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

APR 20 1993

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM:

Subject: Review of Toxicology Studies with MSMA to support reregistration of the test substance. (Tox.Chem No.: 582, PC Code: 013803; Barcode number: D186279)

FROM: Steven L. Malish, Ph.D., Toxicologist S.L. Malish 4/12/93
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and

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ACTION REQUESTED: Review of toxicology studies for reregistration requirements.

Study Summarized

MRID 426046-01, Acute Inhalation Toxicity Study (81-3); Core - guideline.

$LC_{50}$ (4 hour, whole body, inhalation, liquid aerosol): males=2.23 mg/l, females=2.18 mg/l; males and females combined= 2.20 mg/l (Based upon analytical determination of chamber concentrations).

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Reviewed by Steven L. Malish, Ph.D. Steven L. Malish 4/12/93
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DATA EVALUATION REPORT

| | |
|---|---|
| STUDY TYPE: | Acute Inhalation Toxicity Study (81-3) |
| MRID NO.: | 426046-01 |
| PC Code: | 013803 |
| TEST MATERIAL: | MSMA Solution |
| SYNONYMS: | Monosodium Methane Arsonic Acid (MSMA) |
| SPONSOR: | MAA Task Force III |
| TESTING FACILITY: | Bushy Run Research Center<br>Union Carbide Chemicals and<br>Plastics Company, Inc.<br>6702 Mellon Road<br>Export, PA 15632-8902 |
| REPORT NUMBER: | 92N1042 |
| TITLE OF REPORT: | Acute Aerosol Inhalation Toxicity Study in Rats |
| AUTHOR: | D. J. Nachreiner |
| REPORT ISSUED: | November 30, 1992 |
| QUALITY ASSURANCE: | Quality assurance documentation was provided. |
| CONCLUSIONS: | $LC_{50}$ (4 hour, whole body, inhalation, liquid aerosol): males=2.23 mg/l, females= 2.18 mg/l; males and females combined= 2.20 mg/l (Based upon analytical determination of chamber concentrations). |
| CLASSIFICATION: | Core - guideline<br><br>This study satisfies the guideline requirements (81-3) for an "Acute Inhalation Toxicity study". |
| TOXICITY CATEGORY: | -III- (from 0.5 thru 5 mg/l) |

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MATERIALS

| | | |
|---|---|---|
| Test Compound: | Chemical: | MSMA Solution |
| | Synonym: | Monosodium methane arsonic Acid |
| | Batch No.: | 20338-57-38 |
| | Description: | Oily, slightly yellow, non-viscous liquid |
| | Purity: | 50.4% a.i. |
| | Storage: | room temperature |
| | Stability: | Not mentioned in the report |
| Test Animal: | Animal: | Rat (albino) |
| | Strain: | Harlan Sprague-Dawley |
| | Groups: | Four (4) groups of 5 animals/sex |
| | Weight: | Males: 222-289 gm; females: 178-218 gm at study start |
| | Age: | ≈51-58 days at study start. |
| | Source: | Harlan Sprague-Dawley, Inc., Indianapolis, IN |

Animal Husbandry

All animals received standard certified pelleted laboratory diet - AGWAY PROLAB animals Diet Rat, Mouse, Hamster 3000 (Agway, Inc.) and water ad libitum at all times except during the exposure.

STUDY and EXPOSURE PARAMETERS

Rats were conditioned for at least 5 days prior to the study initiation.

Five (5) animals/sex were assigned randomly to 4 test groups. No control group exposure was included. Animals were exposed to the test material by liquid aerosol inhalation of MSMA Solution at concentrations of 2.03 mg/l (Group I), 2.45 mg/l (Group II), 3.10 mg/l (Group III) and (Group IV), 5.11 mg/l for 4 hours by whole body exposure and observed for 14 days.

The day of exposure was counted as day 0; animals in all groups were observed for a total of 14 days (day 1 thru 14).

Statistics

The moving average method of Thompson was used to calculate the median lethal concentration ($LC_{50}$) for males, females and the sexes combined. The 3.10, 2.45 and 2.03 mg/l values were used to calculate the $LC_{50}$ for males. The 2.45 and 2.03 mg/l were used to calculate the $LC_{50}$ for females and for sexes combined.

The number of deaths at 5.11 mg/l were not used in the calculations of the $LC_{50}$ since the Thompson method requires that the ratio

between exposure groups be close to constant. Moreover, the number of deaths at 3.10 mg/l was unacceptable to permit calculation of the $LC_{50}$ for females and the sexes combined and the value was, therefore deleted.

Exposure Chamber

The stainless steel with glass windows chamber had a capacity of 1300 liters and operated dynamically under slight positive pressure. The chamber's initial airflow rate was 300 liters/ min (14 air changes/hour) and the 99% equilibration time was 20 minutes (Figure I).

During the exposure, chamber temperature, relative humidity, air flow rate and static pressure were recorded.

For all exposures, the mean chamber temperature was 19°C and the relative humidities ranged from 43-75%.

Particle Generation Procedure:

The MSMA Solution was metered from a piston pump (Fluid Metering Inc., Oyster Bay, NY) into an atomizer (Spraying Systems Co., Wheaton, IL; a RPG-50 pump with a 1/4" piston was used for each exposure) fitted with a liquid and air nozzle. The atomizer was inserted into the top of the of the inhalation chamber where the liquid aerosol was dispensed throughout the chamber by compressed air (Figure 1).

Chamber Sampling

Exposure levels were determined gravimetrically; 7 or 8 samples were obtained during each 4-hour exposure. The sample flow rate was approximately 4.4 l/min. Samples were collected for 5 minutes through a glass fiber filter paper. Following collection of the aerosol, filters were weighed without drying.

The nominal exposure concentration (mg/l) was determined by dividing the weight of the test substance delivered by the volume of air which passed through the chamber during the exposure period.

The mean gravimetric, standard deviation and nominal concentrations () in the chamber were as follows: $2.03 \pm 0.15$ (14.2), $2.45 \pm 0.10$ (19.7), $3.10 \pm 0.12$ (24.6) and $5.11 \pm 0.18$ (60.9) mg/l.

Particle Size Distribution Analysis

The particle size distribution was measured using a TSI Aerodynamic Particle Sizer, Model APS 3300 (TSI Incorporated, St. Paul, MN) using a dilution ratio of 100:1 and a sample collection time of 30 seconds.

Particle size determinations were made 2 times during the 5.11, 3.10 and 2.03 mg/l exposure. Only 1 particle size determination was made at 2.45 mg/l.

The particle size distributions were illustrated as histograms in the original report. Histograms from all concentrations were similar and were equated with a MMAD of ≈1.95 microns and a geometric standard deviation of 1.45 microns.

RESULTS and DISCUSSION:

Observations

On day 1, the day of exposure, all animals were observed individually immediately prior to exposure and as a group at about 30 minute intervals during exposure. After removal from the exposure chamber, the animals were observed individually and then each day during the post exposure interval. Animals were observed once a day on weekends for overt signs and mortality.

All groups on the day of exposure presented wet oily fur, blepharospasm, perinasal, perioral and periocular wetness and encrustation.

During the first week, loose feces or absence of feces, blepharospasm and periocular wetness were seen. Hypoactivity, decreased respiratory rate, hunched posture and morbidity were noted in the 5.11 mg/l animals shortly before death.

During the postexposure period male survivors at 2.45 mg/l (4/5) and 2.03 mg/l (1/5) presented ulcerated areas of the scrotum or the area around the rectum. This lesion was noted on day 3 and persisted until the terminal necropsy. A milky white discharge from the penis was noted in 4/5 males at 2.03 mg/l from day 4 thru 14.

Mortality

No animals died during the exposure period. All animals died during the first week after exposure with mortality of 20%, 90%, 100% and 100% at 2.03, 2.45, 3.10 and 5.11 mg/l levels, respectively (Table 1).

Table 1

Mortality Summary in Rats Treated with MSMA Solution by Inhalation[1]

| Conc. (ppm) | Sex | Time to Death (Days) 0[2] | 1 | 2 | 3 | 4 | 5 | 6 | 7 | Incidence | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 2.03 | M | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 1/5 | (20%) |
| 2.03 | F | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 1/5 | (20%) |
| 2.45 | M | 0 | 1 | 3 | 0 | 0 | 0 | 0 | 0 | 4/5 | (80%) |
| 2.45 | F | 0 | 1 | 3 | 0 | 1 | 0 | 0 | 0 | 5/5 | (100%) |
| 3.10 | M | 0 | 0 | 1 | 1 | 0 | 2 | 0 | 1 | 5/5 | (100%) |
| 3.10 | F | 0 | 2 | 2 | 1 | 0 | 0 | 0 | 0 | 5/5 | " |
| 5.11 | M | 0 | 0 | 0 | 0 | 0 | 2 | 3 | 0 | 5/5 | " |
| 5.11 | F | 0 | 1 | 4 | 0 | 0 | 0 | 0 | 0 | 5/5 | " |

[1]Adapted from original report, p. 15.
[2]Day of exposure.

Body Weight

In all groups, animals were weighed on day 0 (immediately prior to exposure), on day 7 and day 14 (just prior to sacrifice).

Males and females at 2.03 mg/l showed body weight loss at 7 days following exposure. In all animals, a loss of body weight or a decreased body weight gain (-38 gm M, 4 gm F) was presented 7 days following exposure. During the second week of the postexposure period, body weight gains was observed for all surviving animals; by day 14 body weights were above the 0 day values.

Postmortem and Terminal Necropsy

Complete gross examinations were performed on all animals. Animals scheduled for the terminal necropsy were exsanguinated by the brachial blood vessels under methoxyflurane anesthesia.

In animals that died or were sacrificed moribund, discoloration of the lungs and hemorrhage or discoloration of the stomach was seen in some males and females. Brain hemorrhage was noted in a dose related manner in the males; in females the lesion was higher at 2.45, 3.10 and 5.11 mg/l versus the 2.03 mg/l (lowest) concentration (Table 2).

Table 2

Gross Pathology of Dead/Moribund Animals Exposed to MSMA solution[1]

| | Concentration (mg/l) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 2.03 | 2.45 | 3.10 | 5.11 | 2.03 | 2.45 | 3.10 | 5.11 |
| | Male | | | | Female | | | |
| Animals in group | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| Dead/ sacrificed | 1 | 4 | 5 | 5 | 1 | 5 | 5 | 5 |
| Lungs | | | | | | | | |
| Color change focal, multi-focal, diffuse | 0 | 4 | 4 | 4 | 0 | 5 | 3 | 5 |
| Hyper-inflation | 0 | 0 | 1 | 1 | - | - | - | - |
| Brain | | | | | | | | |
| Hemorrhage | 1 | 4 | 5 | 5 | 1 | 5 | 4 | 4 |
| Stomach | | | | | | | | |
| Color change | 0 | 0 | 0 | 2 | 0 | 1 | 0 | 0 |
| Hemorrhage | 0 | 0 | 0 | 1 | - | - | - | - |

[1]Adapted from the original report p. 25, 27.

Other gross findings occurred sporadically and were not considered to be of any toxicological consequence in animals that died or at the terminal necropsy.

SUMMARY and DISCUSSION:

All mortality resulted within 7 days of exposure (Table 1).

Body weights in the surviving animals were depressed for 7 days following exposure but animals recovered the lost weight by day 14.

In animals that died or were sacrificed in a moribund condition, discoloration of the lungs, and hemorrhage or discoloration of the stomach was seen in animals of both sexes. Brain hemorrhage was noted in a dose related manner in the males; in females the lesion was higher at 2.45, 3.10 and 5.11 mg/l versus the 2.03 mg/l (lowest) concentration (Table 2).

The $LC_{50}$ was determined to be: males=2.23 mg/l, females=2.18 mg/l and males and females combined=2.2 mg/l. The slopes were 12.6 for males, 19.5 for females and 18.1 for both sexes combined (Table 3).

A difference in slope function usually is indicative that the mortality was caused by a different mode of action in the male versus the female. This change may have been caused, however, by the fact that mortality value obtained for females and the combined sexes at 3.10 mg/l were unacceptable to permit calculation of the $LC_{50}$ value.

Table 3

$LC_{50}$ Values and 95% Confidence Limits of Rats Exposed to MSMA Solution for 4 hours

| Sex | $LC_{50}$ (mg/l) | 95% Confidence Limits (mg/l) | Slope |
|---|---|---|---|
| Males | 2.23 | 1.84 to 2.70 | 12.6 |
| Females | 2.18 | 2.01 to 2.36 | 19.5 |
| Combined Sexes | 2.20 | 2.09 to 2.32 | 18.1 |

[1] $LC_{50}$ determined by the method of Thompson.

CONCLUSIONS:

$LC_{50}$ (4 hour, whole body, inhalation, liquid aerosol): males= 2.23 mg/l, females=2.18 mg/l; males and females combined=2.20 mg/l (Based upon analytical determination of chamber concentrations).

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