to 1000 µg/plate in the absence of S9 and from 125 µg/plate to 2000 µg/plate in the presence of S9 were not mutagenic. Compound precipitation was observed at the highest dose tested (12,500 µg/plate +/- S9); doses ≥ 1000 µg/plate -S9 and ≥ 2000 µg/plate +S9 were cytotoxic. Although technical concerns were raised (see Reviewers' Comments), these deviations were judged not to have affected the overall study results, therefore, it is concluded that H 321 was evaluated over an appropriate range of concentrations and was not mutagenic in this bacterial test system.

Core Classification: Acceptable. Satisfies Guideline requirements (84-2) for genetic effects Category I, Gene Mutations.

2. MRID 405081-02. Sister Chromatid Exchange Assay in Chinese Hamster Ovary (CHO) Cells Test Article Mesurol Technical. Study performed by Microbiological Associates, Inc., Bethesda, MD, Report numbers: Study 91334, Lab T4522.334, Toxicology 790, issued 9/25/86.

Mesurol technical was investigated for the potential to induce sister chromatid exchange (SCE) in Chinese hamster ovary (CHO) cells. Owing to severe cytotoxicity and cell-cycle delay, cultures exposed to nonactivated doses of 2-40 µg/ml and S9-activated doses of 4-40 µg/mL were harvested 26-32 hours post-treatment. Results indicated that the test material was cytotoxic at ≥ 10 µg/ml -S9 and at 40 µg/mL +S9 but not genotoxic. It was concluded, therefore, that Mesurol technical was adequately tested and was found to be nongenotoxic in a well-controlled assay.

Core Classification: Acceptable. Satisfies Guideline requirements (84-4) for genetic effects Category III, Other Mutagenic Mechanisms.

3. MRID 407008-01. Unscheduled DNA Synthesis (In vitro) in Rat Primary Hepatocytes, Test Article Mesurol, Lot No. 86I004. Study performed by Microbiological Associates, Inc., Bethesda, MD, Report numbers: Study 96708, Lab T5391.380, Toxicology 1007, issued 6/1/88.

Mesurol technical was evaluated in two independently performed assays for the potential to cause unscheduled DNA synthesis (UDS) in primary rat hepatocytes; cells from a female rat were used in Trial 1 and hepatocytes from a male rat in Trial 2. Results indicate that the test material was not genotoxic over

concentration ranges (1.0-45 μg/mL in Trial 1 and 3.0-60 μg/mL in Trial 2) that included moderately cytotoxic levels. Higher doses (≥60 μg/mL in Trial 1 and 100 μg/mL in Trial 2) were severely cytotoxic. Based on these findings, it was concluded that Mesurol technical was tested over an appropriate range of concentrations with appropriate controls and showed no evidence of UDS.

Core Classification: Acceptable. Satisfies Guideline requirements (84-4) for genetic effects Category III, Other Mutagenic Mechanisms.

4. MRID 404042-01. Acute Four-Hour Inhalation Toxicity Study with Mesurol Technical in Rats. Study performed by Mobay Corporation , Stilwell , Kansas, Report numbers: Study 86-041-25, Report 94635, Tox. Report 870, issued 6/18/87.

Estimated acute inhalation LC_{50}'s for Mesurol technical with 95% confidence intervals following a 4-hour exposure:

0.585 (0.345-0.698) mg/L for males
0.433 (0.286-0.585) mg/L for females

MMAD 4.0 to 5.0 μm (see note in DER).

Core Classification: Acceptable. Satisfies Guideline Series 81-3.
Toxicity Category: II

5. MRID 409223-01. A 21-Day Dermal Toxicity Study of Mesurol Technical in Albino rabbits. Study performed by Bio-Research Laboratories, Ltd., Senneville, Quebec, Study numbers 51901 & 98369 issued 11/23/88.

Although at the highest dose administered (375 mg/kg/day), males showed statistically significantly decreased food consumption primarily during the second week of the study and statistically significantly decreased plasma cholinesterase activity on study day 21, the changes were of insufficient magnitude and duration to be considered adverse. No effect was observed in females at any dose. Convincing LOELs for systemic toxicity and cholinesterase inhibition cannot be established in this study. A higher dose of the test material should have been administered. The NOEL for systemic toxicity and cholinesterase inhibition is ≥ 375 mg/kg/day.

Core Classification: Supplementary. Cannot be upgraded because the test material was not administered at the limit dose (1000 mg/kg/day) or at a dose sufficient to elicit clear-cut signs of toxicity.

<u>Test Material- Mesurol Phenol</u>

6. MRID 00159042. Metabolism of Mesurol Phenol by Rats. Study performed by Mobay Chemical Corp., Kansas City, MO, Study numbers: 88899, issued 1/23/85.

This study performed with Mesurol phenol, a metabolite of Mesurol, was not submitted to fulfill any regulatory requirement or issue, therefore it is not necessary for Toxicology Branch I to prepare a DER for the study at this time. The study hardcopy is being returned to Reregistration Division. A Mobay company representative said that the study had been performed out of curiosity to try to find out when a hydrolysis step in the metabolism of Mesurol took place.

Test Material- Mesurol 75% Concentrate

7. MRID 405181-03C. Acute 4-Hour Inhalation Toxicity Study with Mesurol 75% Concentrate in Rats. Study performed by Mobay Corp., Stilwell, Kansas, Report numbers: Report 95623, Tox. Report 984, Study number 87-041-18, issued 2/5/88.

Estimated acute inhalation LC_{50}'s for Mesurol 75% Concentrate with 95% confidence intervals following a 4-hour exposure:

0.479 mg/L for males
0.403 mg/L for females
MMAD 3.4 to 4.4 μm.

Core Classification: Acceptable. Satisfies Guideline Series 81-3 (end-use product).

Toxicity Category: II

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