7-27-93

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

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OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Sodium N-methyldithiocarbamate (Metam Sodium)

P.C. Code: 039003
ToxChem No: 780

FROM: Timothy F. McMahon, Ph.D. 7/27/93
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TO: Ameesha Mehta
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THRU: Yiannakis M. Ioannou, Ph.D., Section Head
Review Section I, Toxicology Branch II
Health Effects Division (H7509C)
Y M. Ioannou 7/27/93

Action Requested: Provide current information and status of the Toxicology database for Metam Sodium

Data Summary:

1) Title: Acute Oral Toxicity to Rats of Metam Sodium

MRID # 419861-01

Material: metam sodium 510 g/L

Under the conditions of this study, the acute oral LD_{50} of Metam Sodium was 870 mg/kg in male rats with 95% confidence limits of 715 and 1059 mg/kg body weight. The estimated oral LD_{50} in female rats was calculated as 924 mg/kg body weight, with 95% confidence limits of 758 and 1130 mg/kg. The combined oral LD_{50} was calculated as 896 mg/kg, with 95% confidence limits of 779 and 1031 mg/kg body weight.

Toxicity Category III

Core Classification: minimum

2) Title: Acute Dermal Toxicity Study to Rats of Metam Sodium

MRID # 419861-02

Material: metam sodium 510 g/L

Under the conditions of this study, the acute dermal LD_{50} of Metam Sodium was > 2000 mg/kg in male and female rats.

Toxicity Category III

Core Classification: minimum

3) Title: Acute Inhalation Toxicity Study in Rats-4 Hour Exposure

MRID # 421877-01

Under the conditions of this study, the acute inhalation LC_{50} of Metam Sodium was estimated as 2.20 mg/L for male rats, and 2.95 mg/L for female rats. The combined acute inhalation LC_{50} was estimated as 2.54 mg/L. The data adequately demonstrate a median lethal dose of between 0.5 and 5.0 mg/L.

Toxicity Category III

Core Classification: minimum

4) Title: Primary Eye Irritation to Rabbits with Metam Sodium

MRID # 419861-03

Under the conditions of this study, Metam Sodium was determined to be mildly irritating to the eyes of New Zealand White rabbits.

Toxicity Category III

Core Classification: minimum

5) Title Skin Irritation to Rabbits with Metam Sodium

MRID # 419861-04

Under the conditions of this study, Metam Sodium was severely irritating to the skin of male and female rabbits.

Toxicity Category II

Core Classification: minimum

6) Title: Delayed Contact Hypersensitivity in the Albino Guinea Pig

MRID: 419861-05

Under the conditions of this study, metam sodium appeared to function as a skin sensitizer in guinea pigs.

Core Classification: minimum

7) Title: Metam Sodium: 90-Day Oral Dosing Study in Dogs

MRID: 426000-01

Metam sodium was administered by gelatin capsule to male and female dogs at nominal dose levels of 0, 1, 5, and 10mg/kg/day once daily for 13 weeks. Toxic effects were observed at all dose levels tested, but were primarily evident at the 5 and 10 mg/kg/day dose levels. These included decreased body weight and body weight gain in male and female dogs at 10 mg/kg/day, hematologic alterations (increased cell volume, cell hemoglobin, neutrophils, and monocytes; decreased MCHC) at 5 and 10 mg/kg/day, significant increases in plasma ALT, AST, ALK PHOS, and GGT at 5 and 10 mg/kg/day (including significantly increased ALT in female dogs at 1 mg/kg/day), increased amounts of blood, urobilinogen, bilirubin, and protein in urine at 5 and 10 mg/kg/day, and microscopic evidence of hepatitis at 5 and 10 mg/kg/day. A majority of the toxic effects observed in this study appeared dose- and time-related in treated dogs. No evidence of tumors was found in this study.

Based upon the results of this study, the systemic NOEL is < 1 mg/kg/day, and the systemic LEL is $\leq$ 1 mg/kg/day for female dogs, based upon the increase in plasma ALT observed in female dogs at 1 mg/kg/day and the biliary duct proliferation with inflammatory cell infiltration observed in female dogs at the 1 mg/kg/day dose level. For male dogs, the systemic NOEL is = 1 mg/kg/day and the systemic LEL = 5 mg/kg/day, based upon statistically significant increases in plasma ALT, AST, and alkaline phosphatase, as well as the increased incidence of hepatitis and bile duct proliferation.

Classification: core supplementary

This study does not satisfy the guideline requirement (§ 82-1) for a subchronic toxicity study in dogs, due to the lack of establishment of a systemic NOEL for toxicity.

8) Title: Metam Sodium: 90-Day Drinking Water Study in Rats

MRID: 421173-02

In this study, Metam sodium was administered to male and female rats in drinking water at nominal dose levels of 0, 0.018, 0.089, and 0.443 mg/ml (1.7, 8.1, and 26.9 mg/kg/day in males; 2.5, 9.3, and 30.6 mg/kg/day in females). At the high dose in both sexes, systemic toxicity in the form of significantly decreased food and water consumption, decreased body weight gain, and histological changes in the nasal cavity olfactory epithelium were observed. At the high dose, renal tubular dilatation and basophilia, along with increases in blood, protein, and red cells in urine was also observed. In high dose males, an increased incidence of plasma cell hyperplasia in cervical lymph nodes was demonstrated as well as a significant decrease in platelet count. A significant decrease in group mean body weight was observed in female rats at the mid dose, and body weight gain was decreased 11% at this dose for the duration of the study. Significant decreases in red cell count and hematocrit were also observed at the mid dose in both male and female rats.

Tentative NOEL = 1.7 mg/kg/day (males); 2.5 mg/kg/day (females)

Tentative LEL = 8.1 mg/kg/day (males; hematological changes); 9.3 mg/kg/day (females; decreased absolute body weight).

Tentative Maximum Tolerated Dose = 26.9 mg/kg/day (males); 30.6 mg/kg/day (females); decreased absolute body weight, body weight gain; alterations in hematology and clinical chemistry parameters; increased incidence of histopathological abnormalities.

Classification:

supplementary

This study does not satisfy the guideline requirements (§82-1) for a subchronic toxicity study in rats.

9) Title: Metam Sodium: 90-Day Drinking Water Study in Mice with a 28-Day Interim Kill.

MRID: 421173-01

Metam Sodium was administered to male and female mice in the drinking water at dose levels of 0.018 mg/ml (2.7 mg/kg/day for males; 3.6 mg/kg/day for females), 0.088 mg/ml (11.7 mg/kg/day for males; 15.2 mg/kg/day for females), 0.35 mg/ml (52.4 mg/kg/day for males; 55.4 mg/kg/day for females), and 0.62 mg/ml (78.7 mg/kg/day for males; 83.8 mg/kg/day for females) for 90 days. The systemic toxicity NOEL was 0.018 mg/ml (2.7 mg/kg/day for males and 3.6 mg/kg/day for females) and the LEL was 0.088 mg/ml (11.7 mg/kg/day for males and 15.2 mg/kg/day for females) based on urinary bladder lesions (eosinophilic granules, cystitis and mucosal hyperplasia) in both sexes and decreases in hematology parameter values (hemoglobin, red blood cells, hematocrit) in female mice. Based on decreased body weight gains, the MTD appears to have been achieved at 0.35 mg/ml (52.4 mg/kg/day) in males and 0.62 mg/ml (83.3 mg/kg/day) in females.

Classification: supplementary

10) Developmental Toxicity Study in Rats

MRID # 415771-01; 420686-01

Metam sodium (42.2% a.i.) was administered to pregnant Wistar rats on days 6-15 of gestation at doses of 0, 10, 40, and 120 mg/kg/day by gavage. Maternal toxicity was observed at the 40 and 120 mg/kg/day dose levels as significantly decreased body weight gain during the dosing period. There was a significant increase in post-implantation loss, and a significant decrease in the percent of live fetuses per dam at 10 and 120 mg/kg/day. Fetal weights were significantly reduced at 120 mg/kg/day. Examination of the viscera of fetuses that underwent skeletal examination revealed a significant increase in variations at the 40 mg/kg/day dose level. Skeletal examination revealed findings in the 40 and 120 mg/kg/day dose groups. The administration of 120 mg/kg/day in the main study and 240 mg/kg/day in the dose range finding study resulted in meningocoele. Based upon deficiencies, this study cannot be upgraded.

Maternal NOEL = 10 mg/kg/day; Maternal LOEL = 40 mg/kg/day Developmental Toxicity NOEL = < 10 mg/kg/day; Developmental Toxicity LOEL = 10 mg/kg/day. **Classification:** supplementary

11) Developmental Toxicity Study in Rabbits

MRID # 403309-01; 420686-01

Himalayan rabbits were administered metam sodium on gestation days 6 through 18 by gavage at dose levels of 10, 30, and 100 mg/kg/day. Maternal toxicity in the form of reduced body weight gain, reduced food consumption, increased number of dead implantations and reduced numbers of fetuses, and increased post-implantation loss in either the mid or high dose group alone or together. Developmental toxicity was apparent in the mid and high dose groups in the form of increased number of dead implantations and reduced number of fetuses, and increased post-implantation loss. One observation oeach of meningocoele and spina bifida were noted at the high dose. These observations were not reported in the historical control data provided.

Maternal NOEL = 10 mg/kg/day; Maternal LOEL = 30 mg/kg/day. Developmental Toxicity NOEL and LOEL cannot be determined from the available data; additional information is required.

Classification: supplementary

Chronic Toxicity Data

There are no data currently available on the chronic toxicity of metam sodium.

Risk Assessment

For purposes of risk assessment for metam sodium and MITC, the NOEL of < 10 mg/kg/day, derived from the rat developmental toxicity study, should be used for acute effects.

For purposes of risk assessment for metam sodium and MITC, the NOEL of < 1 mg/kg/day, derived from the subchronic toxicty study in dogs, should be used for subchronic effects.