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

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

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MEMORANDUM

SUBJECT: Metam Sodium - Selection of Dose Levels for the Chronic Toxicity Study in Dogs

Tox Chem No.: 780
Submission No.: S419682

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Registrant: ICI America's, Inc.

Action Required: Determine if the proposed dose levels of 0, 0.05, 0.2 and 0.5 mg/kg/day for the chronic toxicity study in dogs are acceptable to EPA.

Recommendations: Based on the evaluation of the limited data submitted by the Registrant, Toxicology Branch II believes that the dose levels to be used in the dog chronic toxicity study should be: 0, 0.05, 0.2 and 0.5 mg/kg/day for females (as proposed by the Registrant). For male dogs the high dose should be at least 1.0 mg/kg/day with the mid and low dose levels as deemed appropriate by the Registrant (possibly 0.3 and 0.1 mg/kg/day, for the mid and low dose levels respectively.

Background and Considerations

ICI America's Inc., on behalf of the Metam Sodium Task Force, has conducted a 90-day study with Metam Sodium in male and female dogs. The test article was administered in gelatin capsules at the dose levels of 0, 1, 5 and 10 mg/kg/day for 90 days. The major findings in this study were as follows:

Dose Level 10 mg/kg/day: One female and one male dog were killed because of poor health on weeks 11 and 12 of study, respectively; body weight gain reduction associated with reduced food intake was noted in some dogs (no details given); slight reductions in RBC and increased kaolin-cephalin and prothrombin times were observed on week 13 of study; marked changes in plasma enzyme activities indicative of liver damage (progressive) were seen in all dogs to some extent; marked hepatitis characterized by hepatocyte necrosis and degeneration, inflammatory cell infiltrations and biliary proliferation were observed in 6/8 dogs.

Dose Level 5 mg/kg/day: Slight reductions in RBC were observed on week 13 of study; changes in plasma enzyme activities (less marked than at the 10 mg/kg/day dose level) indicative of liver damage were observed in all dogs to some extent; microscopic pathology changes were seen in 7/8 dogs and were similar to those observed at the 10 mg/kg/day dose level but the degree of change was less severe.

Dose Level 1 mg/kg/day: One female dog showed marked increases in alanine transaminase (ALT) and aspartate transaminase (AST) activity with evidence of bile duct proliferation and portal inflammatory cell infiltration.

Based on the aforementioned findings the Registrant proposed the dose levels of 0, 0.05, 0.2 and 0.5 mg/kg/day, to be used for the chronic toxicity study in male and female dogs. Toxicology Branch II agrees with the Registrant on the selection of the dose levels for female dogs. However, for male dogs, since there was no toxicity whatsoever at the dose level of 1 mg/kg/day (90-day study), the dose level of 1 mg/kg/day (instead of 0.5 mg/kg/day) appears to be more appropriate as the high dose level to be tested.

The proposed changes in the selection of dose levels for male dogs were communicated (by telephone) to Mr. Patrick Rose, Toxicologist at ICI Central Toxicology Laboratory in U.K., on June 16, 1992. Mr. Rose expressed concern that the high dose of 1 mg/kg/day for male dogs might result in severe toxicity/mortality in animals of that group. His concern was based mainly on the fact that the toxic lesions observed in male and female dogs in the 90-day study were dose-dependent and progressed in severity with time. Mr. Rose was assured that the study would still be acceptable to the Agency provided that the low/mid dose levels tested would be appropriate

for establishing a NOEL. Mr. Rose was also made aware that in the event that the high dose of 0.5 mg/kg/day was chosen to be tested in male dogs (as proposed by the Registrant) the absence of any toxicity to the animals might render the study unacceptable.