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OFFICE OF  
PREVENTION, PESTICIDES AND  
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Metam Sodium: Review of a Subchronic Neurotoxicity Study in Rats

P.C. Code: 039003  
Submission: S468269  
MRID No: 432488-01  
DP Barcode: D204586

FROM: Timothy F. McMahon, Ph.D., Pharmacologist *T.F. McMahon 8/25/94*  
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THRU: Yiannakis M. Ioannou, Ph.D., Section Head *Y.M. Ioannou 8/25/94*  
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) *M. Van Gemert 8/29/94*

Registrant: Metam Sodium Task Force

Action Requested: Review of a Subchronic Neurotoxicity Study with Metam Sodium.



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**Summary:**

The subchronic neurotoxicity of metam sodium was examined in male and female Sprague-Dawley rats. Doses of 0, 0.02, 0.06, and 0.2 mg/ml were administered in drinking water for 13 weeks (doses in mg/kg: 1.4, 5.0, and 12.8 mg/kg for males; 2.3, 7.0, and 15.5 mg/kg for females). Body weight, food consumption, clinical signs, and water consumption were monitored throughout the study. A functional observational battery (including landing foot splay, sensory perception, fore- and hindlimb grip strength) as well as motor activity and histopathology of the nervous system was also performed.

Effects in this study were limited to decreases in body weight for male and female rats at the 0.2 mg/ml dose level (decreases of 7-9% from control), body weight gain (decrease of 14% for males at the 0.2 mg/ml dose level and females at the 0.06 mg/ml dose level; decrease of 18-21% for females at the 0.2 mg/ml dose level), food consumption (decreases similar to body weight), food efficiency (5-7% decrease in males and females at 0.2 mg/ml), and water consumption (decreased at all doses but in a dose-related fashion; up to 60% decreased at the 0.2 mg/ml dose). There appeared to be a mild effect at the 0.2 mg/ml dose level on time to tail flick in male rats, but this was not labeled as statistically significant. There were no other significant findings to report from the conduct of the Functional Observational Battery.

Based on the data in this study, the **systemic LEL = 0.2 mg/ml** for male rats and **0.06 mg/ml** for female rats (decreased body weight gain), and the **systemic NOEL = 0.06 mg/ml** for male rats, and **0.02 mg/ml** for female rats. There was no evidence of a neurotoxic effect for metam sodium in this study.

**Classification:** core minimum

This study satisfies the guideline requirement (§82-7) for a subchronic neurotoxicity study in rats.

Reviewed by: Timothy F. McMahon, Ph.D. *T.F.M. 8/25/94*  
Section I, Toxicology Branch II (7509C)  
Secondary Reviewer: Yiannakis M. Ioannou, Ph.D. *Y.M.I. 8/25/94*  
Section I, Toxicology Branch II (7509C)

Data Evaluation Record

Study type: Subchronic Neurotoxicity - rats  
Guideline: § 82-7

EPA ID Numbers:                   MRID number: 432488-01                   Submission: S468269  
  DP Barcode: D204586                   PC Code: 039003

Test material:                   Sodium N-methyldithiocarbamate

Synonyms:                        Metam-sodium

Study number(s):                CTL/P/4334

Sponsor:                        Metam Sodium Task Force, Los Angeles, California

Testing Facility:                Zeneca Central Toxicology Laboratory, UK

Title of reports:                Metam Sodium: Subchronic Neurotoxicity Study in Rats

Study Director:                 S. L. Allen

Studies Completed:            May 5, 1994

Executive Summary:   In a subchronic neurotoxicity study (MRID # 432488-01), groups of 12 male and 12 female Sprague-Dawley rats were administered metam sodium in drinking water for 13 weeks at doses of 0, 0.02, 0.06, and 0.2 mg/ml. Viability, clinical signs, body weights, functional observational battery, and motor activity evaluations were performed.

Selected nervous system tissues were examined microscopically at study termination.

Body weight gain was decreased by 14% in male rats at 0.2 mg/ml, and by 14% in female rats at 0.06 mg/ml over the 13 week study period. A mild effect on time to tail flick was also observed in male rats at 0.2 mg/ml metam sodium. There were no other significant observations to report from the functional observational battery. Histopathological examination of brain and nervous tissue showed no evidence of neurotoxicity from metam sodium administration.

Based on the data in this study, the **systemic LEL** = 0.2 mg/ml for male rats and 0.06 mg/ml for female rats (decreased body weight gain), and the **systemic NOEL** = 0.06 mg/ml for male rats, and 0.02 mg/ml for female rats. There was no evidence of a neurotoxic effect for metam sodium in this study.

Classification: Core minimum

This study satisfies the guideline requirement (§82-7) for a subchronic neurotoxicity study in rats.

I. MATERIALS AND METHODSA. Test Material: Metam Sodium

purity: 43.15%

CTL reference no. YO6930/008

description: yellow aqueous solution

storage: Under inert gas in sealed glass containers in the dark at room temperature

B. Vehicle: deionized waterC. Test Animals: Species: rat, male and female Alpk:APfSD

Source: SPF breeding colony at Zeneca Pharmaceuticals

Age: supplied as weanlings (at least 27 days old)

Weight range (week -1): males, 124-164g; females, 105-133g

D. Animal Husbandry:

Rats were housed in groups of 4 (sexes separate) in stainless steel cage racks with wire mesh floors, backs, and one side (the other side was solid stainless steel). Food (CT1 diet, Special Diet Services, Ltd.) and pH adjusted drinking water (prior to study start) were supplied ad libitum.

Conditions of temperature and humidity were stated as 19-23 °C and 40-70%, respectively. Accomodation period was 2 weeks, during which rats were randomly allocated to cages. Room air changes were 25-30 changes per hour, and light/dark cycle was 12 hours. Each rat was uniquely identified by ear punch using the number assigned by experimental design.

E. Experimental Design and Dosing:

Treatment of rats commenced between the 20th and 22nd of July 1993.

In the study, animals were assigned by computer-based randomization to four separate dose groups as follows:

Group	Dose (mg/ml)	Dose (mg/kg/day) <sup>a</sup>		Males	Animals
		M	F		Females
1	0	0	0	1-12	49-60
2	0.02	1.4	2.3	13-24	61-72
3	0.06	5.0	7.0	25-36	73-84
4	0.2	12.8	15.5	37-48	85-96

<sup>a</sup>based on average % decomposition over 24 hours (Appendix H, pages 85-89 of the report; see below).

F. Homogeneity and Stability:

Stability data for metam sodium in drinking water at each of the concentrations used in this study was presented in Appendix H, pages 85-89 of the report. These data illustrate decomposition of the test material in drinking water over a 24 hour period, especially at lower concentrations of test material. This has been observed in every other drinking water study submitted on metam sodium. Therefore, as has been the practice, the average % decomposition over the course of the study in conjunction with the average % nominal concentration achieved in the drinking water dose solutions will be used to determine the actual doses received by the animals in this study:

nominal dose x avg. % decomp. x avg. % nominal = approximate actual dose.

G. Statistical Analysis:

A copy of the statistical procedures used in this study is attached to this review.

H. Compliance:

A signed statement of compliance with Good Laboratory Practices was provided.

A signed statement of No Data Confidentiality Claims was provided.

A signed Quality Assurance Statement was provided.

A signed statement of EPA Flagging Criteria under 40 CFR §158.34 was provided. The report stated that the study neither meets nor exceeds any of the applicable criteria.

## II. OBSERVATIONS AND RESULTS:

1) **Clinical Observations and Mortality:** Rats were examined prior to the start of the study to ensure that they exhibited normal activity. During the study, rats were observed daily for changes in clinical condition and behavior. At weekly intervals, each rat was removed from its cage and physically examined for changes in general health status.

Data summarizing general clinical observations were presented in Table 8, pages 54-56. These data showed no alterations in general clinical condition in any dose group over the course of the study.

There were no reported deaths in this study.

2) **Body Weight:** Individual body weights were recorded in replicate order prior to study initiation (week -1), immediately prior to administration of experimental drinking water (week 1) and then on the same day of each subsequent week until study termination. Group mean body weights for male and female rats are summarized below (Table 1a):

**Table 1a**  
Adjusted Group Mean Body Weight in Metam Sodium Treated Rats  
in a Subchronic Neurotoxicity Study<sup>a</sup>

<u>Study Week</u>				
<u>Males</u>	<u>0 mg/ml</u>	<u>0.02 mg/ml</u>	<u>0.06 mg/ml</u>	<u>0.2 mg/ml</u>
1	199.1± 15.7	193.8± 14.9	195.8± 9.2	194.9± 14.4
7	420± 27.6	421.3± 28.2	416.8± 16.7	385.2±** 31.0
13	525.9± 32.5	531.0± 34.9	525.1± 26.2	475.6±** 50.3
<u>Females</u>	<u>0 mg/ml</u>	<u>0.02 mg/ml</u>	<u>0.06 mg/ml</u>	<u>0.2 mg/ml</u>
1	153.7± 6.0	152.3± 5.3	151.6± 8.5	153.3± 10.8
7	242.1± 15.8	235.6± 14.6	227.7±** 14.5	223.1±** 18.1
13	274.2± 17.7	262.9±* 18.1	255.6±** 15.9	251.7±** 20.5

<sup>a</sup>data taken from Table 4, pages 44-47 of the report. \* p < 0.05 vs control;  
\*\* p < 0.01 vs control; N=12.



Statistically significant decreases in group mean body weight gain were observed in both male and female rats at the 0.2 mg/ml dose level throughout the study, and in female rats at the 0.06 mg/ml dose level from week 4 of the study until termination. The decreases did not exceed 10% of control group mean weight at any time, but were usually between 7-9% of control.

**Table 1b**  
Adjusted Group Mean Body Weight Gain in Metam Sodium Treated Rats  
in a Subchronic Neurotoxicity Study<sup>a</sup>

<u>Study Week</u>				
<u>Males</u>	<u>0 mg/ml</u>	<u>0.02 mg/ml</u>	<u>0.06 mg/ml</u>	<u>0.2 mg/ml</u>
1	199.1± 15.7	193.8± 14.9	195.8± 9.2	194.9± 14.4
<u>weight gain</u>				
1-7 % cont.	220.9 -	227.5 102	221.0 100	190.3 86
1-13 % cont.	326.8 -	337.2 103	329.3 100	280.7 86
<u>Females</u>	<u>0 mg/ml</u>	<u>0.02 mg/ml</u>	<u>0.06 mg/ml</u>	<u>0.2 mg/ml</u>
1	153.7± 6.0	152.3± 5.3	151.6± 8.5	153.3± 10.8
<u>weight gain</u>				
1-7 % cont.	88.7 -	83.3 94	76.1 86	69.8 79
1-13 % cont.	120.5 -	110.6 92	104.0 86	98.4 82

<sup>a</sup>data calculated from Table 1a above. \* p < 0.05 vs control; \*\* p < 0.01 vs control; N=12.

In male rats, body weight gain for both the 1-7 study week period as well as the 1-13 week period was decreased to 86% of control at the 0.2 mg/ml dose level. There were no effects on body weight gain in male rats at lower doses of metam sodium.

In female rats, body weight gain at the 0.2 mg/ml dose level was decreased to 79% of control for weeks 1-7, and to 82% of control for weeks 1-13. At the 0.06 mg/ml dose level, body weight gain for weeks 1-7 and weeks 1-13 was decreased to 86% of control.

### 3) Food Consumption

Food consumption was recorded for each cage of rats continuously throughout the study and was calculated on a weekly basis. Food efficiency was calculated as the body weight gained by the rats in the cage per 100 g food eaten. Summary of food consumption is made below:

**Table 2**  
Food Consumption (g/rat/day) in Metam Sodium Treated Rats  
in a Subchronic Neurotoxicity Study<sup>a</sup>

<u>Study Week</u>		<u>0 mg/ml</u>	<u>0.02 mg/ml</u>	<u>0.06 mg/ml</u>	<u>0.2 mg/ml</u>
<u>Males</u>					
1		27.2± 0.6	26.6± 0.5	26.5± 0.7	23.3±*** 0.2
7		30.0± 1.5	29.9± 0.7	29.9± 0.2	27.2±* 0.5
% cont.		-	100	100	91
13		30.5± 2.0	30.5± 0.5	30.5± 0.6	28.3±* 0.8
% cont.		-	100	100	93
<u>Females</u>					
1		20.3± 0.2	19.3± 0.3	19.7± 1.3	17.6±** 1.0
7		20.6± 0.1	19.6± 0.6	18.4±*** 0.5	18.0±** 1.2
% cont.		-	95	89	87
13		20.3± 0.2	19.2±* 0.6	18.6±*** 0.5	18.1±** 1.0
% cont.		-	95	92	89

a- data from Table 5, pages 48-49 of the report. \*p <0.05 vs control; \*\*p <0.01 vs. control.

As the above data show (taken from Table 5, pages 48-49 of the report), decreases in food consumption were observed at the 0.2 mg/ml dose level in male rats during the study, and for female rats at the 0.06 and 0.2 mg/ml dose levels. The decreases did not exceed 10% in male rats, but were decreased to approximately 90% of control in female rats at the 0.06 mg/ml dose level, and to approximately 88% of control in female rats at the 0.2 mg/ml dose level. These decreases in food consumption are in close agreement with the decreases in body weight, but decreases in body weight gain are in excess of the decrease in food consumption, suggesting some type of test article related toxicity. Food efficiency data measured over the course of this study indicate a mild (~ 5% decrease) but significant effect in male rats at the 0.2 mg/ml dose level for the 13 week study period, and in female rats, food efficiency was also reduced by approximately 10% at the 0.2 mg/ml dose level for the first 8 weeks of the study. Overall food efficiency in female rats was decreased by approximately 7% for weeks 1-13.

The changes in food efficiency may not be actually indicative of toxic effects, as for females, efficiency was reduced at all dose levels by approximately the same percentage, while in males, the approximate 5% decrease for overall food efficiency does not support the changes observed in body weight gain. Food efficiency may have been influenced to some degree by the observed decrease in water consumption in treated rats of both sexes, as will be summarized in a subsequent section .

#### 4) Water Consumption

**Table 3**  
Water Consumption (ml/rat/day) in Male and Female Rats  
Receiving Metam Sodium in Drinking Water for 13 Weeks<sup>a</sup>

Weeks of Study	Males (mg/ml)				Females (mg/ml)			
	0.0	0.02	0.06	0.2	0.0	0.02	0.06	0.2
week 1	31.6± 1.6	32.1± 3.6	30.4± 3.3	23.1±* 0.6	27.5± 3.2	29.4± 6.9	23.2± 1.1	16.8±* 0.9
week 13	48.2± 1.5	42.3±* 3.6	42.3±* 4.0	27.9±* 1.6	57.0± 8.7	41.4±* 6.8	36.0±** 4.8	20.4±** 0.3
weeks 1-13	45.1	38.4	39.0	26.2	47.9	37.6	30.9	19.3
% cont.	-	85	86	58	-	78	64	40

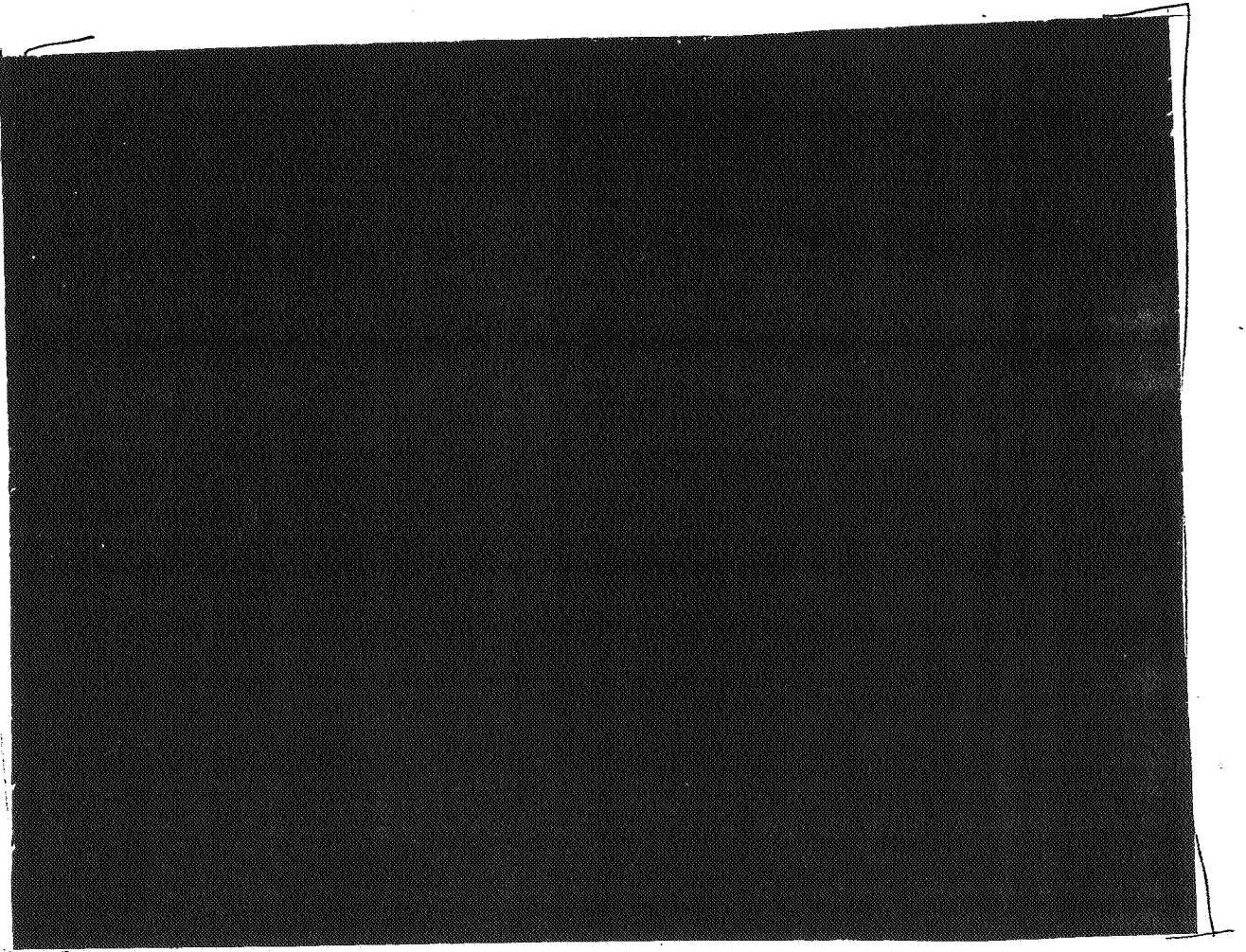
<sup>a</sup>data taken from Table 7, pages 51-52 of the report. N=3 (measured by cage).  
\* p < 0.05 vs control; \*\* p < 0.01 vs control.

Water consumption was affected primarily at the 0.2 mg/ml dose level in both sexes, with dramatic decreases observed over the 13 week study period. The toxicological implications of this effect may be relevant in terms of decreased food intake and efficiency, but the ultimate effect on toxicity of metam sodium in this study was not specifically addressed.

#### 5) Functional Observational Battery

Pages 16 through 18 of the report, reproduced here, summarize the procedures used for the Functional Observational Battery, including motor activity measurements and histopathology of the brain, relevant ganglia, muscles, and nerves.

*FIFRA Registration Data is not included.*



Tox Review 011203

Metam Sodium

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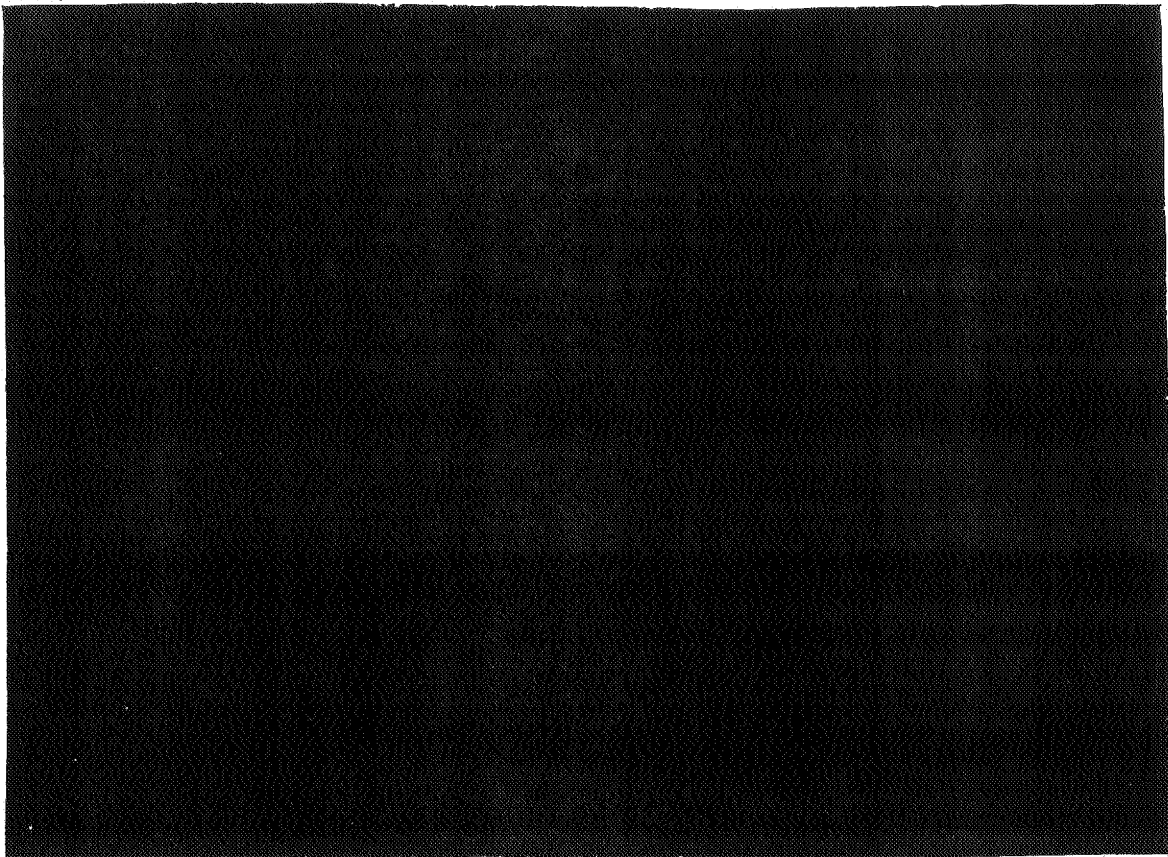
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a) Landing Foot splay

Data summarizing landing foot splay were presented in Table 9, page 57 of the report. Aside from a statistically significant reduction observed in male rats at the 0.2 mg/ml dose level at week 9, there were no significant differences in landing foot splay among treated vs control rats.

b) Time to Tail Flick

Data summarizing time to tail flick were presented in Table 10, page 58 of the report. There appeared to be a slight increase in time to tail flick for male rats at weeks 9 and 13 at the 0.2 mg/ml dose (increased from 3.7 to 4.9 sec at week 9; increased from 5.0 to 5.9 at week 13). These were not labeled as statistically significant, but appear to indicate a mild effect at the 0.2 mg/ml dose in males.

c) Forelimb and Hindlimb Grip Strength

Data summarizing forelimb and hindlimb grip strength were presented in Tables 11A and 11B, pages 59-60 of the report. There were no significant treatment-related changes other than a significant decrease in forelimb grip strength for females at week 13 in the 0.06 mg/ml dose level, a significant decrease in hindlimb grip strength for male rats at week 5 in the 0.2 mg/ml dose level, and a significant decrease in hindlimb grip strength for female rats at week 9 in the 0.06 mg/ml dose level. There was no consistent pattern to these alterations, and thus they were not considered treatment-related.

#### d) Motor Activity

Data summarizing motor activity were presented in Table 12, page 61-68 of the report. During week 5, a significant increase was observed in overall motor activity for female rats at the 0.06 mg/ml dose level, but subsequent measurements showed no significant alterations in motor activity. Males showed no significant changes in motor activity over the study period.

#### e) Brain Parameters

Data summarizing brain parameters were presented in Table 13, pages 69-71 of the report. There were no significant alterations in brain weight, length, or width in male and female rats examined at all dose levels in this study.

#### e) Macroscopic and Microscopic Pathology

Data summarizing macroscopic and microscopic pathology were presented in Tables 14 and 15, pages 72 and 73 of the report. There were no significant observations reported.

### Discussion/Conclusions

In the present study, the subchronic neurotoxicity of metam sodium was examined in male and female Sprague-Dawley rats. Doses of 0, 0.02, 0.06, and 0.2 mg/ml were administered to male and female rats in drinking water for 13 weeks (doses in mg/kg: 1.4, 5.0, and 12.8 mg/kg for males; 2.3, 7.0, and 15.5 mg/kg for females). Effects in this study were limited to decreases in body weight for male and female rats at the 0.2 mg/ml dose level (decreases of 7-9% from control), body weight gain (decrease of 14% for males at the 0.2 mg/ml dose level and females at the 0.06 mg/ml dose level; decrease of 18-21% for females at the 0.2 mg/ml dose level), food consumption (decreases similar to body weight), food efficiency (5-7% decrease in males and females at 0.2 mg/ml), and water consumption (dose-related decreases up to 60% at the 0.2 mg/ml dose). There appeared to be a mild effect at the 0.2 mg/ml dose level on time to tail flick in male rats, but this was not labeled as statistically significant. There were no other significant findings to report from the conduct of the Functional Observational Battery.

Based on the data in this study, the **systemic LEL** = 0.2 mg/ml for male rats and 0.06 mg/ml for female rats (decreased body weight gain), and the **systemic NOEL** = 0.06 mg/ml for male rats, and 0.02 mg/ml for female rats. There was no evidence of a neurotoxic effect for metam sodium in this study.

**Classification:** core minimum

This study satisfies the guideline requirement (§82-7) for a subchronic neurotoxicity study in rats.

Tox. Review 011202

metam Sodium

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