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

CASWELL FILE

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OFFICE OF
PESTICIDES AND TOXICS
REGISTRATION

MEMORANDUM

SUBJECT: Sodium N-methylthiocarbamate: Review of Toxicology Data
Submitted by the Registrant.

Caswell No: 780
HED Project No: 2-1716
MRID Nos: 419861-01 through 419861-05; 421677-01

FROM: Timothy F. McMahon, Ph.D., Toxicologist *T. McMahon 4/1/92*
Review Section I, Toxicology Branch II
Health Effects Division (H7509C)

TO: Christine Rice / PM 52
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THRU: Yiannakis M. Ioannou, Ph.D., Section Head *Y. Ioannou 4/1/92*
Review Section I, Toxicology Branch II
Health Effects Division (H7509C)

and

Marcia Van Gemert, Ph.D., Branch Chief *M. Van Gemert 4/2/92*
Toxicology Branch II
Health Effects Division (H7509C)

Registrant: UCB Chemicals Corporation

Action Requested: Review of the following Toxicology studies with Metam Sodium:

- § 81-1 Acute Oral Toxicity in Rats
- § 81-2 Acute Dermal Toxicity in Rats
- § 81-3 Acute Inhalation Toxicity in Rats

1/3
1/35

- § 81-4 Primary Eye Irritation in Rabbits
- § 81-5 Primary Dermal Irritation in Rabbits
- § 81-6 Dermal Sensitization in Guinea Pigs

Page Summary:

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

MBID # 419861-01

Material: metam sodium 510 g/L

Under the conditions of this study, the acute oral LD₅₀ 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 LD₅₀ in female rats was calculated as 824 mg/kg body weight, with 95% confidence limits of 756 and 1130 mg/kg. The combined oral LD₅₀ was calculated as 896 mg/kg, with 95% confidence limits of 779 and 1031 mg/kg body weight.

Toxicity Category III

Core Classification: supplementary

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

MBID # 419861-02

Material: metam sodium 510 g/L

Under the conditions of this study, the acute dermal LD₅₀ of Metam Sodium was > 2000 mg/kg in male and female rats.

Toxicity Category III

Core Classification: supplementary

3) Title: Acute Inhalation Toxicity Study in Rats-4 Hour Exposure**MBID # 421877-01**

Under the conditions of this study, the acute inhalation LC₅₀ 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 LC₅₀ 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: supplementary****4) Title: Primary Eye Irritation to Rabbits with Metam Sodium****MBID # 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: supplementary****5) Title: Skin Irritation to Rabbits with Metam Sodium****MBID # 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: supplementary**

009:16

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: supplementary

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Section I, Toxicology Branch II (H7509C)
Secondary Reviewer: Yiannakis M. Ioannou, Ph.D. *Y.M.I. 4/1/92*
Section I, Toxicology Branch II (H7509C)

Data Evaluation Report

Study type: Acute oral-rats (81-1) Tox. Chem. No.: 780

MBID number: 419851-01

Test material: Sodium methyldithiocarbamate

Synonyms: Metam Sodium

Study number: 801048D/UCB 386/AC

Testing Facility: Huntingdon Research Centre, Ltd.
England

Sponsor: UCB Chemicals Corporation
Norfolk, VA

Title of report: Acute Oral Toxicity to Rats of Metam Sodium

Author(s): Paul Baldrick and Guy Healing

Study completed: January 7, 1991

Conclusions:

Under the conditions of this study, the acute oral LD₅₀ of Metam Sodium was 870 mg/kg in male rats with 95% confidence limits of 715 and 1058 mg/kg body weight. The estimated oral LD₅₀ in female rats was calculated as 924 mg/kg body weight, with 95% confidence limits of 758 and 1130 mg/kg. The combined oral LD₅₀ was calculated as 893 mg/kg, with 95% confidence limits of 779 and 1031 mg/kg body weight.

Toxicity Category III

Core Classification: supplementary

This study does not fulfill the guideline requirements (81-1) for an acute oral toxicity study in rats. The purity of the test article was not reported.

I. MATERIALS

A. Test Material: Metam Sodium, 510 g/L; description: clear yellow liquid; purity: not stated. According to the report (page 8), metam sodium is synthesized in aqueous solution, then diluted with water, if necessary, to the desired concentration to meet the label guarantee for the formulated product. Thus, there is no 'technical' metam sodium as such, since the technical material is never isolated.

B. Test Animals: Male and female Sprague-Dawley CD rats (CD® (SD) BR VAF plus). Source: Charles River UK limited, Margate, Kent, England, Inc. Age: 4-6 weeks; Weight: on day 1 of the study): males: 126-147g; females, 117-136g.

II. METHODS

Five male and 5 female rats per dose group were selected for use in this study. Rats were given a commercially available rodent diet (SDS LAD 1) and tap water *ad libitum*, with the exception of an overnight fast prior to and four hours following dosing. Rats were housed in groups of up to 5 rats/cage in metal cages with wire mesh floors. Temperature and humidity were in the range of 23-27 °C and 62%, respectively. A 12 hour light/dark cycle was used. An acclimation period of five days was allowed prior to dosing.

Five male and 5 female rats were selected per dose group for dosing. Separate groups of rats were administered single oral doses of 640, 800, 1000, and 1600 mg/kg body weight of Metam Sodium in water in dose volumes of 0.52, 0.65, 0.82, and 1.31 ml/kg, respectively. Each animal was observed for signs of clinical toxicity frequently on the day of dosing, and twice daily thereafter up to study termination (day 15 post-dosing). A check for mortality was performed twice daily. Body weights were recorded on study days 1, 8, and 15. Animals were killed on day 15 by CO₂ asphyxiation. Gross necropsy was performed on rats at the time of death or sacrifice.

The data from this study did not permit the fitting of a probit line using the standard method of Finney. It was possible to fit a line if a fixed slope was assumed. A value of 8.333, estimated from background data which consisted of the average slope of all LD₅₀ determinations carried out in the laboratory over a one year period, was used. A test for differences in response by sex was carried out on the individual responses using a test for trend in contingency tables with dose as a stratifying factor.

III. RESULTS

Mortality

At the 640 mg/kg dose level, no deaths were observed. At 800 mg/kg, one male rat was found dead on day 2. At 1000 mg/kg, all 5 male rats died between 4 and 5 hours after

dosing. All female rats also died at this dose, one at 5 hours post-dosing, and 4 at 2 days after dosing. At the 1600 mg/kg dose, all male and female rats were dead between 4 and 5 hours post-dosing.

Clinical Toxicity

Signs of clinical toxicity were evident at all dose levels tested in both sexes of rats. According to the registrant (page 12 of the report), piloerection and increased salivation were observed in all rats within 10 minutes of dosing. Piloerection persisted, and was accompanied by hunched posture, abnormal gait, decreased respiratory rate, ptosis and pallor of the extremities in all rats. In addition, clonic convulsions were observed in all but one female rat at the 1000 and 1600 mg/kg dose levels, as was increased lachrymation in all rats at the 800 mg/kg dose level.

Effects of treatment on body weight were inconclusive, due to the rapid death of rats at the 1000 and 1600 mg/kg dose levels. At the 640 and 800 mg/kg dose levels, there were no apparent differences in body weight gain, but concurrent controls were not run in this study.

According to the registrant (page 12 of the report), no macroscopic abnormalities were present at terminal autopsy.

Median Lethal Dose Estimation

The estimated oral LD₅₀ in male rats was calculated as 870 mg/kg with 95% confidence limits of 715 and 1059 mg/kg body weight. The estimated oral LD₅₀ in female rats was calculated as 924 mg/kg body weight, with 95% confidence limits of 758 and 1130 mg/kg. The combined oral LD₅₀ was calculated as 896 mg/kg, with 95% confidence limits of 779 and 1031 mg/kg body weight.

IV. CONCLUSIONS

Under the conditions of this study, the acute oral LD₅₀ of Metarn Sodium was 870 mg/kg in male rats with 95% confidence limits of 715 and 1059 mg/kg body weight. The estimated oral LD₅₀ in female rats was calculated as 924 mg/kg body weight, with 95% confidence limits of 758 and 1130 mg/kg. The combined oral LD₅₀ was calculated as 896 mg/kg, with 95% confidence limits of 779 and 1031 mg/kg body weight.

Toxicity Category III

V. CORE CLASSIFICATION: supplementary

This study does not fulfill the guideline requirements (81-1) for an acute oral toxicity study in rats. The purity of the test article was not reported.

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Secondary Reviewer: Yiannakis M. Ioannou, Ph.D. *Y.M.I.* 4/1/92
Section I, Toxicology Branch II (H7509C)

CAUTION FILE
000-116

Date Evaluation Report

Study type: Acute dermal-rats (81-2) Tox. Chem. No.: 780

MBID number: 419851-02

Test material: Sodium methylthiocarbamate

Synonyms: Metam Sodium

Study number: 90955D/UCB 357/AC

Testing Facility: Huntingdon Research Centre, Ltd.
England

Sponsor: UCB Chemicals Corporation
Norfolk, VA

Title of report: Acute Dermal Toxicity to Rats of Metam Sodium

Author(s): Paul Baldrick and Guy Healing

Study completed: January 7, 1991

Conclusions:
Under the conditions of this study, the acute dermal LD₅₀ of Metam Sodium was greater than 2000 mg/kg in both male and female rats.

Toxicity Category III

Core Classification: supplementary

This study does not fulfill the guideline requirements (81-2) for an acute dermal toxicity study in rats. The purity of the test article was not reported.

I. MATERIALS

A. Test Material: Metam Sodium, 510 g/L; description: clear yellow liquid; purity: not stated. According to the report (page 9), metam sodium is synthesized in aqueous solution, then diluted with water, if necessary, to the desired concentration to meet the label guarantee for the formulated product. Thus, there is no 'technical' metam sodium as such, since the technical material is never isolated.

B. Test Animals: Male and female Sprague-Dawley CD rats (Cr: CD® (SD) BR). Source: Charles River UK limited, Margate, Kent, England, Inc. Age: 7-10 weeks; Weight prior to dosing: males, 233-250g; females, 213-226g.

II. METHODS

Five male and 5 female rats per dose group were selected for use in this study. Rats were given a commercially available rodent diet (SDS LAD 1) and tap water *ad libitum*. Rats were housed individually in metal cages with wire mesh floors. Temperature and humidity were in the range of 23-27 °C and 57%, respectively. A 12 hour light/dark cycle was used. An acclimation period of five days was allowed prior to dosing.

One day prior to dosing, the fur of each rat was clipped from the dorso-lumbar region to expose an area equivalent to 10% of body surface. No shaving or chemical depilation was used. Test chemical was applied the following day at a volume of 1.63 ml/kg (2000 mg/kg) to the prepared skin. The treated area was then promptly covered with gauze which was held in place with impermeable dressing wrapped around the trunk.

Following the 24 hour exposure period, all dressings and tape were removed, and the exposure site rinsed with warm water to remove residual test article. The test area was then blotted dry with absorbent paper. Day of dosing was designated day 1 of the study. Each animal was observed for signs of clinical toxicity frequently on the day of dosing, and twice daily thereafter up to study termination (day 15 post-dosing). Treated areas of skin were observed daily for signs of dermal irritation and assessed according to the Draize scale. Body weights were recorded on study days 1, 8, and 15.

On day 15, surviving rabbits were killed by cervical dislocation. All rats dying during the study or those killed on day 15 were subjected to a macroscopic post mortem examination.

III. RESULTS

Death occurred for one female rat on day 2 of the study. It was noted that for this rat, body weight loss had occurred (loss of 9 grams), and necropsy showed slight congestion in the subcutaneous region which was green in color. No other deaths were recorded during the study period. Clinical signs consisted of hypothermia which was noted on day 2 of the study in all rats, but not at subsequent observation times.

Dermal irritation was observed in both male and female rats. In male rats, erythema characterized as well defined to moderate was observed in all rats on day 2 of the study. This erythema was accompanied by green-yellow staining of the dosing site. Erythema in male rats did not persist beyond day 2. However, scab formation was noted for 2 male rats from study days 3 to 15 and 8 to 15, respectively. Localized hard white areas were noted for one male rat on study days 6 and 7.

Well-defined to moderate edema was observed for all male rats on study day 2. Edema persisted as slight to well-defined in 3 male rats to study days 4, 5, and 7, respectively. In the rat showing edema to day 7, staining and/or scab formation prevented further assessment of the skin reaction.

In female rats, erythema characterized as well-defined was noted in 2 of five females. In the remaining female rats, one had died on day 2, and scab formation and/or staining prevented assessment of the skin condition in the other 2 rats. Scab formation at the dose site was present in 4 of 5 female rats beginning as early as day 3 in one rat (starting on day 6 on other rats) and persisting to study termination, with healing scabs and/or localized ulceration in 2 rats on day 15.

Well-defined to moderate edema was also present in all surviving female rats on day 2 of the study. This persisted as such until day 5 of the study, when it was not possible to assess edema formation due to staining and/or scab formation, according to the registrant.

Body weight gain was reduced in one male rat on day 4 (gain of 28 grams in this rat vs an average of 50 grams in the other rats), and final body weight of this rat was also reduced vs other male rats (324 grams vs an average of 370 grams for the other rats). Body weight gain in female rats was less than that of male rats, but with the exception of the one female rat which died, there did not appear to be any differences among treated rats in body weight gain. However, no control rats were employed for comparison. It is noted that in one female rat, body weight gain was reported as 46 grams, while weight gain in the other three rats was an average of 20 grams. Thus, body weight gain may have been affected in female rats as well.

At necropsy, scabs of subcutaneous origin were reported for one male and three female rats. Localized ulceration was reported in one male and one female rat. Individual necropsy records were not provided to verify this information.

IV. CONCLUSIONS

Under the conditions of this study, the acute dermal LD₅₀ of Metam Sodium was > 2000 mg/kg in male and female rats.

Toxicity Category III

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V. CORE CLASSIFICATION

suppiementary

This study does not fulfill the guideline requirements (B1-2) for an acute dermal toxicity study in rats. The purity of the test article was not reported.

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Section I, Toxicology Branch II (H7C09C)

000120

Data Evaluation Report

Study type: Acute Inhalation-rate (81-3) Tox. Chem. No.: 780

MBID number: 421877-01

Test material: Sodium methylthiocarbamate

Synonyms: Metam Sodium

Study number: UCB 371/91206

Testing Facility: Huntingdon Research Centre, Ltd.
England

Sponsor: UCB Chemicals Corporation
Norfolk, VA

Title of report: Acute Inhalation Toxicity Study in Rats-4 Hour Exposure

Author(s): Graham C. Jackson and Colin J. Herdy

Study completed: January 8, 1992

Conclusions:

Under the conditions of this study, the acute inhalation LC₅₀ 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 LC₅₀ 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: supplementary

This study does not fulfill the guideline requirements (81-3) for an acute inhalation toxicity study in rats. The purity of the test article was not reported.

009116

MATERIALS

Test Material. An amber/yellow liquid identified as: METAM SODIUM 510 G/L. According to the report (page 12), metam sodium is synthesized in aqueous solution, then diluted with water, if necessary, to the desired concentration to meet the label guarantee for the formulated product. Thus, there is no 'technical' metam sodium as such, since the technical material is never isolated. Stability of test article for at least 1 year was indicated in a statement provided by the performing laboratory.

Test Animals: Male and female Sprague-Dawley rats. Source: Charles River UK limited, Margate, Kent, England. Inc. Age: 6-8 weeks; Weight (on day of exposure): males: 196-235g; females, 194-241g. Rats used in the study were selected from 3 shipments of rats received by the performing laboratory.

METHODS

Animal Husbandry

Five male and 5 female rats per dose group were selected for use in this study. Rats were allocated to dose groups on the day of arrival, but whether this was a random allocation was not stated. Rats were housed 5 of similar sex per cage (polypropylene, 38cm x 56cm x 18cm height) and given food (Biosure LAD 1) and tap water *ad libitum* while in these cages. Temperature and humidity were in the range of 18-24 °C and 35-65%, respectively. Minor deviations from these limits occurred during the study period but were not felt to have a significant impact upon the study results. Light cycle duration was not stated. An acclimation period of five days was allowed prior to dosing.

Atmosphere Generation

An aerosol generator designed to produce a high proportion of respirable particles was employed, and a diagram of this apparatus is appended to this review.

Test material was pumped to the aerosol generator from a syringe driven at a constant rate by a syringe pump. Doses used were 0, 1.23, 2.43, 3.03, and 3.15 mg/L as measured in the inhalation chamber air. Two groups of five rats/sex were used at each dose. Air flow rates were monitored by an in-line flow meter to maintain a flow rate of 25 L/min. Aerodynamic particle size was measured by means of a Marple cascade impactor. Atmospheric concentration of metam sodium was determined by passing 4 liters of the test atmosphere at five separate times during exposures through a glass fiber filter. The change in weight of the filter was then used to calculate atmospheric concentration of metam sodium.

B. Exposure

Rats were subjected to whole body exposure in a perspex type inhalation chamber. Chamber volume was stated as 120 liters. Exposure duration was for 4 hours to test material. The exposure procedure is attached to this review.

Aerodynamic mass median diameter and geometric standard deviation were calculated from linear regression of log/probit transformed data. Temperature was measured during exposure every 30 minutes. As mentioned, atmospheric concentrations of test material in the chambers housing the rats during exposure were made five times during the exposure period.

C. Post-Exposure Observations

Animals were observed for toxic signs and mortality continuously during exposure, and then twice daily during the remainder of the study period. Body weights were recorded daily from the date of receipt until the end of the observation period. All survivors to day 15 were euthanized by i.p. injection of pentobarbitone sodium and then killed by exsanguination. Gross necropsy was performed on all rats which died or were sacrificed during the study.

Estimation of the inhalation LC₅₀ was performed using the log probit method of Miller and Tainter.

III. RESULTS

A. Atmosphere Generation

Measured and calculated parameters from inhalation exposure to test material are summarized in the following table (Table 1):

Table 1

Atmosphere Characterization in the Acute Inhalation Toxicity of Metam Sodium^a

Dose Group	chamber particle conc. (mg/l)	MMAD	sigma g	% analyzed particles	
				<1.55µm	<3.5µm
2	3.03	3.1	2.10	16.8	53.2
3	1.23	3.0	2.04	15.9	59.7
4	2.43	3.2	2.05	12.3	58.0
5	3.15	3.2	2.27	15.8	52.6

^adata from pages 17 and 28-31 of report.

As stated in the registrant's report (page 17), the particle size was the smallest attainable under the conditions of this study. It was not indicated whether higher chamber concentrations of test article were possible. Atmospheric concentrations in the inhalation chamber were in the following ranges for each dose level: 3.03 mg/L dose, 2.94-3.66 mg/L; 1.23 mg/L dose, 1.07-1.47 mg/L; 2.43 mg/L dose, 2.28-2.65 mg/L; 3.15 mg/L dose, 2.87-3.45 mg/L. Mass median aerodynamic diameter was in the range of 3.0-3.2 μm at all dose levels. Particle size distribution analysis indicated that approximately 12-15% of analyzed test material concentration contained particles of less than 1.55 μm , while particles of less than 3.5 μm constituted between 52-60% of total analyzed test article. It is noted that according to current Agency guidelines, at least 25% of the total particle distribution should be $\leq 1 \mu\text{m}$, and that this was not achieved in the present study. However, it appears that the registrant attempted to generate the smallest particle size possible with this chemical.

B. Animal Observations

At the 5.18 mg/L exposure level, all rats died on day 1 following exposure. At the 0.53 mg/L exposure level, 1 rat died on day 7 post-exposure.

During exposure to test material, clinical toxicity was observed at all dose levels. Initially, signs of partially closed eyes and wet snout were recorded during the first 15 minutes of exposure, including an additional equilibration time of 11 minutes. Beyond this time, several other signs (wetness around the eyes, piloerection, reddening of the ears, feet, and tail, exaggerated respiratory movements, prone posture, and arched back) were observed for the duration of exposure. There appeared to be some relationship between the number and frequency of these toxic signs and test article dose.

Following removal of rats from the test chamber, clinical signs were recorded once daily as shown on pages 35-38 of the report. According to the registrant, rats were observed with exaggerated and noisy respiration, wet and stained body fur, peripheral vasodilation, and lethargy upon removal from the chamber. Over the subsequent 14 day observation period, several toxic signs were recorded in all exposed rats (Table 4, attached). Some of these persisted for the entire 14 day post-dosing interval at the higher concentrations of test article, such as exaggerated respiratory movements. In addition, swollen forepaws and scabby scrotal sac were observed at the higher concentrations of metam sodium, and appeared to indicate dermal irritation with the test article. This is somewhat different than the response observed from the acute dermal toxicity study (MRID # 419861-02), but is supportive of evidence from the primary dermal irritation study (MRID # 419861-04) and indicates the potential for more severe dermal irritation at other bodily sites.

Body weight gain was recorded for all surviving rats in this study daily over the 14 day observation period. From available data (pages 39-41 of the report) there appeared to be a dose-related decrease in body weight gain for both sexes when comparing control weight gain with that in the 1.23 and 2.43 mg/L dose groups. Reliable data was not available at the 2 higher doses due to mortality. Body weight gain was as follows: Males, 138, 98, and 69 grams from days 0-14 in the 0, 1.23, and 2.43 mg/L dose groups; Females, 46, 44, and 20 grams for the same time period in the 0, 1.23, and 2.43 mg/L dose groups. It is noted that decreased food consumption was also observed following exposure of rats to test article, and that the duration of

decreased food consumption appeared to correlate with increasing dose of test chemical. Thus, at least some of the decreased body weight gain can be explained by decreased food intake following exposure.

At necropsy, it was noted that in rats exposed at the 2.43, 3.03, and 3.15 mg/L dose levels which died prior to necropsy, the lung to body weight ratio was increased from control rats. This occurred in decedent male rats at the 2.43 mg/L dose level, and in decedents of both sexes at the 3.03 and 3.15 mg/L dose levels (pages 44-46 of the report). Macroscopic histopathology of exposed rats showed swelling and alveolar congestion in rats at the 2.43, 3.03, and 3.15 mg/L dose levels. In addition, significant microscopic pathology was observed in the lungs of exposed rats. These findings are summarized below.

Table 2
Incidence of Microscopic Pathology in Rats
from Acute Inhalation Exposure to Metam Sodium^a

Dose group (mg/L)	0	<u>1.23</u>	<u>2.43</u>	<u>3.03</u>	<u>3.15</u>
Lungs					
foci of prominent alveolar macrophages / interstitial alveolar thickening	2/10	4/10	4/10	0/10	1/10
Bronchial epithelial necrosis with inflammatory exudate / Alveolar congestion / perivascular edema	0/10	0/10	2/10	8/10	8/10

^adata taken from Appendix 2, pages 48-70 of the report.

In addition to the microscopic pathology observed in the lungs of exposed rats, centrilobular hepatocyte necrosis and/or vacuolation was observed in the livers of some rats exposed at 2.43, 3.03, and 3.15 mg/L.

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IV. CONCLUSIONS

Under the conditions of this study, the acute inhalation LC₅₀ 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 LC₅₀ 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

V. CLASSIFICATION: supplementary

This study does not fulfill the guideline requirements (81-3) for an acute inhalation toxicity study in rats. The purity of the test article was not reported.

METAN SODIUM

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Pages 18 through 22 are not included in this copy.

The material not included contains the following type of information:

- Identity of product inert ingredients.
 - Identity of product inert impurities.
 - Description of the product manufacturing process.
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 - Identity of the source of product ingredients.
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 - The product confidential statement of formula.
 - Information about a pending registration action.
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CASREB
009416

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Section I, Toxicology Branch II (H7509C)
Secondary Reviewer: Yiannakis M. Ioannou, Ph.D. *Y.M. Ioannou 4/11/92*
Section I, Toxicology Branch II (H7509C)

009116

Data Evaluation Report

Study type: Primary eye irritation-rabbits (81-4) **Tox. Chem. No.:** 780

MRID number: 419861-03

Test material: Sodium methyldithiocarbamate

Synonyms: Metam Sodium

Study number: 90998D/UCB 369/SE

Testing Facility: Huntingdon Research Centre, Ltd.
England

Sponsor: UCB Chemicals Corporation
Norfolk, VA

Title of report: Eye Irritation to Rabbits with Metam Sodium

Author(s): Michael P. Liggett
Lewis A. McRae

Study completed: January 7, 1991

Conclusions:

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

Con. Classification: supplementary

This study does not fulfill the guideline requirements (81-4) for a primary eye irritation study in rabbits. The purity of the test article was not reported.

I. MATERIALS

A. Test Material: Metam Sodium, 510 g/L; description: clear yellow liquid; purity: not stated. According to the report (page 7), metam sodium is synthesized in aqueous solution, then diluted with water, if necessary, to the desired concentration to meet the label guarantee for the formulated product. Thus, there is no 'technical' metam sodium as such, since the technical material is never isolated.

B. Test Animals: Male and female New Zealand White rabbits; Source: A. Smith, Warlingham, Surrey, England. Weight: 2.1-2.9 kg. Age: 9-13 weeks.

II. METHODS

Three female and 3 male rabbits were employed for study of the primary eye irritation of Metam Sodium. Rabbits were given free access to food (SDS standard rabbit diet) and tap water *ad libitum*. Rabbits were acclimated to the lab environment prior to experimentation, but the period of acclimation was not stated. Rabbits were housed individually in metal cages with perforated floors under conditions of controlled temperature (19 °C) and humidity (30-70%). A 12 hour light/dark cycle was used.

Prior to test article administration, both eyes of each rabbit selected for use were examined for corneal abnormalities or conjunctival inflammation.

Test article (0.1 ml) was instilled into the lower everted lid of one eye of each rabbit. The other eye was employed as an untreated control. After test article instillation, upper and lower lids of the treated eye were gently held together for approximately 1 second following test article instillation. No rinse procedure was employed in this study.

Irritation to the cornea, iris, and conjunctiva was evaluated in both eyes of all rabbits at 1, 24, 48, and 72 hours and again at 4 and 7 days following test article instillation according to a numerical scoring system as described in the report (attached to this review).

The fate of the rabbits at the end of the study period was not stated in the report.

III. RESULTS

At one hour following instillation of test article, no reaction of the cornea or iris was observed. Conjunctival redness of grade "1" (2 rabbits) or grade "2" (4 rabbits) was recorded. Grade "2" is considered a positive response, and indicates a diffuse,

crimson color of the conjunctiva with individual blood vessels not easily discernible. Chemosis of grade "1" (any swelling above normal; not considered a positive response) was also recorded for 4 of the 6 rabbits at 1 hour, as was discharge of grade "2" in 5 of the 6 rabbits (criteria defining the severity of this response were not provided).

At 72 hours following test article administration, no ocular abnormalities were recorded except in one rabbit, which showed redness and discharge of the conjunctiva of grade "1". Overall, a positive response was considered to have occurred in 4 of the six rabbits.

IV. CONCLUSIONS

Metam Sodium was found to be mildly irritating to the eyes of New Zealand White rabbits.

Toxicity Category III

V. CORE CLASSIFICATION

supplementary

This study does not fulfill the guideline requirements (81-4) for a primary eye irritation study in rabbits. The purity of the test article was not reported.

METAM SODIUM

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009116

Reviewed by: Timothy F. McMahon, Ph.D. 2/192

Section I, Toxicology Branch II (M7509C)

Secondary Reviewer: Yiannakis M. Ioannou, Ph.D. JML 4/1/92

Section I, Toxicology Branch II (M7509C)

Data Evaluation Report

Study type: Primary dermal-rabbits (51-5) Tox. Chem. No.: 730

MFID number: 418801-04

Test material: Sodium N-methylthiocarbamate, 510 g/l.

Synonyms: Metam Sodium

Study number: 90967D/UCB 368/SE

Testing Facility: Huntingdon Research Centre Ltd
England

Sponsor: UCB Chemicals Corporation
Norfolk, Virginia

Title of report: Skin Irritation to Rabbits with Metam Sodium

Author(s): Michael P. Liggett and Lewis A. McRae

Study completed: January 7, 1981

Conclusions:

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

Toxicity Category II

Core Classification: supplementary

This study does not fulfill the guideline requirements (51-5) for a primary dermal irritation study in rabbits. The purity of the test article was not reported.

009116

I. MATERIALS

A. Test Material: Metam Sodium, 510 g/L. description: clear yellow liquid; purity: not stated. According to the report (page 7), metam sodium is synthesized in aqueous solution, then diluted with water, if necessary, to the desired concentration to meet the label guarantee for the formulated product. Thus, there is no 'technical' metam sodium as such, since the technical material is never isolated.

B. Test Animals: New Zealand White Rabbits ; Source: Intersauna UK Ltd., England. Age: 13-14 weeks; Weight: 3.0-3.6 kg.

II. METHODS

Three male and 3 female rabbits were selected for use in this study. Rabbits were given free access to food (SDS standard rabbit diet) and tap water *ad libitum*. Rabbits were acclimated to the lab environment prior to experimentation, but the period of acclimation was not stated. Rabbits were housed individually in metal cages with perforated floors under conditions of controlled temperature (19 °C) and humidity (30-70%). A 12 hour light/dark cycle was used.

Approximately 24 hours prior to application of the test material, hair was clipped from the dorso-lumbar area of each rabbit with electric clippers.

A 0.5 ml amount of test material was applied to the test site under a 2.5 x 2.5 cm patch of gauze. The patch was then covered with Elastoplast elastic adhesive dressing and left in place for 4 hours.

Four hours after application of test material, the semi-occlusive dressing and gauze pads were removed, and the treatment sites were washed with water to remove residual test substance. The degree of erythema and edema was assessed 30 minutes following removal of test material, and again at 24, 48, and 72 hours using the Draize scale. No other examinations were performed.

III. RESULTS

At 30 minutes following removal of the semi-occlusive dressing and patches, well-defined erythema and slight edema were observed in 3 of the six rabbits tested, while well-defined erythema and moderate edema were observed in 1 of the six rabbits tested. In the remaining 2 rabbits, slight edema was accompanied by severe erythema.

Of the 4 rabbits which showed well-defined erythema and slight to moderate edema at 30 minutes, these reactions subsided in 2 of the rabbits and were gone by day 10 post-application. In the remaining 4 rabbits, severe erythema was observed from day 2 until study termination or sacrifice. Sacrifice was necessary in 2 of the 4 rabbits which displayed this severe reaction, due to the presence of necrosis with fissuring and associated hemorrhage. In the remaining 2 rabbits showing the severe erythema, the

severe reaction subsided by day 10 to well-defined erythema with desquamation of the stratum corneum. Edema was very slight to slight in these 2 rabbits for the remainder of the study period.

IV. CONCLUSIONS

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

Toxicity Category II

V. CORE CLASSIFICATION

supplementary

This study does not fulfill the guideline requirements (B1-5) for a primary dermal irritation study in rabbits. The purity of the test article was not reported.

METAM Sodium

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Reviewed by: Timothy F. McMahon, Ph.D.
Section I, Toxicology Branch II (H7509C)
Secondary Reviewer: Yiannakis M. Ioannou, Ph.D.
Section I, Toxicology Branch II (H7509C)

J.M.I. 4/1/92
J.M.I. 4/1/92

009416

Data Evaluation Report

Study type: Dermal sensitization-guinea pigs (81-6) Tox. Chem. No.: 780

MRID number: 419861-05

Test material: Sodium N-methyldithiocarbamate

Synonyms: Metam Sodium

Study number: 901002D/UCB 370/SS

Testing Facility: Huntingdon Research Centre, Ltd
England

Sponsor: UCB Chemicals Corporation
Norfolk, Virginia

Title of report: Delayed Contact Hypersensitivity in the Albino Guinea Pig

Author(s): Brenda I. Parcell and Stuart M. Denton

Study completed: January 7, 1991

Conclusions:

Under the conditions of this study, metam sodium is a skin sensitizer in guinea pigs.

Core Classification: supplementary

This study does not satisfy the guideline requirements (81-6) for a dermal sensitization study in guinea pigs. The purity of the test article was not reported.

I. MATERIALS

A. Test Material: Metam Sodium, 510 g/L; description: clear yellow liquid; purity: not stated. According to the report (page 7), metam sodium is synthesized in aqueous solution, then diluted with water, if necessary, to the desired concentration to meet the label guarantee for the formulated product. Thus, there is no 'technical' metam sodium as such, since the technical material is never isolated.

B. Positive Control Material: presented as historical control data in Appendix 3 of the report.

C. Vehicles: distilled water for both induction and challenge

C. Test Animals: Female Dunkin/Hartley albino guinea pigs. Source: D. Hall, Newchurch, Staffordshire, England. Age: not stated. Weight : 322-390g.

II. METHODS

General:

An acclimation period to the laboratory environment of five days was allowed prior to experimentation. Guinea pigs had free access to food (Vitamin C-enriched guinea pig diet F.D. 1.; hay was given weekly) and tap water. Guinea pigs were housed in a temperature (21 °C) and humidity (30-70%) controlled animal room. A 12 hour light/dark cycle was used. Prior to the main study, a preliminary study was performed to identify an irritant test article concentration suitable for the induction phase of the main study as well as a non-irritating concentration for use in the induction phase of the main study. Two guinea pigs received intradermal injections of test material diluted in water (0.1-10% v/v) for the preliminary induction study, while 4 guinea pigs were given topical application of 1.0, 2.5, 5.0, and 7.5% test material for the preliminary challenge phase. Based upon the results of this preliminary investigation (Appendix 2 of the report), a concentration of 5% metam sodium in distilled water was chosen for the induction phase, while a concentration of 2.5% metam sodium was chosen for the challenge phase of the main study.

Induction:

Hair was shaved from the dorsal scapular region (4 x 6 cm) using an electric clipper. Three pairs of intradermal injections were made simultaneously in this area for the induction test group. Injections (0.1 ml) were as follows:

Induction Test Group

1. 0.1 ml Freund's complete adjuvant diluted 1:1 with water for injection
2. 0.1 ml of 5% test article in distilled water (v/v)
3. 0.1 ml of 5% (v/v) test article in a 50:50 mixture of Freund's complete adjuvant and distilled water.

Induction Control Group

1. 0.7 ml Freund's complete adjuvant diluted 1:1 with water for injection
2. 0.7 ml distilled water
3. 0.7 ml of a 1:100 mixture of Freund's complete adjuvant and distilled water

Seven days after the injections, the same dorsal scapular region was clipped free of hair and a 2 x 4 cm patch of Whatman # 3 paper was saturated with approximately 0.4ml metam sodium, 2.5% v/v in distilled water. The patch was placed on the skin and covered with impermeable plastic adhesive tape. This was firmly secured with an adhesive bandage wound around the trunk. This dressing was left in place for 48 hours.

It was stated in the report (page 10) that control animals were used during this phase of the study and were treated similarly as the test animals with the exception that test compound was omitted from the intradermal injections and topical application

Challenge:

For challenge exposure, hair was clipped from an area on the left flanks of all guinea pigs in both test and control groups. In both groups, a 2 x 2 cm Whatman # 3 MM paper was saturated with approximately 0.2ml of 1% metam sodium in water and placed on the left flank of all guinea pigs. Metam sodium at 0.5% in distilled water was applied in a similar manner to a posterior site. Patches were covered with strips of Blenderm covered by Elastoplast wound around the trunk and secured with Sleek impervious plastic adhesive tape. Patches were removed after 24 hours of challenge exposure in both groups.

Challenge sites were read at 24, 48, and 72 hours following patch removal. Scoring of skin reaction was based upon an arbitrary scale as presented in the report (page 11, attached). Dermal reactions elicited by challenge application in test animals were compared with the findings obtained in controls.

III. RESULTS

No evidence of delayed contact hypersensitivity was observed in control guinea pigs over the 72 hour study period. In test guinea pigs, slight to well-defined erythema and edema were observed in all guinea pigs at the 24 hour time point. The presence of either a necrotic edge, dryness and sloughing of the epidermis, or thickening of the epidermis was also noted in most of the test article treated guinea pigs. Based upon the comparison of these data to the control guinea pigs, it appears that metam sodium is a sensitizer. The absence of data showing dermal reactions (if any) following the induction phase of the main study is considered a deficiency of the present study, but would have no significant impact upon the conclusions drawn. Individual animal data for historical control guinea pigs showing sensitization with formalin should also be provided in future reports.

009416

IV. CONCLUSIONS

Under the test conditions employed in this study, metam is a skin sensitizer in guinea pigs.

V. CORE CLASSIFICATION

supplementary

This study does not satisfy the guideline requirements (81-6) for a dermal sensitization study in guinea pigs. The purity of the test article was not reported.

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Tox. Chem. No. 780 _____ File Last Updated _____ Current Date: 03/25/92

Study/Lab/Study #/Date	Material	EPA MRID No.	Results	TOX Category	CORE Grade/Doc. No.
Acute Oral Toxicity species: rat Huntingdon Res. Ctr. # 901046D/UCB 366/AC 1/7/91	metam sodium 510 g/L	419861-01	LD50, LC50, PIS, NOEL, LEL Acute oral LD50 = 870 mg/kg in male rats, = 924 mg/kg in female rats. Combined acute oral LD50 = 896 mg/kg.	III	supplementary
Acute Dermal Toxicity species: rat Huntingdon Res. Ctr. # 90955D/UCB 367/AC 1/7/91	metam sodium 510 g/L	419861-02	Acute dermal LD50 > 2000 mg/kg in both sexes.	III	supplementary
Acute Inhalation Tox. species: rat Huntingdon Res. Ctr. # UCB 371/91206 1/8/91	metam sodium 510 g/L	421877-01	Acute inhalation LC50 = 2.20 mg/L in male rats, = 2.95 mg/L in female rats. Combined acute LC50 = 2.54 mg/L.	III	supplementary
Primary Eye Irritation species: rabbit Huntingdon Res. Ctr. # 90998D/UCB 369/SE 1/7/91	metam sodium 510 g/L	419861-03	Metam sodium was mildly irritating to the eyes of New Zealand White rabbits.	III	supplementary
Primary Dermal Irritation species: rabbit Huntingdon Res. Ctr. # 90997D/UCB 368/SE 1/7/91	metam sodium 510 g/L	419861-04	Metam sodium was severely irritating to the skin of New Zealand White rabbits.	II	supplementary
Dermal Sensitization species: guinea pig Huntingdon Res. Ctr. # 901002D/UCB 370/SS 1/7/91	metam sodium 510 g/L	419861-05	Metam sodium was a sensitizer in guinea pigs.		supplementary

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