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WASHINGTON, D.C. 20460

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OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

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MEMORANDUM

SUBJECT: Metam Sodium: Review of a Mouse Carcinogenicity Study Submitted under FIFRA Section 6(a)(2) by the Registrant.

Shaugnessey: 039003
Submission: S467006
MRID No: 432335-01
DP Barcode: D204012

FROM: Timothy F. McMahon, Ph.D., Pharmacologist 7/28/94
Review Section I, Toxicology Branch II
Health Effects Division (7509C)

TO: Tom Myers / PM 51
Special Review and Reregistration Division (7508W)

THRU: Yiannakis M. Ioannou, Ph.D., Section Head Y. M. Ioannou 7/28/94
Review Section I, Toxicology Branch II
Health Effects Division (7509C)

and

Marcia Van Gemert, Ph.D., Branch Chief
Toxicology Branch II
Health Effects Division (7509C) Marcia Van Gemert 7/28/94

Registrant: Metam Sodium Task Force

Action Requested: Review of a mouse carcinogenicity study submitted under FIFRA Section 6(a)(2) in support of reregistration of metam sodium.

Executive Summary:

In a two year carcinogenicity study in mice (MRID # 432335-01), Metam sodium technical (43.15% a.i.) was administered in the drinking water to groups of 55 male and 55 female C57BL/10JfCD-1/Alpk mice for 104 weeks at nominal dose levels of 0, 0.019, 0.074, and 0.23 mg/ml (**1.6 mg/kg, 6.5 mg/kg, and 27.7 mg/kg** for male mice and **2.3 mg/kg, 8.7 mg/kg, and 29.9 mg/kg** for female mice).

At 0.074 and 0.23 mg/ml, dose-related and statistically significant increases in absolute liver weight were observed in male and female mice (111% and 119% of control at 0.074 mg/ml; 135% and 122% of control at 0.23 mg/ml). At 0.23 mg/ml, decreased body weight gain in male mice (14% for weeks 1-13, 20% for weeks 1-104) was observed. Increases in the incidence of macroscopic pathology were observed in the liver (accentuated lobular pattern, pale appearance) and urinary bladder (wall thickening) were also observed. Non-neoplastic microscopic pathology in male and female mice was increased at 0.23 mg/ml, and included increases in extramedullary hemopoiesis of the spleen and several alterations in the urinary bladder, including epithelial hyperplasia, eosinophilic/hyaline cytoplasmic inclusions, increased submucosal connective tissue, and submucosal hyalinization. Fat vacuolation in the liver was also observed in both sexes at this dose. **The LEL of 0.074 mg/ml** (6.5 mg/kg in male mice, 8.7 mg/kg in female mice)**is based upon the significant increase in liver weight in male and female mice. The NOEL is 0.019 mg/ml** (1.6 mg/kg in male mice, 2.3 mg/kg in female mice).

Carcinogenic potential was evidenced in this study by an increase in the incidence of angiosarcoma of the liver, spleen, and subcutaneous tissue, as well as the presence of a transitional cell papilloma in a single high dose male, and a transitional cell carcinoma in a single high dose female.

Dosing was considered adequate in male mice based upon the decrease in body weight gain, increase in liver weight with accompanying pathology, increased incidence of non-neoplastic urinary bladder pathology, and increase in angiosarcoma incidence observed at the 0.23 mg/ml dose level. Dosing was considered adequate in female mice based on the increased incidence of non-neoplastic urinary bladder pathology and angiosarcoma at the 0.23 mg/ml dose level.

This study is classified **core minimum** and satisfies the guideline requirements for §83-2, Carcinogenicity Study in Mice.

Reviewed by: Timothy F. McMahon, Ph.D. 7/28/94
Section I, Toxicology Branch II (7509C)
Secondary Reviewer: Yiannakis M. Ioannou, Ph.D. 7/28/94
Section I, Toxicology Branch II (7509C)

Data Evaluation Record

Study type: Carcinogenicity - mice
Guideline: 83-2

EPA ID Numbers: MRID number: 432335-01 P.C. Code: 039003
Submission: S467006 DP Barcode: D204012

Test material: Metam Sodium

Chemical name: Sodium N-methyldithiocarbamate

Project I.D. : Report # CTL/P/4095 Study # PM0841

Sponsor: Metam Sodium Task Force

Testing Facility: Zeneca Central Toxicology Laboratory
Alderley Park, Macclesfield, Cheshire, UK

Title of report: Metam Sodium: Two Year Drinking Study in Mice

Author(s): S. A. Horner

Study Completed: April 20, 1994

Executive Summary:

In a two year carcinogenicity study in mice (MRID # 432335-01), Metam sodium technical (43.15% a.i.) was administered in the drinking water to groups of 55 male and 55 female C57BL/10JfCD-1/Alpk mice for 104 weeks at nominal dose levels of 0, 0.019, 0.074, and 0.23 mg/ml (**1.6 mg/kg, 6.5 mg/kg, and 27.7 mg/kg** for male mice and **2.3 mg/kg, 8.7 mg/kg, and 29.9 mg/kg** for female mice).

At 0.074 mg/ml, statistically significant increases in absolute liver weight were observed in male and female mice (111% and 119% of control, respectively). At 0.23 mg/ml, decreased body weight gain in male mice (14% for weeks 1-13, 20% for weeks 1-104) was observed. Increases in the incidence of macroscopic pathology were observed in the liver (accentuated lobular pattern, pale appearance) and urinary bladder (wall thickening) were also observed. Non-neoplastic pathology in male and female mice was increased at 0.23 mg/ml, and included increases in extramedullary hemopoiesis of the spleen and several alterations in the urinary bladder, including epithelial hyperplasia, eosinophilic/hyaline cytoplasmic inclusions, increased

submucosal connective tissue, and submucosal hyalinization. Fat vacuolation in the liver was also observed in both sexes at this dose. **The LEL of 0.074 mg/ml** (6.5 mg/kg in males, 8.7 mg/kg in females) **is based upon the significant increase in liver weight in male and female mice. The NOEL is 0.019 mg/ml** (1.6 mg/kg in males, 2.3 mg/kg in females).

Carcinogenic potential was evidenced in this study by an increase in the incidence of angiosarcoma of the liver, spleen, and subcutaneous tissue, as well as the presence of a transitional cell papilloma in a single high dose male, and a transitional cell carcinoma in a single high dose female.
Dosing was considered adequate in male mice based upon the decrease in body weight gain and increase in liver weight observed at the 0.23 mg/ml dose level. Dosing was considered adequate in female mice based on the increase in liver weight observed at the 0.23 mg/ml dose level.

This study is classified core minimum and satisfies the guideline requirements for §83-2, Carcinogenicity Study in Mice.

4

I. MATERIALS AND METHODS

A. Test Material:

Metam Sodium technical; purity: 43.15% (written verification provided on page 242 of the report)
description: yellow colored aqueous solution
sample reference No: BAS/005/00N 90-2

B. Test Animals

A total of 315 male and 315 female C57BL/10JfCD-1/Alpk mice were received on February 4, 5, and 6 of 1991 from the SPF Barriered Animal Breeding Unit of Zeneca Pharmaceuticals, UK. Age: approximately 35-36 days upon receipt. Acclimation period: approximately 2 weeks. Body Weight (at time of dosing): males, approximately 22g; females, approximately 18g.

C. Animal Husbandry

Mice were transported to the barriered animal unit in containers sealed with a plastic sleeve. The sealed containers were introduced into the barriered unit via a dunk tank and the sleeve then removed to ensure the SPF status of the mice during transport. Mice were quarantined for the first 10 days after arrival, during which health status was carefully observed. Mice were housed initially in multiple mouse cages containing no more than 8 per cage, and in groups of 5 after assignment to treatment groups. Cages were of stainless steel construction with mesh floors, front, and back. Food (CT1 Diet, Special Diets Services, Witham, Essex, UK) was supplied *ad libitum*. During the first few days after arrival, mice received moistened control diet due to immaturity. Drinking water was supplied in polycarbonate bottles fitted with glass ball-bearing nozzles. Prior to start of treatment, all mice were given purified drinking water *ad libitum*. The pH was adjusted to approximately 8.0-9.0 using a small quantity of 0.05M phosphate buffer. After the start of treatment, mice received experimental drinking water (purified water containing test article) at approximately the same time each afternoon (between 2-4pm). Temperature of the animal room was set to maintain a temperature of 21± 2 ^{o}C and humidity of 55 ± 15%. Actual values were stated as 15-29 ^{o}C and 20-80% humidity for the study overall. Ventilation ensured a minimum of 15 air changes/hour. A single animal room was used for the entire study.

D. Drinking Water Mixtures

All experimental drinking water preparations were prepared daily in batches of 2.5 or 5 liters. For each dose level, the appropriate amount of metam sodium was added to the drinking water. This was then thoroughly mixed and dispensed into polycarbonate drinking bottles. This preparation supplied enough water to last each cage one day, after which bottles were removed, emptied, refilled, and replaced with drinking water from a new, freshly prepared batch.

D. Stability and Homogeneity

Amounts of metam sodium required for 2.5 or 5 liter batches of drinking water preparations at each dose level (corrected for purity) are summarized below (page 244 of the report):

Group	Concentration of METAM SODIUM in water (mg/ml)	Quantity of Test Substance to Prepare 2.5 or 5 litres of water (g)		Colour Code
		2.5 litres	5 litres	
1	0 (Control)	0	0	Blue
2	0.019	0.108	0.215	Green
3	0.074	0.430	0.860	Yellow (Gold)
4	0.23	1.344	2.688	Red

Concentration of metam sodium in drinking water was determined by reacting portions of stock solution with cupric chloride-acetic acid reagent and measuring the resultant yellow solutions spectrophotometrically at 420nm.

During the pre-experimental period, drinking water analysis was performed twice to confirm the acceptability of the preparation procedure. Stability over a 24 hour period was also determined. After the start of treatment, drinking water was analyzed twice weekly for the first 2 weeks, and thereafter, one batch was analyzed monthly to confirm established concentrations of metam sodium. Concentration was determined from samples taken from the bulk preparation immediately prior to administration to test animals.

Results of test article analysis in drinking water as well as 24 hour stability were presented in Appendix H, pages 253-263 of the report. The percent of nominal concentration for each dose level is based upon the mean analyzed concentration at 24 hours post-preparation from 12 different sampling times.

Table 1

Dosing Solution Stability of Metam Sodium in Drinking Water[a]

Group	Nominal Conc.(mg/ml)	Analyzed Conc.(mg/ml)[b]	% Nominal
1	Control	ND	
2	0.019	0.016	87.6
3	0.074	0.067	91.3
4	0.23	0.221	96.2

[a]data taken from Appendix H of the report. [b]analyzed concentration and % nominal represent the mean of 12 measurements made at 24 hours post-dose preparation.

Appendix I, pages 264-271, summarized the doses received by male and female mice over the course of this study, with corresponding mean values for the overall study period. As the report appeared to indicate no significant degradation of test material which would influence the calculation of intake (page 23 of the report), and the calculation of dose received was based on nominal dose levels (page 272 of the report), the mean doses received are presumed to be based on nominal dose levels. These were stated as follows:

Males: **1.9 mg/kg** (low dose); **7.2 mg/kg** (mid dose); **28.9 mg/kg** (high dose)

Females: **2.6 mg/kg** (low dose); **9.6 mg.kg** (mid dose); **31.2 mg/kg** (high dose)

Based on the decomposition over 24 hours at each dose level, corrected doses received are as follows:

Males: **1.6 mg/kg** (low dose); **6.5 mg/kg** (mid dose); **27.7 mg/kg** (high dose)

Females: **2.3 mg/kg** (low dose); **8.7 mg.kg** (mid dose); **29.9 mg/kg** (high dose)

E. Experimental Design and Dosing

The following experimental design was used for this study:

Group #	Drinking Water Level (mg/ml)	Sacrifice Interval (104 Weeks) Number of Mice	
		M	F
1 (Control)	0	55	55
2 (Low)	0.019	55	55
3 (Mid)	0.074	55	55
4 (High)	0.23	55	55
5 (Sentinel)	0	10	10
6 (Senitnel)	0.23	10	10

In this design, 55 animals/sex were assigned to treatment with metam sodium technical in the drinking water for a period of 104 weeks. A total of 10 mice/sex were used at dose levels of 0 and 0.23 mg/ml metam sodium to provide information on the microbiological status of the experimental mice in the study. Sentinel mice were treated in the same manner as experimental mice.

All mice requiring euthanasia prior to week 104 were sacrificed by overexposure to halothane followed by exsanguination. They were subjected to full post-mortem examination, together with any animals found dead during the study.

Dose selection for the present study was based on results of a 90-day

drinking water study in the same strain of mouse conducted at the performing laboratory. Additional details were not provided.

E. Statistical Analysis

A copy of the statistical analyses used in this study is attached to this report.

F. Compliance

A signed statement of no data confidentiality claims was provided.

A signed statement of GLP compliance was provided.

A signed statement of quality assurance was provided.

A signed statement of flagging studies for potential adverse effects was provided. Under the criteria of 40 CFR 158.34, this study meets or exceeds criteria 2 and 3, based on the increase in incidence of angiosarcoma in high dose male and female mice, and on the presence of a transitional cell papilloma of the urinary bladder for one high dose male and a transitional cell carcinoma in one high dose female.

II. OBSERVATIONS AND RESULTS

A. **Mortality and Clinical Observations**

Mice were examined prior to the start of the study to ensure that they were physically normal and that they exhibited normal activity. Any abnormal mice found prior to randomization were discarded, and any mice found suffering during the study and unlikely to survive to the next observation time were removed from the study and necropsied. Detailed clinical examinations were carried out weekly during the study at the same time as body weight determinations. Mortality in treated and control mice was presented in the report as results of Kaplan-Meier survival rates for both sexes, and is reproduced from the report follows:

TABLE 1

Survival in Mice Given Metam Sodium in the Diet for 104 Weeks[a]

Weeks of Study	Males (mg/ml) 0.0	0.019	0.074	0.23	Females (mg/ml) 0.0	0.019	0.074	0.23
1	55/55	55/55	55/55	55/55	55/55	55/55	55/55	55/55
% alive	100	100	100	100	100	100	100	100
13	55/55	54/55	55/55	54/55	55/55	55/55	52/55	53/55
% alive	100	98	100	98	100	100	94	96
27	54/55	54/55	55/55	54/55	55/55	55/55	47/55	52/55
% alive	98	98	100	98	100	100	85	94
53	53/55	53/55	55/55	53/55	55/55	55/55	46/55	52/55
% alive	94	94	199	94	100	100	84	94
79	45/55	45/55	48/55	45/55	50/55	45/55	41/55	47/55
% alive	82	82	87	82	91	82	74	85
105	21/55	20/55	27/55	20/55	30/55	25/55	20/55	22/55
% alive	38	36	49	36	54	45	36	40

[a]data taken and/or calculated from Table 6, pages 77-86 of the report.

According to the data presented above, there were no apparent treatment related effects on mortality in either male or female mice in this study. The decrease in the number of female mice alive between the 13 and 27 week time period for the 0.074 mg/ml dose level was due to accidental death of 5 female mice at week 25. Cause of the accident was not stated, but as it involved 5 mice and mice were housed 5 per cage, it would appear that the mishap involved a single cage of mice.

B. **Clinical Observations**

As stated, clinical examinations were carried out weekly during the study period in addition to observations made prior to study initiation. A summary of effects observed was provided in the report (Table 4, pages 59-73). In male mice, the incidence of coat greying was decreased at the high dose level, while the incidence of hair loss was decreased at the mid and high dose level. The incidence of torn left ears was increased at the 2 highest dose levels, by contrast. In female mice, the incidence of coat graying did not show any definite dose-response relationship, but the incidence of hair loss was decreased at the mid and high dose levels as observed in male mice. The incidence of torn left ear was increased as in male mice. These observations are summarized below (Table 2):

Table 2

Clinical Observations in Metam Sodium Treated Mice[a]

	Males (mg/ml)			
	0.0	0.019	0.074	0.23
coat greying				
no. obs.	642	762	932	398
no. of animals	17	24	25	9
hair loss				
no. obs.	164	246	67	49
no. of animals	16	20	9	3
left ear torn				
no. obs.	57	232	925	808
no. of animals	2	4	15	11

	Females (mg/ml)			
	0.0	0.019	0.074	0.23
coat greying				
no. obs.	542	403	218	476
no. of animals	14	13	9	13
hair loss				
no. obs.	557	541	245	186
no. of animals	28	27	21	16
left ear torn				
no. obs.	0	200	1134	759
no. of animals	0	3	18	13

[a]data taken from Table 4, pages 59-72 of the report.

Although some of the observations noted above showed an apparent dose dependency, it was stated in the report that these were not of toxicological significance.

C. **Body Weights**

Body weight measurements were taken immediately before administration of experimental drinking water and then on the same day each subsequent week for the first 14 weeks of the study. Thereafter, body weights were recorded every 2 weeks. Group mean body weights at selected times are presented in **Table 3**.

TABLE 3

Group Mean Body Weights (grams) in Male and Female Mice Given Metam Sodium in the Diet for 104 Weeks[a]

Weeks of Study	Males (mg/ml) 0.0	0.019	0.074	0.23	Females (mg/ml) 0.0	0.019	0.074	0.23
1	22.6± 1.1	22.3± 1.1	22.3± 1.2	22.3± 1.2	17.8± 1.1	18.1± 1.0	17.7± 1.2	17.9± 1.0
13	28.6± 1.7	28.0± 1.4	28.0± 1.7	27.5±** 1.5	23.7± 1.4	24.2± 1.1	23.9± 1.2	23.6± 1.2
25	31.2± 2.1	30.6± 1.7	30.4±* 1.8	29.5±** 1.6	25.6± 1.7	25.9± 1.4	25.4± 1.5	25.0±* 1.2
53	34.2± 3.0	33.6± 2.2	33.1±* 2.9	32.0±** 1.9	27.2± 2.1	28.1±* 1.8	27.1± 1.7	26.5±** 1.5
N	46	45	48	45	50	48	42	48
77	34.6± 3.0	33.4±* 2.6	33.7± 2.3	32.2±** 1.8	28.0± 2.4	28.9± 1.9	27.8± 1.9	27.5±* 1.9
N	21	20	27	20	30	25	20	22
105	32.7± 2.8	31.6± 1.8	32.5± 1.9	30.4±** 1.4	27.6± 2.3	28.2± 2.1	27.3± 2.0	27.1± 1.7

[a]data taken from Table 6, pages 77-86 of the report.

For the time periods shown above, absolute body weight in male mice was decreased by 4-8% relative to untreated controls ($p < 0.01$). Consistent decreases were observed in high dose male mice from weeks 2 through study termination, and were listed as statistically significant, although the decreases did not exceed 10% of controls. In female mice, significant decreases of 2-3% were observed at the high dose for weeks 25, 53, and 77 of

the study. Consistent decreases in absolute body weight were only observed in high dose females from weeks 43 to 87 of the study. As with male mice, these decreases did not exceed 10% of control values. Occasional significant decreases in group mean body weight were observed in male mice at the 0.074 mg/ml dose level, but the changes were not consistently observed. However, based on the frequency of occurrence, it would appear that the body weight effect observed at the high dose is treatment related.

Effects of test article treatment on group mean body weight gain in male and female mice are summarized in the following Table (**Table 4**):

TABLE 4

Group Mean Body Weight Gains in Male and Female Mice Given Metam Sodium in the Diet for 104 Weeks[a]

Weeks of Study	Males (mg/ml) 0.0	0.019	0.074	0.23	Females (mg/ml) 0.0	0.019	0.074	0.23
1	22.6± 1.1	22.3± 1.1	22.3± 1.2	22.3± 1.2	17.8± 1.1	18.1± 1.0	17.7± 1.2	17.9± 1.0
weight gain (g)								
1-13	6.0	5.7	5.7	5.2	5.9	6.1	6.2	5.7
% cont.	-	95	95	86	-	103	105	97
1-53	9.4	10	9.4	9.7	9.4	10	9.4	8.6
% cont.	-	106	100	103	-	106	100	91
1-105	10.1	9.3	10.2	8.1	9.8	10.1	9.6	9.2
% cont.	-	92	100	80	-	103	98	94

[a]data calculated from Table 6 in the report.

Group mean body weight gain as calculated from available body weight data demonstrated effects at the high dose for both sexes of mouse. The effects in male mice were more pronounced than in female mice, as shown by the 14% decrease for weeks 1-13 in high dose males, and the 20% decrease for the entire study period in high dose males. The effects in females, as for absolute body weight, were not as pronounced and did not exceed 10% of control at any of the times shown above.

C. **Food Consumption and Efficiency**

According to the report, food consumption was measured weekly from weeks 1-14 of the study, during week 16 of the study, and then every 4 weeks thereafter. Food efficiency calculations were not performed. Compound intake was based on water consumption and will be shown in a subsequent section.

Group mean food consumption data are presented in **Table 5** below:

TABLE 5

Group Mean Food Consumption (g/mouse/day) in Male and Female Mice Given Metam Sodium in the Diet for 104 Weeks[a]

Weeks of Study	Males (mg/ml) 0.0	0.019	0.074	0.23	Females (mg/ml) 0.0	0.019	0.074	0.23
1	4.2± 0.2	4.2± 0.3	4.1± 0.1	4.1± 0.2	4.2± 0.2	4.2± 0.3	4.3± 0.3	4.2± 0.2
13	3.9± 0.3	3.8± 0.2	3.7± 0.1	3.7± 0.3	4.1± 0.2	4.2± 0.2	4.3± 0.4	4.1± 0.2
1-13								
Total	51.6	51.3	50.2	49.4	55.3	56.7	56.9	55.5
52	3.9± 0.2	3.8± 0.2	3.6±** 0.2	3.7±* 0.2	3.8± 0.2	3.9± 0.2	3.9± 0.2	3.8± 0.2
76	3.9± 0.3	3.7± 0.2	3.7± 0.2	3.7± 0.3	3.8± 0.2	4.0± 0.3	3.8± 0.2	3.9± 0.3
104	4.6± 0.9	4.5± 1.1	4.2± 0.5	4.2± 0.5	4.2± 0.5	4.7± 0.8	4.8± 1.0	4.7± 1.0

[a]data from Table 7, pages 87-92 of the report.

In male mice, significant food consumption decreases were recorded during the first 13 weeks of this study at the 0.23 mg/ml dose, at weeks 2, 5, and 7 through 11. These decreases, while identified as statistically significant, were on the average of 5%. In females, no significant decreases in food consumption were recorded for the first 13 weeks of the study.Total food consumption for both male and female mice for the first 13 weeks of the study was not affected in treated vs control mice.
At later times in the study, statistically significant decreases in food consumption were recorded for male mice at the 0.074 and 0.23 mg/ml dose levels, during weeks 24 to 52, although these data were only reported every 4 weeks during this time. Decreases in food consumption were not observed in female mice during this time.

TABLE 6

Group Mean Food Efficiency (%) in Male and Female Mice Given Metam Sodium in the Diet for 104 Weeks [a]

Weeks of Study	Males (mg/ml) 0.0	0.019	0.074	0.23	Females (mg/ml) 0.0	0.019	0.074	0.23
weeks 1-2	10.9	11.1	11.2	7.5	12.0	10.5	12.9	9.6
weeks 1-13	11.6	11.1	11.3	10.5	10.6	10.7	10.8	10.2

[a]data calculated by reviewer.

Food efficiency in male and female mice appeared decreased at the high dose for weeks 1-2 of the study, but not for the first 13 weeks of the study. Further calculation would have been difficult, due to the discontinuous nature of food consumption measurement beyond the 13 week time point.

Data on food efficiency are not suggestive of an effect of test article. Body weight gain decreases in male mice at the high dose exceeded that of the decrease in food consumption, however.

D. **Water Consumption**

Water consumption was recorded for each cage on a daily basis, and is reported on a weekly basis. Summary is made below for selected time points:

Table 7

Water Consumption (ml/mouse/day) in Male and Female Mice Receiving Metam Sodium in Drinking Water[a]

Weeks of Study	Males (mg/ml) 0.0	0.019	0.074	0.23	Females (mg/ml) 0.0	0.019	0.074	0.23
week 1	4.0± 0.3	3.8±* 0.3	3.6±* 0.1	3.4±* 0.1	4.0± 0.4	4.1± 0.5	3.7± 0.2	3.3±** 0.3
week 13	3.4± 0.3	3.2± 0.2	3.0±** 0.2	3.9±** 0.4	4.2± 0.6	4.0± 0.5	4.0± 1.4	3.8± 0.5
weeks 1-13	**45.4**	**44.2**	**41.3**	**47.0**	**54.9**	**55.3**	**48.7**	**46.9**

Table 7, cont.

Weeks of Study	Males (mg/ml) 0.0	0.019	0.074	0.23	Females (mg/ml) 0.0	0.019	0.074	0.23
week 26	3.2± 0.3	3.1± 0.2	2.9±** 0.1	3.7±** 0.2	4.1± 0.7	3.7± 0.6	3.8± 1.3	3.6± 0.3
week 52	3.4± 0.7	3.1± 0.5	3.0± 0.3	3.8±* 0.4	3.4± 0.3	3.5± 0.5	3.2± 0.6	3.4± 0.3
week 78	3.3± 0.2	3.1± 0.3	2.9±* 0.3	3.8±** 0.4	3.0± 0.2	3.2± 0.2	2.9± 0.2	3.3±* 0.3
week 104	3.9± 0.6	3.6± 0.6	3.6± 0.7	4.3± 0.8	3.3± 0.5	3.4± 0.5	3.5± 0.7	3.8±* 0.7

[a]data taken from Table 8, pages 93-108 of the report. *p < 0.05 vs control; **p < 0.01 vs control.

As shown, water consumption in male and female mice was decreased during the first week of the study, and was statistically significant at the 0.23 mg/ml dose level for both sexes, and at all dose levels for male mice. The trend for decreased water consumption continued in male mice for the first 2 weeks of the study, and then by week 9, was significantly increased at the high dose. By week 11, water consumption was significantly increased at both the 0.074 and 0.23 mg/ml dose levels compared to control intake in male mice. Significantly increased water intake was observed at the 0.23 mg/ml dose level in male mice throughout the rest of the study.

In female mice, water consumption at the high dose tended to be decreased relative to control, but statistical significance was not consistently achieved. In addition, by about week 48 of the study, water consumption at all dose levels vs control was approximately equal, and by about week 75, water consumption in high dose females was slightly increased over control values. .

E. Intake of Metam Sodium

According to the report (Appendix I, pages 264-271), the dose received by both male and female mice dropped during the first 4 weeks of the study, which, according to the report, was based upon the rapid growth of the mice during this time. Mean intake values for metam sodium (in mg/kg) are shown below, based upon the evaluation of test article stability and decomposition observed in this study and summarized on pages 4 and 5 of this review.

TABLE 8

Group Mean Achieved Dosage of Metam Sodium in Male and Female Mice Over 104 Weeks[a]

Dose Group (mg/ml)	Average Intake (weeks 1-104) (mg/kg/day) males	females
0.0	-	-
0.019	1.6	2.3
0.074	6.5	8.7
0.23	27.7	29.9

[a]data taken from pages 4 and 5 of this review.

F. Ophthalmoscopic Examination

Opthalmoscopic examination was not performed in this study and is not required for §83-2.

G. Clinical Pathology

Blood samples were collected from 10 male and 10 female mice per dose group at week 53 and 79 of the study. Bleeding was done from the tail vain, and a peripheral blood smear prepared. Differential white cell count and red cell morphology was performed on control and high dose animals only.

At week 104, all surviving mice were bled by cardiac puncture and blood parameters (shown below) determined using a TECHNICON H1 analyzer. Bone marrow smears were prepared at necropsy but were stored and not examined.

a) Hematology

The following CHECKED hematological parameters were examined:

- x total leucocyte count*
- x erythrocyte count*
- x hemoglobin*
- x hematocrit*
- - platelet count
- - packed cell volume
- - reticulocyte count
- - total plasma protein*
- x leukocyte differential*
- x mean corpuscular HGB
- x mean corpusc. HGB conc.
- x mean corpusc. volume
- - methemoglobin
- - prothrombin

*EPA guideline requirement

"-" not analyzed

Hematological findings were summarized in Tables 9a and 9b, pages 109-116 of the report. There were no significant findings from differential blood smears obtained at week 53 or 79 in male and female mice. At week 105, clinical analysis of blood samples showed a significant decrease in red cell count in high dose female mice vs control, but there were no corresponding changes in hemoglobin or hematocrit. In fact, mean cell hemoglobin was observed to be significantly increased at the high dose in female mice at week 105.

H. **Macroscopic Observations**

Mice surviving to study termination as well as those mice requiring sacrifice during the study were killed by overexposure to halothane followed by exsanguination. A full post-mortem examination was performed. Prior to fixation, the weight of the adrenal glands, brain, epididymides, kidneys, liver, and testes were recorded.

Summary of macroscopic observations was presented in the report (Table 11, pages 123-140). A summary of apparent treatment-related findings is made below (Table 9):

Table 9

Macroscopic Findings in Metam Sodium Treated Mice[a]

	Males (mg/ml)				Females (mg/ml)			
	0.0	0.019	0.074	0.23	0.0	0.019	0.074	0.23
No. examined	55	55	55	55	55	55	55	55
eye								
discharge	4	8	4	9	5	6	6	7
liver								
accentuated lobular pattern	2	1	3	5	0	1	2	6
pale	7	5	6	11	6	5	6	9
multiple masses	6	1	4	9	1	3	3	4
subcutaneous tissue								
no. examined	5	4	4	6	3	4	1	5
mass	2	2	2	5	1	3	1	5
seminal vesicle								
enlarged	16	7	7	1				
urinary bladder								
wall thickened	0	0	0	5	0	0	1	3

[a]data taken from Table 11, pages 123-140 of the report.

A slight increase in the incidence of accentuated lobular pattern, pale appearance, and multiple masses (description not given) in the liver was observed for both sexes at the 0.23 mg/ml dose level. Thickening of the urinary bladder wall was also slightly increased at the high dose in both sexes, as were the presence of masses in subcutaneous tissue. Interestingly, the number of male mice with enlarged seminal vesicles appeared markedly decreased at all dose levels in this study.

H. Organ Weights

As stated, organ weights were recorded for terminal kill animals from all dose groups. The weight of the following organs was recorded:

liver
kidneys
testes
adrenals
brain
epididymides

Organ / body weight ratios were also calculated.

Absolute organ weights and organ/body weight ratios were calculated and presented in Table 10, pages 117-122 of the report. Treatment related changes in organ weight are summarized below:

Table 10

Organ Weights at 104 Weeks in Metam Sodium Treated Mice[a]

	Males (mg/ml)				Females (mg/ml)			
	0.0	0.019	0.074	0.23	0.0	0.019	0.074	0.23
No. examined	21	20	27	20	28	25	19	22
liver	1.51± 0.21	1.59± 0.2	1.69±* 0.16	2.05±** 0.56	1.40± 0.26	1.53± 0.45	1.67±* 0.45	1.72±** 0.24
% cont.	-	105	111	135	-	109	119	122
liver/ b.w.	4.65	5.00	5.16	6.81	5.12	5.39	6.07	6.32

Table 10, cont.

	Males (mg/ml)				Females (mg/ml)			
	0.0	0.019	0.074	0.23	0.0	0.019	0.074	0.23
No. examined	21	20	27	20	28	25	19	22
epididymides	0.105± 0.028	0.094± 0.019	0.090±* 0.014	0.085±** 0.024				
% cont.	-	89	85	81				
kidneys	0.57± 0.05	0.54± 0.07	0.52±* 0.05	0.52±** 0.04	0.42± 0.04	0.44±* 0.04	0.44±* 0.06	0.47±** 0.04
% cont.	-	95	91	91	-	104	104	111
kidney / b.w.	1.76	1.71	1.60	1.71	1.52	1.56	1.60	1.71

[a]data taken from Table 10, pages 117-123 of the report.
*$p < 0.05$ vs control; **$p < 0.01$ vs control.

Absolute and relative weight of the liver was noted to be increased in both male and female mice at the 0.074 and 0.23 mg/ml dose levels, and was cited as statistically significant. The increase in liver weight for male mice was 111% and 135% of control at the 0.074 and 0.23 mg/ml dose levels, respectively, while the increase for female mice was 119% and 122% of control at these same dose levels.
Absolute weight of the epidiymides in male mice displayed a dose-related decrease, consistent with the observation of a decreased incidence of enlarged seminal vesicles. Kidney weight, while decreased by 9% in male mice at the 0.074 and 0.23 mg/ml dose levels, was increased by approximately the same percentage in female mice at thee dose levels. There were no other significant organ weight changes reported in this study.

I. **Microscopic Observations**

Samples of the following tissues were removed during post-mortem examination, fixed in 10% neutral buffered formalin (except eyes, fixed in Davidson's solution, and skin, mammary gland, and testes/epididymides, fixed in Bouin's solution), processed, embedded in paraffin wax, cut a 5 µm, and stained with hematoxylin and eosin for light microscopic examination.

Digestive

- tongue
x salivary glands*
x esophagus*
x stomach*
x duodenum*
x jejunum*
x ileum*
x cecum*
x colon*
x rectum*
x liver*
x pancreas*
x gall bladder*

Respiratory

x trachea
x lungs*
x nasal cavity

Cardiovascular

x aorta*
x heart*
x bone marrow
x lymph nodes*
x spleen*
x thymus*

Urogenital

x kidneys*
x urinary bladder*
x testes*
x epididymides*
x seminal vesicle*
x prostate
x ovaries
x uterus*
x cervix

Neurologic

x brain*
x peripheral nerve*
x spinal cord (3 levels)*
x pituitary*
x eyes

Glandular

x adrenals *
x lacrimal gland
x thymus
x mammary gland
x parathyroids*
x thyroids*

Other

x bone (femur)
x sternum
x skeletal muscle
x skin*
x lesions and tumors*

*EPA guideline requirement "-" not examined

1a) Non-Neoplastic Observations

A number of observations were recorded for animals in the unscheduled sacrifice and terminal sacrifice groups. These findings are summarized in the following tables (Table 11a and 11b):

Table 11a

Histopathologic Findings in Metam Sodium Treated Mice[a]

	Males (mg/ml)				Females (mg/ml)			
	0.0	0.019	0.074	0.23	0.0	0.019	0.074	0.23
Intercurrent Deaths								
No. examined	34	35	28	35	26	30	33	33
sciatic nerve								
demyelination	18	18	13	15	8	16	16	19
minimal	11	13	10	6	4	11	10	10
slight	6	4	3	7	4	5	6	7

Table 11a, cont.

	Males (mg/ml)				Females (mg/ml)			
	0.0	0.019	0.074	0.23	0.0	0.019	0.074	0.23
spleen								
extramedullary hemopoiesis	8	18	9	17	11	13	12	16
minimal	3	2	2	1	2	3	2	3
slight	2	10	3	6	6	4	5	6
moderate	2	5	3	9	3	6	4	7
marked	1	1	1	1	0	0	1	0
urinary bladder								
epithelial hyperplasia								
total	0	0	2	26	0	0	2	23
minimal	0	0	0	12	0	0	2	11
slight	0	0	2	13	0	0	0	12
moderate	0	0	0	1	0	0	0	0
eosinophilic/hyaline cytoplasmic inclusions								
total	0	5	24	25	3	19	33	28
minimal	0	2	3	9	3	16	7	9
slight	0	3	13	8	0	3	13	12
moderate	0	0	6	7	0	0	12	6
marked	0	0	2	1	0	0	1	1
increased submucosal connective tissue								
total	1	0	0	10	0	0	0	15
minimal	0	0	0	2	0	0	0	4
slight	1	0	0	6	0	0	0	6
moderate	0	0	0	2	0	0	0	5
submucosal hyalinization								
total	0	0	0	27	0	0	0	14
minimal	0	0	0	4	0	0	0	7
slight	0	0	0	21	0	0	0	7
moderate	0	0	0	2	0	0	0	0

[a]data taken from Table 12A, pages 141-164 of the report.

While there was a suggestion of some sciatic nerve degeneration, this was characerized mainly as slight when looking at the data from a dose-response viewpoint. Extramedullary hemopoiesis in the spleen was also observed in increased incidence at the high dose, but the dose-response relationship was not consistent. The strongest evidence for a treatment-related effect in those mice sacrificed or dying during the study was found in the urinary bladder, where increased incidence of epithelial hyperplasia, eosinophilic/hyaline cytoplasmic inclusions, increased submucosal tissue, and submucosal hyalinization were all found at the 0.23 mg/ml dose level in both sexes.

Table 11b

Histopathologic Findings in Metam Sodium Treated Mice[a]

	Males (mg/ml)				Females (mg/ml)			
	0.0	0.019	0.074	0.23	0.0	0.019	0.074	0.23
Terminal Sacrifice								
No. examined	21	20	27	19	28	25	17	21
sciatic nerve								
demyelination	15	18	24	15	20	21	16	16
minimal	11	9	12	7	12	11	7	8
slight	3	9	11	8	7	9	8	8
urinary bladder								
no. examined	21	20	27	20	27	24	19	22
epithelial hyperplasia								
total	0	0	0	19	0	0	8	21
minimal	0	0	0	3	0	0	5	6
slight	0	0	0	16	0	0	3	14
moderate	0	0	0	0	0	0	0	1
eosinophilic/hyaline cytoplasmic inclusions								
total	0	0	26	8	2	23	18	19
minimal	0	0	8	3	2	21	6	8
slight	0	0	16	5	0	2	10	10
moderate	0	0	2	0	0	0	2	1

Table 11b, cont.

	Males (mg/ml)				Females (mg/ml)			
	0.0	0.019	0.074	0.23	0.0	0.019	0.074	0.23
increased submucosal connective tissue								
total	0	0	0	1	0	0	2	4
slight	0	0	0	0	0	0	2	3
moderate	0	0	0	1	0	0	0	1
submucosal hyalinization								
total	0	0	0	18	0	0	1	12
minimal	0	0	0	1	0	0	0	3
slight	0	0	0	12	0	0	1	8
moderate	0	0	0	5	0	0	0	1

[a]data taken from Table 12A, pages 165-183 of the report.

As shown above for those mice surviving to study termination, similar non-neoplastic observations were present, including the changes observed in the urinary bladder in those mice sacrificed while on study. Of interest is the observation that a similar dose-response pattern appeared with regard to urinary bladder non-neoplastic pathology in both the terminal sacrifice groups and those sacrificed while on study, i.e. notable increases occurred mainly at the high dose when considering the total number of mice with a given lesion.

Table 11c summarizes the non-neoplastic observations in all mice combined (see next page):

Table 11c

Histopathologic Findings in Metam Sodium Treated Mice[a]

	Males (mg/ml)				Females (mg/ml)			
	0.0	0.019	0.074	0.23	0.0	0.019	0.074	0.23
All Animals								
Urinary Bladder								
no. examined	54	55	55	55	54	52	53	55
epithelial hyperplasia								
total	0	0	2	45	0	0	10	44
minimal	0	0	0	15	0	0	7	17
slight	0	0	2	29	0	0	3	26
moderate	0	0	0	1	0	0	0	1
mononuclear cell infiltration								
total	8	7	5	32	34	25	21	29
minimal	7	7	3	24	14	18	16	13
slight	1	0	2	7	17	7	3	13
moderate	0	0	0	1	3	0	2	3
eosinophilic/hyaline cytoplasmic inclusions								
total	0	5	50	33	5	42	51	47
minimal	0	2	11	12	5	37	13	17
slight	0	3	29	13	0	5	23	22
moderate	0	0	8	7	0	0	14	7
marked	0	0	2	1	0	0	1	1
increased submucosal connective tissue								
total	1	0	0	11	0	0	2	19
minimal	0	0	0	2	0	0	0	4
slight	1	0	0	6	0	0	2	9
moderate	0	0	0	3	0	0	0	6
submucosal hyalinization								
total	0	0	0	45	0	0	1	26
minimal	0	0	0	5	0	0	0	10
slight	0	0	0	33	0	0	1	15
moderate	0	0	0	7	0	0	0	1

Table 11c, cont.

	Males (mg/ml)				Females (mg/ml)			
	0.0	0.019	0.074	0.23	0.0	0.019	0.074	0.23
All Animals								
Liver								
No. examined	55	55	55	55	55	55	55	55
fat vacuolation								
total	4	2	5	20	1	0	1	6
minimal	3	1	1	1	0	0	0	2
slight	1	1	4	10	1	0	1	3
moderate	0	0	0	9	0	0	0	1

[a]data taken from Table 12B, pages 184-212 of the report.

When all mice were considered together, the liver and urinary bladder were found to be the main sites of non-neoplastic pathology. At the 0.23 mg/ml dose level, increased incidence of epithelial hyperplasia, mononuclear cell infiltration, eosinophilic/hyaline cytoplasmic inclusions, submucosal connective tissue, and submucosal hyalinization were observed in both sexes in the urinary bladder. In the liver, increased incidence of hepatocyte fat vacuolation was observed at the 0.23 mg/ml dose level in both male and female mice.

1b) Neoplastic Observations

Table 12a

Neoplastic Findings in Metam Sodium Treated Mice[a]

	Males (mg/ml)				Females (mg/ml)			
	0.0	0.019	0.074	0.23	0.0	0.019	0.074	0.23
Intercurrent Deaths								
No. examined	34	35	28	35	26	30	36	33
Liver								
hepatocellular adenoma (benign)	0	0	0	2	0	0	0	0

Table 12a, cont.

	Males (mg/ml)				Females (mg/ml)			
	0.0	0.019	0.074	0.23	0.0	0.019	0.074	0.23
hepatocellular carcinoma	0	0	1	0	1	0	0	0
angiosarcoma (malignant)	0	2	2	3	0	0	0	1
Spleen								
angiosarcoma (malignant)	4	2	6	12	0	1	2	2
Urinary Bladder								
transitional cell papilloma (benign)	0	0	0	1	0	0	0	0

adata taken from Table 15a, pages 223-227 of the report.

Table 12b

Neoplastic Findings in Metam Sodium Treated Mice[a]

	Males (mg/ml)				Females (mg/ml)			
	0.0	0.019	0.074	0.23	0.0	0.019	0.074	0.23
Terminal Sacrifice								
No. examined	21	20	27	20	28	25	19	22
Liver								
hepatocellular adenoma (benign)	0	0	1	0	0	0	0	2
angiosarcoma (malignant)	0	4	1	4	0	0	1	2

Table 12b, cont.

	Males (mg/ml)				Females (mg/ml)			
	0.0	0.019	0.074	0.23	0.0	0.019	0.074	0.23
Spleen								
No. examined	21	20	27	20	28	25	19	22
angiosarcoma (malignant)	1	0	2	3	0	0	1	2
Urinary Bladder								
transitional cell carcinoma (malignant)	0	0	0	0	0	0	0	1

adata taken from Table 15a, pages 228-231 of the report.

Table 12c

Neoplastic Findings in Metam Sodium Treated Mice[a]

	Males (mg/ml)				Females (mg/ml)			
	0.0	0.019	0.074	0.23	0.0	0.019	0.074	0.23
All Animals								
No. examined	55	55	55	55	55	55	55	55
Liver								
hepatocellular adenoma (benign)	0	0	1	2	0	0	0	2
hepatocellular carcinoma (malignant)	0	0	1	0	1	0	0	0
angiosarcoma (malignant)	0	6	3	7	0	0	1	3

Table 12c, cont.

	Males (mg/ml)				Females (mg/ml)			
	0.0	0.019	0.074	0.23	0.0	0.019	0.074	0.23
Spleen								
No. examined	55	55	55	55	55	55	55	55
angiosarcoma (malignant)	5	2	8	15	0	1	3	4
Subcutaneous Tissue								
No. examined	6	5	4	7	4	4	2	5
angiosarcoma (malignant)	1	1	1	3	0	1	1	3
Urinary Bladder								
transitional cell carcinoma (malignant)	0	0	0	0	0	0	0	1
transitional cell papilloma (benign)	0	0	0	1	0	0	0	0

[a]data taken from Table 15b, pages 232-237 of the report.

For the mice sacrificed while on study and those surviving to study termination, the sites of tumorigenicity were similar. These involved the liver (hepatocellular adenoma and carcinoma, angiosarcoma), spleen (angiosarcoma), and urinary bladder (transitional cell pappiloma and carcinoma).

As shown for all animals considered (Table 12c, above), there was an increased incidence of angiosarcoma in the liver for male mice at all dose levels in comparison to concurrent controls. Females showed an increased incidence of this neoplasm at the 0.23 mg/ml dose level only.

Increased incidence of angiosarcoma was also observed in the spleen at the 0.074 and 0.23 mg/ml dose levels for both male and female mice. At the 0.074 mg/ml dose level, 8/55 male mice (14.5%) and 3/55 (5%) of female mice were observed with this lesion, compared to 9% of male mice and 0% of female mice. At 0.23 mg/ml, 15/55 male mice (27%) and 4/55 female mice (7%) were observed with angiosarcoma of the spleen.

Increased incidence of angiosarcoma was also observed in the subcutaneous tissue of male and female mice at the 0.23 mg/ml dose level, where 3/55 mice (5%) per sex were observed with this lesion vs 0% in controls.

The report stated that the question of whether the angiosarcomas observed at multiple sites represented primary tumors with metastatic deposits or multicentric tumors was debatable. In addition, it was stated that it was technically difficult to accurately identify the primary site of the tumor. Thus, the total number of mice with angiosarcoma regardless of site was considered appropriate as a representation of this neoplastic lesion. This is summarized below from page 29 of the report:

	Overall incidence of mice with angiosarcoma in any site			
	0.00mg/ml	0.019mg/ml	0.074mg/ml	0.23mg/ml
Males	7/55	12/55	12/55	27/55
Females	4/55	2/55	6/55	10/55

In males, the incidence of angiosarcoma in controls (12%) increased to 21% at the 0.019 and 0.074 mg/ml dose levels, and to 49% at the 0.23 mg/ml dose level. In female mice, the incidence in controls (7%) was exceeded only by the incidence at 0.074 mg/ml (11%) and 0.23 mg/ml (18%). According to the report, there was no treatment-related change in tumor latency for this tumor type.

A transitional cell papilloma of the urinary bladder was observed in one male mouse at the 0.23 mg/ml dose level, as well as a transitional cell carcinoma in one female mouse at the 0.23 mg/ml dose level. The treatment-related increase in angiosarcoma in a variety of sites was found to be a factor contributory to death for those mice receiving 0.23 mg/ml metam sodium in drinking water.

III. DISCUSSION

This study examined the carcinogenicity of Metam Sodium technical in male and female C57BL/10JfCD-1/Alpk mice through administration of the test material in drinking water. Dose levels used were 0, 0.019, 0.074, and 0.23 mg/ml, corrected for test article purity (43.14% a.i.). Actual doses received, based on available data demonstrating decomposition of test article in water over 24 hours, were **1.6 mg/kg, 6.5 mg/kg,** and **27.7 mg/kg** for male mice, and **2.3 mg/kg, 8.7 mg.kg,** and **29.9 mg/kg** for female mice. The study was conducted according to Subdivision F guideline §83-2 without any significant deviation.

There were no significant detrimental effects of treatment with metam sodium on survival in male and female mice at any dose level used in this study. Clinical signs in treated male and female mice were also unremarkable. Absolute group mean body weight was decreased by 4-8% in high dose male mice from about week 2 of the study until study termination, while absolute body weight in high dose female mice was decreased approximately 2-3% at the high dose vs controls. However, the decreases in absolute body weight for female mice were not as frequent as those observed for males in considering week to week decreases.

In contrast to absolute body weight, weight gain for high dose male mice was decreased by 14% for weeks 1-13 and by 20% for the entire study period. The effects in females, as for absolute body weight, were not as pronounced and did not exceed 10% of control at any of the times shown above.

For weeks 1-13, food consumption and efficiency were unaffected in male and female mice at any dose level of metam sodium. At later times in the study, statistically significant decreases in food consumption were recorded for male mice at the 0.074 and 0.23 mg/ml dose levels, during weeks 24 to 52, although these data were only reported every 4 weeks during this time. Decreases in food consumption were not observed in female mice during this time. The decreases in food consumption, while reported as significant, were similar to the body weight decreases (~ 5%).

Water consumption in male and female mice was decreased during the first week of the study, and was statistically significant at the 0.23 mg/ml dose level for both sexes, and at all dose levels for male mice. The trend for decreased water consumption continued in male mice for the first 2 weeks of the study, and then by week 9, was significantly increased at the high dose. By week 11, water consumption was significantly increased at both the 0.074 and 0.23 mg/ml dose levels compared to control intake in male mice. Significantly increased water intake was observed at the 0.23 mg/ml dose level in male mice throughout the rest of the study.

In female mice, water consumption at the high dose tended to be decreased relative to control, but statistical significance was not consistently achieved. In addition, by about week 48 of the study, water consumption at all dose levels vs control was approximately equal, and by about week 75, water consumption in high dose females was slightly increased over control values. The significance of these changes is unknown at this time.

Hematological investigation showed no significant treatment-related effect in this study for either male or female mice. Macroscopic observations showed several changes at the 0.23 mg/ml dose level in both male and female mice, including accentuated lobular pattern and pale appearance of the liver, subcutaneous tissue masses, thickened wall of the urinary bladder, and a reduction in the incidence of enlarged seminal vesicles.

Absolute and relative weight of the liver was noted to be increased in both male and female mice at the 0.074 and 0.23 mg/ml dose levels, and was cited as statistically significant. The increase in liver weight for male mice was 11% and 35% over control at the 0.074 and 0.23 mg/ml dose levels, respectively, while the increase for female mice was 19% and 22% over control at these same dose levels.
Absolute weight of the epidiymides in male mice displayed a dose-related decrease, consistent with the observation of a decreased incidence of enlarged seminal vesicles. Kidney weight, while decreased by 9% in male mice at the 0.074 and 0.23 mg/ml dose levels, was increased by approximately the same percentage in female mice at these dose levels. There were no other significant organ weight changes reported in this study.

Microscopic examination of tissues showed several non-neoplastic effects in male and female mice at the 0.23 mg/ml dose level, and included extramedullary hemopoiesis of the spleen, hyperplasia of the bladder epithelium, eosinophilic/cytoplasmic inclusions of the bladder epithelium, increased submucosal connective tissue and hyalinization of the bladder epithelium, and hepatocyte fat vacuolation of the liver.

There was evidence for carcinogenicity of metam sodium in this study. In both male and female mice at the 0.23 mg/ml dose level, there was an increased incidence of hepatic adenoma and angiosarcoma, splenic angiosarcoma, subcutnaeous tissue angiosarcoma, and a single incidence each of a transitional cell papilloma in one high dose male mouse and a transitional cell carcinoma in one high dose female mouse. The overall incidence of mice with angiosarcoma regardless of site was increased in both high dose male and female mice. The treatment-related increase in angiosarcoma was also considered a factor contributory to death for animals in the 0.23 mg/ml dose group. By way of comparison, historical control data were provided for angiosarcoma at all sites from 9 studies presumably conducted at the same laboratory using the same strain of mouse. These data (attached to this review) show that the incidence of angiosarcoma at the high dose in this study exceeded that found from historical control data. However, it also appears that the incidence of angiosarcoma in the spleen could be considered significant at the 0.074 mg/ml dose level, unless this is an inappropriate designation based on the registrant's argument that the primary site(s) of angiosarcoma are difficult to determine.
The dosing in this study was considered adequate for male mice, based on the significant decrease in body weight gain observed for weeks 1-13 of this study, and the increased liver weight with accompanying pathology at the 0.23 mg/ml dose level. In females, dosing was not considered adequate for this study. Although increases in liver weight and accompanying pethology were observed at the 0.23 mg/ml dose level, there were no other systemic effects

in female mice, despite the appearance of tumors. A subchronic toxicity study in mice (MRID # 421173-01) identified an MTD of 0.62 mg/ml for female mice based on decreases in body weight gain at that dose in the 90-day study, with no significant effects observed at the next lowest dose (0.35 mg/ml). It is of interest in this regard that both the subchronic and carcinogenicity studies display apparent sex specific sensitivity to metam sodium. In both studies, males appear more sensitive than females to the systemic effects at similar doses.

Based on the significant increase observed in liver weight in male and female mice, **the LEL is considered to be 0.074 mg/ml. The NOEL is considered to be 0.019 mg/ml.**

Carcinogenic potential was evidenced in this study by an increase in the incidence of angiosarcoma of the liver, spleen, and subcutaneous tissue, as well as the presence of a transitional cell papilloma in a single high dose male, and a transitional cell carcinoma in a single high dose female.

Dosing was considered adequate in male mice based upon the decrease in body weight gain, increase in liver weight with accompanying pathology, increased incidence of non-neoplastic urinary bladder pathology, and increase in angiosarcoma incidence observed at the 0.23 mg/ml dose level. Dosing was considered adequate in female mice based on the increased incidence of non-neoplastic urinary bladder pathology and angiosarcoma at the 0.23 mg/ml dose level.

IV. Classification

This study is classified **core minimum** and satisfies the guideline requirement for §83-2, Carcinogenicity Study in Mice.

TOX Review 011139 Metam Sodium

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