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Date 8/19/04
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Template version 11/01

TXR#:0051475

DATA EVALUATION RECORD

Updated Executive Summary to Previous TXR # 0051394

STUDY TYPE: Subchronic toxicity - dog (capsule); OPPTS 870.4100b [§83-1b]; OECD 452.

PC CODE: 39003

DP BARCODE: D303925
SUBMISSION NO.: S618557

TEST MATERIAL (PURITY): Metam sodium (43.15% a.i.)

SYNONYMS: Sodium n-methyldithiocarbamate

CITATION: Brammer, A. (1992) Metam Sodium: 90-day Oral Dosing Study in Dogs: Lab Project Number: CTL/P/3679. Unpublished study prepared by ICI Central Toxicology Lab. MRID no. 42600001. Unpublished.

SPONSOR: Metam Sodium Task Force

EXECUTIVE SUMMARY:

In a 90-day oral toxicity study (MRID 42600001), metam sodium (Purity 43.15%, Batch No. not stated) was administered to 4 Beagle dogs/sex/dose by gelatin capsules at dose levels of 0, 1, 5, and 10 mg/kg/day (0, 0.56, 2.8 and 5.6 mg/kg/day MITC equivalent) once daily for 13 weeks.

Compound related mortality was observed in this study. One male and one female were sacrificed during weeks 11 and 12, respectively, at the 10 mg/kg/day dose level. The animals were sacrificed due to poor clinical condition such as appearance of jaundice, inappetance and emaciation. No mortality was observed during administration of the test material at lower doses.

Some signs of vomiting were noted in males and females dogs at the 5 and 10 mg/kg/day dose levels. The incidence of this was more evident at the 10 mg/kg/day (75) than the 5 mg/kg/day (9) and it appears that the occurrence was slightly higher in the male (48) than female (36) dogs. One incidence of vomiting occurred in the control group.

Statistically significant decreases (9%) in absolute body weight were noted at the 10 mg/kg/day dose level in male dogs beginning at week 10 of the study and continued through until study

termination. Body weight gain was also affected in the male dogs at the 10 mg/kg/day dose level, such that overall weight gain for weeks 1-13 was decreased by 39% vs. control. In female dogs, no significant effects were noted in group mean absolute body weight for the study period.

Results for food consumption showed food residues left by some of the dogs at the 5 and 10 mg/kg/day dose levels. It appeared that the amount of food left by three male dogs at the 10 mg/kg/day dose level increased with increasing duration of treatment 9%-99%). However, residue measurements were presented only from approximately week 8 until study termination.

Abnormal urine color (orange or orange/brown) was recorded for 3 males and 2 females at the 10 mg/kg/day dose group and for 1 male at the 5 mg/kg/day dose level. An increased presence of urobilinogen and bilirubin was observed in both sexes at 10 mg/kg/day and an increase bilirubin was also present in both sexes at the 5 mg/kg/day dose level.

The observed group mean kidney weight of the male dogs at the 10 mg/kg/day dose level were higher than control group. Also, testes weight was decreased by 24% in comparison to control values for male dogs at the 10 mg/kg/day dose level. Reduced weights of the epididymides were also observed in 2 of th 4 male dogs at the 10 mg/kg/day dose level. The epididymides of 2 dogs were approximately 2g in weight, while those of the affected dogs were approximately 0.95g in weight, a reduction of about 50%.

A slight reduction (5-10%) in the number of red blood cells was noted in male and female dogs at the 5 and 10 mg/kg/day dose levels, but was not labeled as statistically significant. Mean cell volume was significantly increased at the 10 mg/kg/day dose level during week 8 (4% and 4%, male and female dogs. respectively) and during week 13 (7.5% and 11%, male and female dogs, respectively). Similar changes were observed in mean cell hemoglobin, with the exception that a significant increase was not observed in female dogs at week 8 of the study. A statistically significant reduction in mean cell hemoglobin concentration was observed at the 5 mg/kg/day dose level on week 13 (1.5%, female only), and at the 10 mg/kg/day dose level on weeks 8 (2%, males only) and week 13 (3% males and 1.5% females).

The white blood cell differential analysis showed time and dose- related increases in the number of neutrophils and monocytes in both male and female dogs. There was a statistically significant increase in neutrophils at week 4 (32%) and week 8 (17%) at the 1 mg/kg/day dose level in comparison to control. Statistically significance was achieved for the increase in monocytes at the 10 mg/kg/day dose level in both male (71%) and female (61%) dogs at week 13 of the study. There was also a statistically significant increase in prothrombin time in female dogs at the 1 mg/kg/day (6.4%), 5 mg/kg/day (45), and 10 mg/kg/day (11%) dose level during week 4. Significant increase was observed at the 10 mg/kg/day dose level in male dogs during week 8 (15%) and week13 (31%).

Significant increases in AST were evident at the 10 mg/kg/day dose level in male dogs by week 6 (39%), and in female dogs by week 12 (69%). By week 13, AST was increased 454% vs control in male dogs, and by 108% in female dogs.

A statistically significant increase in ALT was noted in males dogs at the 10 mg/kg/day dose level at week 6 (88%) and week 8 (92%) of the study. Also significant increase in ALT (2395% vs. control and 794% vs. control for male and female dogs, respectively) was observed by week 13 at the 10 mg/kg/day dose level. By week 13 ALT activity in female dogs were increased by 351% vs. control at the 1 mg/kg/day dose level.

Statistically significant increases in ALP were evident in male dogs by week 6 and in female dogs on week 4 and at weeks 8 through 13. The increase in ALP were more evident at the 10 mg/kg/day dose level. In male dogs, ALP was elevated by 659% vs. control at week 13, while in female dogs, ALP was elevated by 95% vs. control. The increase in ALP for male and female dogs appeared dose and time-related beginning at the 1 mg/kg/day dose level.

Plasma GGT showed statistically significant increases in male dogs at the10 mg/kg/day and in female dogs at the 5 and 10 mg/kg/day dose levels. In male dogs, the increase in plasma GGT was approximately 470% for weeks 12 and 23, while in female dogs, GGT at 10 mg/kg/day was increased by 187% at week 12 and by 400% on week 13 in comparison to control.

In those dogs surviving to study termination, the most prominent observations from the macroscopic examination were those in the liver. In 2 of the 3 surviving male dogs at the 10 mg/kg/day dose level, an accentuated lobular pattern, depressed red area(s), and pale (yellow) appearance were noted. Also at the 10 mg/kg/day dose level, depressed red areas were noted in 2 of the surviving 3 female dogs and pale appearance of the liver was noted in 1 female dog. At the 5 mg/kg/day dose level, depressed red areas of the liver were noted in 1 male and 1 female dog. Livers of all dogs were reported as macroscopically normal at the 1 mg/kg/day dose level.

***For female dogs*, the LOAEL is 1 mg/kg/day (0.56 mg/kg/day MITC eqvi.) based on increase in plasma ALT, AST, and alkaline phosphatase, as well as increase incidence of biliary duct proliferation with inflammatory cell infiltration. In female dogs, the NOAEL was not established (< 1 mg/kg/day (<0.56 mg/kg/day MITC eqvi.)).**

***For male dogs*, the LOAEL is 5 mg/kg/day (2.8 mg/kg/day MITC eqvi.) based upon statistically significant increases in plasma ALT, AST, and alkaline phosphatase, as well as the increased incidence of hepatitis and bile duct proliferation. The NOAEL is = 1 mg/kg/day (0.56 mg/kg/day MITC eqvi.).**

This subchronic study in the dog is **acceptable, guideline** but **does *not* satisfy** the guideline requirement for a subchronic oral study [OPPTS 870.4100, OECD 452] in dog due to the lack of establishment of a NOAEL for female dogs.

COMPLIANCE: Signed and dated GLP, Quality Assurance, and No Data Confidentiality statements were provided.

DATA FOR ENTRY INTO ISIS

Subchronic Study - dogs (870.4100b)

PC code	MRID	Study	Species	Duration	Route	Admin	Dose range mg/kg/day	Doses mg/kg/day	NOAEL mg/kg/day	LOAEL mg/kg/day	Target organ	Comments
39003	42600001	chronic	dogs	90 days	oral	capsule	1-10	0, 1, 5, 10	Male 1 Female < 1 (not established)	Male 5 Female 1	Liver enzymes BIliary duct pathology	

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

OFFICE OF
PREVENTION PESTICIDES AND
TOXIC SUBSTANCES

August 19, 2004

TXR no: 0051475 (D303925)

Memorandum

SUBJECT: **Data Evaluation Records for *Metam sodium (039003) and Methyl isothiocyanate (MITC, PC Code 068103)***

FROM: Anna Lowit, Ph.D., Toxicologist 8/19/04
Judy Facey, Ph.D., Toxicologist 8/19/04
Reregistration Branch 2
Health Effects Division (7509C)

THRU: Alan Nielsen, Branch Senior Scientist 8/19/
Reregistration Branch 2
Health Effects Division (7509C)

TO: Veronique LaCapra
Chemical Review Manager
Special Review and Reregistration Division (7508C)

Mark Seaton
Chemical Review Manager
Special Review and Reregistration Division (7508C)

Data evaluation records or revised executive summaries have been produced for the MITC and metam sodium toxicology studies listed below.

42600001 Brammer, A. (1992) Metam Sodium: 90-day Oral Dosing Study in Dogs: Lab Project Number: CTL/P/3679. Unpublished study prepared by ICI Central Toxicology Lab. 349 p.

MRID 44400401. Russell, M.J. and Rush, T.I. (1996) Methyl Isothiocyanate: Determination of human olfactory detection threshold and human no observable effect level for eye irritation. Sensory Testing Laboratory, University of California at Davis. Report No. RR 96-049B. September 10, 1996

MRID 45314802. Klimisch, H.J. (1987). Study of the Subchronic Inhalation Toxicity of Methyl Isothiocyanate in Wistar Rats (4 weeks study). Department of Toxicology. BASF Aktiengesellschaft, D-W6700 Ludwigshafen, Federal Republic of Germany. Project No 4010231/8539, BASF Reg. Document Number 87/0244, January 29, 1987.

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