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

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APR 21 1994

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OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Metam Sodium: Review of a 2-Generation Reproduction Study in Rats Submitted by the Registrant.

Shaugnessey: 039003
Submission: S460441
MRID No: 431361-01
DP Barcode: D200464

FROM: Timothy F. McMahon, Ph.D., Pharmacologist 4/21/94
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THRU: Yiannakis M. Ioannou, Ph.D., Section Head
Review Section I, Toxicology Branch II
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Stephen C. Lapan for 4/20/94

and

Marcia Van Gemert, Ph.D., Branch Chief
Toxicology Branch II
Health Effects Division (7509C)
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Registrant: Metam Sodium Task Force

Action Requested: Review of a 2-generation reproduction study submitted in support of reregistration of metam sodium.

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Executive Summary:

In a multigeneration reproduction study, male and female Alpk:APfSD rats (30 / sex/dose), obtained from the Specific Pathogen Free (SPF) colony at the Barriered Animal Breeding Unit at Zeneca Pharmaceuticals, Alderley Park, Macclesfield, Cheshire, UK received the following doses of metam sodium in drinking water: at the 0.01 mg/ml dose level, **1.2 mg/kg/day** (males) and **1.8 mg/kg/day** (females); at the 0.03 mg/ml dose level, **3.2 mg/kg/day** (males) and **3.9 mg/kg/day** (females); at the 0.1 mg/ml dose level, **11.5 mg/kg/day** (males), and **13.5 mg/kg/day** (females). Test drinking water was administered continuously throughout the study. After the first 10 weeks, animals were mated on a one-to-one ratio. At 21 days of age, pups from the F_0 generation were selected as parents for the F_1 generation (30/sex/group).

Systemic toxicity was observed at the 0.1 mg/ml dose level in adult female rats of the F_0 and F_1 generations. This toxicity consisted of Bowman's gland duct hypertrophy with loss of alveolar cells, degeneration/disorganization and/or atrophy of the olfactory epithelium, and dilatation of the Bowman's gland ducts. The change in Bowman's glands was accompanied in all affected animals by degeneration, disorganization, and/or atrophy of the olfactory epithelium. In pups, findings were limited and observed mainly at the high dose. These consisted of a decrease in mean pup weight of 14% vs control on day 22 for the F_1 parents, a 16% decrease in body weight gain for male and female pups in the F_2 litter at the high dose, and decreases of 8-9% in testes and epididymis weights for male pups in the F_{1a} and F_{2a} litters at the high dose. **The NOEL for systemic toxicity is 0.03 mg/ml (3.2 mg/kg/day** (males) and **3.9 mg/kg/day** (females) **) and the systemic LOEL is 0.1 mg/ml (11.5 mg/kg/day** (males), and **13.5 mg/kg/day** (females) **)**.

There were no apparent effects of metam sodium on reproductive performance in the F_0 or F_1 generations in this study. **The NOEL for reproductive toxicity is 0.1 mg/ml and the LOEL for reproductive toxicity is $\geq$ 0.1 mg/ml.**

The study is classified as **core minimum data** and **satisfies** the guideline requirement (§83-4) for a multigeneration reproduction study in rats.

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Metam Sodium

Page _____ is not included in this copy.

Pages 3 through 4 are not included in this copy.

The material not included contains the following type of information:

_____ Identity of product inert ingredients.

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_____ The product confidential statement of formula.

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Reviewed by: Timothy F. McMahon, Ph.D. 4/20/94
Pharmacologist, Section I, Toxicology Branch II (7509C)
Secondary Reviewer: Stephen C. Dapson, Ph.D. Stephen C. Dapson 4/20/94
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Data Evaluation Record

Study type: Multigeneration Reproduction - Rat (§83-4)

EPA ID Numbers: MRID number: 431361-01
Submission: S460441
P.C. Code: 039003

Test material: Sodium N-methyldithiocarbamate

Synonyms: Metam sodium

Study number(s): RRO564/F0 ; RRO564/F1

Sponsor: Metam Sodium Task Force

Testing Facility: Zeneca Central Toxicology Laboratory

Title of report: Metam Sodium: Multigeneration Study in the Rat

Author(s): G.M. Milburn

Study Completed: December 23, 1993

Executive Summary:
In a multigeneration reproduction study (MRID # 431361-01), male and female Alpk:APfSD rats (30 / sex/dose), obtained from the Specific Pathogen Free (SPF) colony at the Barriered Animal Breeding Unit at Zeneca Pharmaceuticals, Alderley Park, Macclesfield, Cheshire, UK received the following doses of metam sodium in drinking water: at the 0.01 mg/ml dose level, **1.2 mg/kg/day** (males) and **1.8 mg/kg/day** (females); at the 0.03 mg/ml dose level, **3.2 mg/kg/day** (males) and **3.9 mg/kg/day** (females); at the 0.1 mg/ml dose level, **11.5 mg/kg/day** (males), and **13.5 mg/kg/day** (females). Test drinking water was administered continuously throughout the study. After the first 10 weeks, animals were mated on a one-to-one ratio. At 21 days of age, pups from the F_0 generation were selected as parents for the F_1 generation (30/sex/group).

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Systemic toxicity was observed at the 0.1 mg/ml dose level in adult female rats of the F_0 and F_1 generations. This toxicity consisted of Bowman's gland duct hypertrophy with loss of alveolar cells, degeneration/disorganization and/or atrophy of the olfactory epithelium, and dilatation of the Bowman's gland ducts. The change in Bowman's glands was accompanied in all affected animals by degeneration, disorganization, and/or atrophy of the olfactory epithelium. In pups, findings were limited and observed mainly at the high dose. These consisted of a decrease in mean pup weight of 14% vs control on day 22 for the F_1 parents, a 16% decrease in body weight gain for male and female pups in the F_2 litter at the high dose, and decreases of 8-9% in testes and epididymis weights for male pups in the F_{1a} and F_{2a} litters at the high dose. **The NOEL for systemic toxicity is 0.03 mg/ml (3.2 mg/kg/day** (males) and **3.9 mg/kg/day** (females)) **and the systemic LOEL is 0.1 mg/ml (11.5 mg/kg/day** (males), and **13.5 mg/kg/day** (females)).

There were no apparent effects of metam sodium on reproductive performance in the F_0 or F_1 generations in this study. **The NOEL for reproductive toxicity is 0.1 mg/ml and the LOEL for reproductive toxicity is $\geq$ 0.1 mg/ml.**

The study is classified as **core minimum data** and **satisfies** the guideline requirement (§83-4) for a multigeneration reproduction study in rats.

I. MATERIALS AND METHODS

A. Test Material: Metam Sodium
purity: supplied as an aqueous solution with purity stated as 43.148%
reference number: BAS/005/00N

B. Vehicle: drinking water

C. Test Animals: Species: Alpk: APfSD albino rats, male and female
Source: SPF colony at Zeneca Pharmaceuticals, UK
Age: supplied as weanlings (22 days old)
Weight: week 1 study weights (mean values) ranged between 66.0-67.3 grams for males, and 64.1-65.4 grams for females.

D. Animal Husbandry

A total of 33 litters of at least 4 males per litter and 33 litters of at least 4 females per litter were delivered to the testing laboratory on 22-23 October 1991. Rats were transported to the SPF Barriered Unit in sealed containers, and were introduced into the SPF unit via a dunk tank, ensuring the preservation of the SPF status of the rats. For 10 days following delivery, access to the animal room was restricted as a quarantine procedure. Rats were housed initially in litters, and then two rats of the same sex per cage after assignment to experimental groups and during pre-mating. Cages were of stainless steel construction with wire mesh floors, front, and back. Females were housed individually during gestation and lactation, and at approximately 15 days of gestation the cages housing the females were fitted with solid floors and supplied with paper bedding material. Females remained in these cages throughout gestation and lactation.

Environmental controls were set to maintain a temperature of 19-22 ^{o}C and average humidity of 45% with a 12 hour light/dark cycle. Food (CT1 diet, Special Diet Services, Witham, Essex) was supplied in glass jars ad libitum. Drinking water was supplied in polycarbonate bottles with a nominal capacity of 250ml. All drinking water was based on water purified by reverse osmosis with pH adjusted to approximately 8.0-9.0 using a small quantity of 0.5M phosphate buffer. Until the start of the experiment, F_0 rats were given buffered purified water ad libitum. All experimental drinking water was prepared in batches of several liters, and rats were supplied daily with a fresh bottle of the appropriate drinking water.

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E. Dietary Preparation and Analysis:

For each dose level of metam sodium, the appropriate amount of test substance was added to purified water, thoroughly mixed, and then the mixture dispensed into polycarbonate drinking bottles. Enough water was prepared to last each cage of rats one day, after which the bottles were removed and replaced with clean water bottles containing the next batch of freshly prepared drinking water.

Drinking water was analyzed twice a week in the first 2 weeks of the study, and then at least one batch was analyzed each month thereafter. Time course studies were also undertaken to investigate the pattern of stability of metam sodium in drinking water. Results of dosing solution achieved concentration and stability over a 24 hour period were presented in Tables 2 and 3, pages 79-85 of the report. These results are summarized below:

Table 1

Group No.	Nominal Concn. (mg/ml)	Number of batches analysed	Mean Concn. (mg/ml)	% of Nominal Concn.	Concn. range (mg/ml)
1	Control	15	ND		
2	0.01	16	0.0102	102.0	0.0078 - 0.0122
3	0.03	16	0.029	96.7	0.026 - 0.033
4	0.1	16	0.100	100.0	0.091 - 0.109

Limit of detection 0.005mg/ml ND - not detected.

Table 2

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

Group	Nominal Conc. (mg/ml)	Analyzed Conc.[b]	% Nominal
1	Control	ND	
2	0.01	0.0093	93
3	0.03	0.024	80
4	0.10	0.094	94

[a]data taken from pages 79-85 of the report. [b]values for analyzed concentration as well as % nominal concentration represent the mean of 13 measurements made at each dose level 24 hours after preparation of drinking water solutions.

As these data show, the average concentration at 24 hours after dose preparation in the drinking water was within 10% of nominal for the low and high dose (groups 2 and 4). For the mid dose group, an average analyzed concentration was found which was 80% of nominal. Thus, the concentrations of metam sodium given to the groups of rats in this study are considered as **0.009** mg/ml, **0.024** mg/ml, and **0.08** mg/ml, based on the stability data provided.

F. Procedures and Study Design

1) Mating:

Males and females from the same group were housed in adjacent cages during the period prior to mating to avoid anoestrus. During mating, one male was replaced with a female from the adjacent cage. Vaginal smears were examined daily to determine when mating had occurred. Any female with a positive smear was immediately separated from the male and individually housed. Any female failing to show evidence of mating during the 3 week mating period was re-mated with another proven male from the same treatment group after a rest period of at least 3 days. Males used in re-mating were ones which had shown positive evidence of mating with at least one female.

2) Mating schedule

According to the report, test drinking water was administered continuously throughout the study. Thus, it is assumed that rats in the F_0 generation were administered metam sodium continuously in the drinking water for 10 weeks prior to mating, throughout mating, gestation, and lactation of the F_1 litters, and until necropsy. F_1 males and females would then be exposed to metam sodium throughout the duration of this study, as well as the F_2 litters until necropsy. F_1 parents were selected after weaning. They were selected from litters containing 6 to 18 pups and excluded litters derived from remating. After selection, the pre-mating and breeding program was continued until an F_2 litter had been produced and weaned.

3) Animal Assignment

F_0 rats were assigned to test groups using a randomization program. Dose groups are summarized below:

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Test groups		Conc. (mg/ml)*	Animals per group ** Males	Females
1	Control	0	30	30
2	Low (LDT)	0.01	30	30
3	Mid	0.03	30	30
4	High	0.10	30	30

*Diets were administered from the beginning of the study until the animals were sacrificed.

**The same number of animals were picked from the F1 litters as parents for the F2 generation. It was not stated where additional animals came from if sufficient litters were not available for 30 males and females per group.

G. Observation Schedule

1. Parental animals: Observations and the schedule for those observations is summarized from the report as follows:

Type of observation	Number of animals per sex per group	Frequency
Mortality and signs of toxicity	All	Once daily during pre-mating and growth periods.
Detailed clinical observations	All	Once daily during growth and breeding periods.
Body Weight	Male	At beginning of study and weekly through growth and mating periods; then every 2 weeks until necropsy.
Body Weight	Female	At beginning of study; weekly during pre-mating; on days 1, 8, 15, and 22 of gestation; on days 1, 5, 11, 16, 22 and 29 of lactation; and at necropsy.
Food consumption	All	weekly during pre-mating period

2. Reproductive performance

The following indices were calculated:

$$\text{Fertility index} = \frac{\text{No. fertile}}{\text{No. fertile + No. infertile}} \times 100$$

$$\text{Pups born alive} = \frac{\text{No. pups born alive}}{\text{No. pups born}} \times 100$$

$$\text{Pups surviving to day 22} = \frac{\text{No. of live pups on day 22}}{\text{No. live pups on day 1}} \times 100$$

The following were also recorded for parental rats: length of gestation, pre-coital interval.

3. Litter observations: According to the report, the following litter observations were made:

	Time of observation (lactation day)				
Observation	Birth	Day 5	Day 11	Day 16	Day 22
Number of live pups	x	x	x	x	x
Pup weight	x	x	x	x	x
External alterations	x	x	x	x	x
Number of dead pups	x	x	x	x	x
Sex of each pup	x	x	x	x	x

Any dead, missing, or abnormal pups were recorded at each examination interval.

4) Necropsy

a. Parental Animals: Females which appeared pregnant but which failed to litter were killed on or after the 25th day from the last mating. Females which showed no positive signs of mating and did not litter were killed at least 3 weeks after the last day of their mating period. All remaining females were killed as soon as practical after weaning their offspring. All male rats were killed at

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approximately the same time after the pairing period for each generation.

F_0 animals were subjected to post mortem examination as follows:

Animals examined	Macroscopic	Microscopic
Found dead	x	x
Unscheduled sacrifice	x	x
Scheduled sacrifice	x	x

Sections of the testes, epididymides, prostate, seminal vesicles, coagulating gland, ovaries, uterus, vagina, pituitary, mammary gland, nasal cavities, and all organs with macroscopic abnormalities were examined in rats from all animals scheduled to receive a post mortem examination.

b. Offspring: All pups surviving to termination and not selected for the next generation were killed as near to day 29 post partum as possible. Five male and five female F_1 pups and 10 male and female F_2 pups were scheduled to receive a full post mortem examination. After this selection of pups, all remaining pups showing any clinical abnormality were given a full necropsy as well as two of any remaining clinically normal pups of each sex from each litter, if possible. Pups over 18 days of age dying or killed intercurrently were also necropsied. The animals selected for full post mortem necropsy were examined as follows:

Animals examined	Macroscopic	Microscopic
Found dead	x	x (limited)
Scheduled sacrifice	x	x (limited)

c. Necropsy observations: In the report, it was stated that initial histological examination was to be restricted to nasal cavities from adults and pups in control and high dose groups killed at scheduled termination, and to the uterus, cervix, vagina, ovary, mammary gland, testis, epididymis, prostate, and seminal vesicle from all adults suspected of being infertile. However, the examination was expanded to include nasal cavities from all F_0 and F_1 adult females in the 0.03 mg/ml dose group. Grossly abnormal pituitary glands from two high dose females and extraocular tissue from one female F_1 pup with no visible eyes were also examined.

The following tissues were prepared for microscopic examination from animals suspected to be **infertile** only:

X Ovaries	X Epididymides
X Uterus	X Prostate
	X Seminal vesicles
X Vagina	X Testes
X Pituitary	

The uterus of each female was examined for evidence and number of implantation sites. In addition, as stated, the nasal cavities from control and high dose adults and pups as well as from low and mid dose female adults were histologically examined.

H. Data Analysis

A copy of the statistical procedures employed in this study is attached to this review as pages 29-31 of the report.

II. REPORTED RESULTS

A. Parental Animals

1. Mortality and clinical signs: Summaries of clinical observations made in male and female rats were presented in Tables 4-5, pages 87-96 of the report. No significant treatment-related signs of clinical toxicity were apparent in male and female P_1 rats during pre-mating, gestation, or lactation. No treatment-related effects on mortality of P_1 male and female rats were observed.

2. Body weight and food consumption:
Reported body weight (mean ± S.D.) and selected food consumption (mean ±S.D.) results are summarized as follows:

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F_0 Generation Males - Pre-mating

Observation and study week	Dose group 0 mg/ml	10 mg/ml	100 mg/ml	750 mg/ml
Mean body weight (g)				
week 1	67.1±7.8	67.0±6.3	66.0±7.0	67.3±6.5
week 10	419.5±33.4	410.7±18.9	419.9±31.8	410.6±21.2
Mean weight gain (g)				
weeks 1 - 10	352.4	343.7	353.9	343.3
Mean food consumption (g/rat/day; N = 15))				
week 1	18.5±1.7	17.9±1.7	17.9±1.2	17.7±1.0
week 2	24.7±1.7	24.0±1.7	24.0±1.2	23.7±0.9*
week 3	27.0±1.4	26.6±1.4	26.8±1.4	26.2±0.7*
	0 mg/ml	10 mg/ml	100 mg/ml	750 mg/ml
weeks 1-10	28.6±4.23	27.9±4.15	28.4±4.43	27.8±4.26

F_0 Generation Females - Pre-mating

Observation and study week	Dose group 0 mg/ml	10 mg/ml	100 mg/ml	750 mg/ml
Mean body weight (g)				
week 1	64.9±6.8	64.7±6.3	64.1±7.3	65.4±5.5
week10	243.9±16.2	242.4±16.4	243.7±18.0	238.0±18.1*
Mean weight gain (g)				
weeks 1 - 10	179.0	177.7	179.6	172.6
Mean food consumption (g/rat/day)				
week 1	17.1±1.5	16.9±1.0	16.5±1.2	16.3±1.0*
week 6	22.2±1.5	22.4±1.3	22.2±1.1	21.2±1.5*

F_0 Generation Females - Pre-mating (cont.)

Study week	Dose group 0 mg/ml	10 mg/ml	100 mg/ml	750 mg/ml
week 7	21.9±1.3	22.0±1.2	22.3±1.3	21.0±1.1*
week 8	21.8±1.2	21.5±1.5	21.6±1.5	21.1±1.3
week 9	21.4±1.3	21.2±1.1	21.3±1.1	20.6±1.0*
week 10	20.6±0.7	20.6±0.9	20.5±1.2	19.7±0.8**

* Statistically significantly different from control, $p<0.05$.
** Statistically significantly different from control, $p<0.01$.

F1 Generation Males - Pre-mating

Observation and study week	Dose group 0 mg/ml	10 mg/ml	100 mg/ml	750 mg/ml
Mean body weight (g; N=15)				
week 1	78.8±7.6	77.6±8.9	77.6±6.7	74.6±9.7
week 10	438.9±32.0	448.0±27.6	440.5±24.6	418.5±30.4*
Mean weight gain (g)				
weeks 0 - 10	360.1	370.4	362.9	343.9
Mean food consumption (g/rat/day)				
week 1	18.7±1.0	18.5±1.2	18.5±1.0	17.4±1.3*
week 6	33.3±2.0	33.7±1.7	33.5±1.7	32.0±1.8*
week 10	32.6± 1.7	33.3±1.7	33.0±2.2	31.6±2.3

F1 Generation Females - Pre-mating

Observation and study week	Dose group 0 mg/ml	10 mg/ml	100 mg/ml	750 mg/ml
Mean body weight (g; N=15)				
week 0	73.2±6.8	71.1±7.3	72.5±8.2	69.8±8.6
week 10	251.8±18.5	250.3±14.2	246.1±18.1	236.5±19.7**
Mean weight gain (g)				
week 0 - 10	178.6	179.2	173.6	166.7
Mean food consumption (g/rat/day)				
week 1	17.0±1.3	16.1±0.8*	16.0±1.0*	15.7±1.1**
week 4	22.9±1.2	21.9±1.2*	21.9±1.2*	21.6±0.9*
week 8	22.7±1.2	22.6±1.2	21.9±1.0	21.2±1.2**
week 10	21.8±1.4	22.1±1.2	21.6±1.2	21.1±1.6

* Statistically significantly different from control, $p<0.05$.
** Statistically significantly different from control, $p<0.01$.

Selected group mean body weight values for pregnant or nursing dams are summarized as follows:

F_0 Generation - Female

Observation and study week	Dose group 0 mg/ml	10 mg/ml	100 mg/ml	750 mg/ml
Mean body weight (g; N=30)				
Day 1 of gestation	256.4±17.9	252.6±16.5	255.9±20.9	246.8±17.3*
Day 22 of gestation	386.3±23.8	381.3±23.4	374.5±32.0	355.3±21.9
Mean body weight (g)				
Day 1 of lactation	299.4±22.2	296.3±21.1	291.1±20.5	281.2±21.4**
Day 22 of lactation	339.5±18.4	336.6±18.0	329.9±21.1	311.3±18.0
Mean body weight gain (g)				
Days 1-22 of gestation	129.9	128.7	118.6	108.5
Day 1-22 of lactation	40.1	40.3	38.8	30.1

F_1 Generation-Female

Observation and study week	Dose group 0 mg/ml	10 mg/ml	100 mg/ml	750 mg/ml
Mean body weight (g)				
Day 1 of gestation	262.6±18.3	266.9±16.8	261.4±20.4	249.5±22.3**
Day 22 of gestation	400.1±17.2	389.4±23.9	387.6±23.3	360.2±24.5
Day 1 of lactation	304.8±17.2	300.0±21.3	292.1±25.7*	270.8±22.7**
Day 22 of lactation	342.8±13.0	340.6±16.3	334.9±15.4	308.2±19.1

F_1 Generation-Female, cont.

Observation and study week	Dose group 0 mg/ml	10 mg/ml	100 mg/ml	750 mg/ml
Mean body weight gain (g)				
Days 1-22 of gestation	137.5	122.5	126.2	110.7
Day 1-22 of lactation	38.0	40.6	42.8	37.4

*Statistically significantly different from control, $p<0.05$. **Statistically significantly different from control, $p<0.01$.

3. Test Substance Intake

Dose rates (in mg/kg/day) were calculated from the cage mean bodyweight and cage mean water consumption for the weeks measured according to the following formula:

$$\text{dose} = \frac{1000 \times wc_i \times \text{dose (in mg/ml)}}{bw_i}$$

wc_i = water consumption measurement for week i

Intake of Metam Sodium (mg/kg/day)

	Dose group 0 mg/ml	0.01 mg/ml	0.03 mg/ml	0.1 mg/ml
F_0 generation				
males: pre-mating	0	1.7 (1.6)[a]	4.6 (3.7)	14.0 (13.2)
females: pre-mating	0	2.4 (2.2)	6.2 (4.9)	16.9 (15.9)
females: gestation	0	2.8 (2.6)	6.9 (5.5)	17.6 (16.5)
F_1 generation				
males: pre-mating	0	1.4 (1.3)	4.0 (3.2)	12.3 (11.5)
females: pre-mating	0	2.0 (1.9)	4.9 (3.9)	14.4 (13.5)
females: gestation	0	2.0 (1.9)	5.7 (4.5)	14.4 (13.5)

[a]values in parentheses represent calculated values of intake based on the percent of nominal intake as determined from Table 2, page 4 of this review.

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Water Consumption

Water consumption data were presented in Tables 14-19, pages 110-117 of the report and are summarized below:

F_0 generation-males

	0 mg/ml	0.01 mg/ml	0.03 mg/ml	0.1 mg/ml
water consumption (ml/rat/day)				
week 1	20.8±1.7	20.3±1.8	20.3±1.6	19.0±1.1**
week 4	43.7±9.8	42.4±9.2	38.0±4.9*	36.4±6.9**
week 8	52.6±11.1	57.7±14.1	49.7±8.7	43.0±7.9*
week 10	53.8±8.1	55.9±12.3	52.0±8.9	45.0±7.9**

F_0 generation-females

	0 mg/ml	0.01 mg/ml	0.03 mg/ml	0.1 mg/ml
water consumption (ml/rat/day)				
week 1	19.3±2.1	19.2±1.5	18.4±1.6	18.2±1.7*
week 4	42.3±12.6	40.7±12.6	34.0±7.2*	28.2±4.1**
week 8	60.7±15.8	59.2±16.8	49.5±13.4*	36.0±7.9**
week 10	62.1±13.8	64.0±16.5	51.7±14.5*	37.4±6.2**

F_1 generation-males

	0 mg/ml	0.01 mg/ml	0.03 mg/ml	0.1 mg/ml
water consumption (ml/rat/day)				
week 1	20.8±1.0	20.7±1.9	20.8±1.9	18.5±1.5**
week 4	35.2±3.7	36.5±4.8	35.0±2.8	31.9±3.1*
week 8	45.0±5.3	48.6±10.7	41.8±5.8	36.3±3.5**
week 10	45.5±5.8	45.5±6.8	42.3±6.8	37.0±3.8**

F_1 generation-females

	0 mg/ml	0.01 mg/ml	0.03 mg/ml	0.1 mg/ml
water consumption (ml/rat/day)				
week 1	19.8±1.8	18.6±1.1*	17.8±1.5*	16.7±1.7**
week 4	34.0±5.3	30.3±4.8*	26.3±3.4**	24.7±2.5**
week 8	51.1±10.8	53.0±12.9	35.7±5.7**	28.7±3.2**
week 10	53.8±11.2	55.1±12.0	39.4±8.1**	30.5±5.7**

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F_0 generation-females (gestation)

	0 mg/ml	0.01 mg/ml	0.03 mg/ml	0.1 mg/ml
water consumption (ml/rat/day)				
week 1	75.7±23.1	85.1±26.0	71.8±23.6	48.1±14.7**
week 2	84.7±21.0	90.9±23.5	72.6±17.8*	55.5±13.1**
week 3	68.8±12.9	72.2±16.7	58.4±9.3**	46.4±7.0**

F_0 generation-females (lactation)

	0 mg/ml	0.01 mg/ml	0.03 mg/ml	0.1 mg/ml
water consumption (ml/rat/day)				
week 1	57.1±9.2	60.1±11.1	51.0±12.1*	46.0±6.1**
week 2	95.0±20.0	94.0±15.5	82.3±19.6**	75.6±10.9**
week 3	121.0±23.7	116.9±17.8	105.6±27.5**	96.5±14.1**
week 4	176.9±34.0	174.1±28.0	161.7±46.5*	155.5±24.4*

F_1 generation-females (gestation)

	0 mg/ml	0.01 mg/ml	0.03 mg/ml	0.1 mg/ml
water consumption (ml/rat/day)				
week 1	71.4±18.1	63.6±19.2	58.7±18.1**	40.0±9.9**
week 2	78.6±16.0	66.6±17.4**	60.4±17.9**	43.9±9.9**
week 3	62.2±10.6	55.1±8.6**	53.5±7.2**	40.0±4.3**

F_1 generation-females (lactation)

	0 mg/ml	0.01 mg/ml	0.03 mg/ml	0.1 mg/ml
water consumption (ml/rat/day)				
week 1	51.6±8.4	45.5±8.5	47.0±7.5	39.7±6.1
week 2	83.2±11.2	76.6±16.8	82.7±15.1	69.4±12.0
week 3	116.1±14.5	100.7±24.4	109.7±22.2	92.8±17.6
week 4	179.5±21.6	159.8±43.0	178.3±35.0	159.7±37.5

As can be observed from the above data, water consumption was affected in both sexes at the high dose during the pre-mating period as well as during gestation and lactation in female rats. In rats of the F_0 generation, pre-mating water intake was decreased from 8-18% in males and from 33-40% in females at the high dose. In F_1 parental rats, a similar pattern of decreased water intake was observed, with females showing the greater decrease in water intake. During gestation, female rats showed decreases in water intake at both the high and mid dose levels, where decreases at the high dose were from 32-44% for both F_0 and F_1 females, and from 14-23% for F_1 females only. During lactation, decreases of 9-20% were observed at the high dose for both F_0 and F_1 female rats. Despite the apparently larger decreases in water consumption in female vs male rats, the intake of metam sodium appeared equivalent in both sexes, and even slightly higher in female rats overall (page 14 of this review).

4. Reproductive performance

Results for the parental animals are summarized from the report as follows:

F_0 Generation

Observation and study week	Dose group 0 mg/ml	0.01 mg/ml	0.03 mg/ml	0.1 mg/ml
Median precoital interval (days)[a]	3.19±3.42	2.69±1.23	3.44±3.36	2.57±1.22
Males				
Mated	30	30	30	30
Fertile	29	28	28	30
Infertile	1	2	2	0
Intercurrent deaths	0	1	0	0
Females				
Number mated	30	30	30	30
Number fertile	30	30	30	30
Infertile	0	0	0	0
Intercurrent deaths	0	0	0	0

F_0 Generation, cont.

Observation and study week	Dose group 0 mg/ml	.01 mg/ml	.03 mg/ml	0.1 mg/ml
Mean gestation interval (days)	22.0±0.2	22.0±0.2	22.0±0.2	22.0±0.3
Number of litters	29	28	29	30
Total litter losses	1	2	1	0
Mean litter size (Day 1)	11.7	12.0	10.9	11.6
Mean litter size (Day 22)	10.9	11.0	10.2	10.7
Number of live pups (Day 1)	341	359	316	348
Number of live pups (Day 22)	317	309	296	323
Pup deaths (Days 1-5)	22	25	20	23
Pup deaths (Days 5-22)	2	25[a]	0	2
Mean pup weight (g)				
(Day 1; M)	6.1	6.0	6.1	6.0
(Day 1; F)	5.7	5.7	5.8	5.7
Mean pup weight (g)				
(Day 5; M)	8.8	8.7	8.8	8.8
(Day 5; F)	8.6	8.4	8.5	8.4
Mean pup weight (g)				
(Day 22; M)	41.7	41.5	41.9	39.0
(Day 22; F)	40.7	39.8	40.7	37.9

*Statistically significantly different from control, $p<0.05$; **Statistically significantly different from control, $p<0.01$.

a- excludes 2 litters (25 pups) lost completely on day 5 as indicated from the data (page 391).

Data taken from Appendix 10, pages 389-396 and Tables 20-24, pages 118-127 of the report.

F_1 Generation

Observation and study week	Dose group 0 mg/ml	.01 mg/ml	.03 mg/ml	0.1 mg/ml
Median precoital interval (days)[a]	2.53±1.14	2.82±2.39	2.43±1.07	2.40±1.14
Males				
Mated	29	30	30	29
Fertile	28	26	26	26
Infertile	1	4	4	3
Intercurrent deaths	0	0	0	0
Females				
Number mated	29	30	30	30
Number fertile	29	30	30	29
Infertile	0	0	0	0
Intercurrent deaths	1	0	0	1
Mean gestation interval (days)	22.2±0.4	22.1±0.4	22.1±0.4	22.1±0.3
Number of litters	27	30	30	29
Total litter losses (no. rats)	3 (32)	0(0)	0(0)	1(0)
Mean litter size (Day 1)	12.0	10.8	12.0	11.4
Mean litter size (Day 22)	10.9	9.5	11.0	10.7
Number of live pups (Day 1)	353	324	361	332
Number of live pups (Day 22)	293	284	331	311
Pup deaths (Days 1-22)	60[a]	40	30	21
Mean pup weight (g) (Day 1; M)	6.2	6.2	6.1	6.0
(Day 1; F)	5.9	5.9	5.7	5.6
Mean pup weight (g) (Day 22; M)	44.1	44.0	41.4	37.7
(Day 22; F)	41.9	42.0	39.5	35.8

*Statistically significantly different from control, $p<0.05$. **Statistically significantly different from control, $p<0.01$. [a]includes 2 whole litter losses as indicated by the data (pages 1353-1354).

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5. Necropsy results

a. Organ and Final Body Weights: Summaries of terminal body weights for F_0 and F_1 male parental rats as well as testes and epididymis weight in male F_0 and F_1 parental and offspring rats were summarized in Tables 36-39, pages 139-146 of the report. Body weight and organ weight changes were observed in parental male rats of the F_0 and F_1 generations at the high dose, but the changes observed were mild and not statistically significant (decreases of 2-5% vs control). In the F_{1a} and F_{2a} litters, male rats showed body weight and organ weight decreases of between 5-11% at the high dose, but again, none of these changes was identified as statistically significant.

b. Pathology

i. Macroscopic examination

The incidence of gross observations in male and female F_0 and F_1 rats was summarized in Tables 40-41, pages 147-153 of the report. The tables included both intercurrent and terminal sacrifice animals from the parental generations. With the exception of pelvic dilatation of the kidney in male F_1 parental rats, there did not appear to be any significant macroscopic effects in any treated group of male or female parental rats. In the male F_1 parents, the incidence of pelvic dilatation was slightly increased at all dose levels (incidence of 7, 9. 11, and 10 out of 30 at the 0 mg/ml, 0.01 mg/ml, 0.03 mg/ml, and 0.1 mg/ml dose levels).

ii. Microscopic examination

Data on microscopic observations in male and female F_0 and F_1 parental rats were presented in Tables 42 and 43, pages 155-158 of the report. The microscopic examination was restricted primarily to an examination of the nasal passages of adult males and females in control and high dose groups. For F_0 males and F_1 females, the 0.03 mg/ml dose group was examined additionally, while for F_1 males, animals suspected as being infertile from the 0.01 and 0.03 mg/ml dose groups were also examined in a similar manner. This is in contrast to the tissues listed for histological examination on page 28 of the report.

There were no apparent abnormalities detected in the nasal passages of parental male rats from the F_0 generation. In female F_0 rats, changes were evident in the nasal passages at the 0.1 mg/ml dose level. These are best summarized in tabular format (below):

Microscopic Observations in Female F_0 Rats Treated with Metam Sodium

	Dose Group (mg/ml)			
	0	0.01	0.03	0.10
No. examined	30	0	30	30
Nasal Cavity				
- Bowman's gland duct hypertrophy with loss of alveolar cells (TOTAL)	0	0	0	29
minimal	0	0	0	2
slight	0	0	0	6
moderate	0	0	0	15
marked	0	0	0	6
- Disorganization/ degeneration/atrophy of olfactory epithelium (TOTAL)	4	0	2	29
minimal	4	0	2	3
slight	0	0	0	10
moderate	0	0	0	13
marked	0	0	0	3
- Dilatation of ducts of Bowman's glands (TOTAL)	0	0	0	14
minimal	0	0	0	13
slight	0	0	0	1

Microscopic Observations in Female F_1 Rats Treated with Metam Sodium

	Dose Group (mg/ml)			
	0	0.01	0.03	0.10
No. examined	29	0	30	29
Nasal Cavity				
- Bowman's gland duct hypertrophy with loss of alveolar cells (TOTAL)	0	0	0	27
minimal	0	0	0	2
slight	0	0	0	10
moderate	0	0	0	12
marked	0	0	0	3

Microscopic Observations in Female F_1 Rats, cont.

- Disorganization/ degeneration/atrophy of olfactory epithelium (TOTAL)	3	0	1	26
minimal	3	0	1	5
slight	0	0	0	14
moderate	0	0	0	5
marked	0	0	0	2
- Dilatation of ducts of Bowman's glands (TOTAL)	0	0	0	10
minimal	0	0	0	9
slight	0	0	0	1

Data taken from Tables 42-43, pages 155-158 of the report.

For both the F_0 and F_1 female parental rats, there was a noticeable increase in the number of rats at the high dose level with Bowman's gland duct hypertrophy with loss of alveolar cells, degeneration/disorganization and/or atrophy of the olfactory epithelium, and dilatation of the Bowman's gland ducts. According to the report, duct hypertrophy was mainly confined to the nasal septum and dorsal arch with occasional foci on the opposing turbinates. The change in Bowman's glands was accompanied in all affected animals by degeneration, disorganization, and/or atrophy of the olfactory epithelium. This lesion comprised vacuolation and separation of cells in the basal layers of the olfactory epithelium with a few necrotic cells evident, loss of normal cellular arrangement and apical cytoplasm and reduction in number of cell layers. According to the report, no changes which could be related to treatment with metam sodium were detected in the nasal cavities of males receiving the high dose or in females receiving the 0.03 mg/ml dose of metam sodium.

In addition to the above, the report noted (as was also noted in this review) that the number of F_1 males suspected of being infertile was increased in treated groups vs. control males. However, it was stated that no lesions to account for infertility were detected in the reproductive tract of any of these animals. One control female and one at the 0.1 mg/ml dose level failed to produce litters; in both cases, an imperforate vagina or cervix was considered to be the cause from macroscopic examination.

C. Offspring

1. Viability and clinical signs:

Viability results from pups during lactation following culling of litters on day 4 are summarized from the report as follows:

F_{1a} Litter (page 123 of report)

	Dose Group (mg/ml)			
	0	0.01	0.03	0.10
Observation				
Mean percentage surviving in each litter (day 21)	93.4	92.5	94.3	93.1
No. litters with all pups surviving to Day 21 / total no. litters	16/29(55%)	16/28(57%)	17/29 (59%)	17/30(57%)

F_{2a} Litter

Mean percentage surviving in each litter (day 21)	90.8	88.7	92.2	93.1
No. litters with all pups surviving to Day 21 / total no. litters	13/27(48%)	16/30(53%)	19/30 (63%)	22/29(76%)

*Statistically significantly different from control, $p<0.05$ **Statistically significantly different from control, $p<0.01$.

Changes in mean number of pups/litter were summarized in the report as follows:

F_{1a} Litter (page 124)

Observation and study week	Dose group			
	0	0.01	0.03	0.10
Day 1(alive)	11.7	12.0	10.9	11.6
Day 5	11.0	11.1	10.2	10.8
Day 16	11.0	11.1	10.2	10.8
Day 22	10.9	11.0	10.2	10.8

F_{2a} Litter (page 125)

	0	0.01	0.03	0.10
Day 1(alive)	12.0	10.8	12.0	11.4
Day 5	11.0	9.7	11.1	10.9
Day 16	10.9	9.5	11.1	10.7
Day 22	10.9	9.5	11.0	10.7

* Statistically significantly different from control, $p<0.05$.
** Statistically significantly different from control, $p<0.01$.

2. Body weight:
Selected group mean body weights are summarized from the report as follows:

F_{1a} Litter (page 126 of report)

	Dose group			
Observation and study week	0	0.01	0.03	0.10
Males				
Body weight (g) - Day 1	6.1±0.6	6.0±0.5	6.1±0.4	6.0±0.4
Weight gain (g) - Days 1-22	35.6	35.5	35.8	33.0
Females				
Body weight (g) - Day 1	5.7±0.6	5.7±0.4	5.8±0.6	5.7±0.4
Weight gain (g) - Days 1-22	35.0	34.1	34.9	32.2

F_{2a} Generation (page 128 of the report)

Males				
Body weight (g) - Day 1	6.2±0.6	6.2±0.7	6.1±0.7	6.0±0.5
Weight gain (g) - Days 1-22	37.9	37.8	35.3	31.7
Females				
Body weight (g) - Day 1	5.9±0.6	5.9±0.8	5.7±0.7	5.6±0.5
Weight gain (g) - Days 1-22	36.0	36.1	33.8	30.2

According to the report, total F_{1a} litter weight was lower at the 0.1 mg/ml and 0.03 mg/ml dose levels vs. control at days 22 and 29, but the differences were not statistically significant. Table 30 of the report (page 130) shows total litter weights decreased by 7% and 9% vs control at the 0.03 and

0.1 mg/ml dose levels on day 22 . On day 29, total litter weight was decreased by approximately 9% at both dose levels. In the F_{2a} litter (Table 31, page 131), total litter weight was decreased by 4% and 14% on day 22 at the 0.03 and 0.1 mg/ml dose levels vs control, respectively. On day 29, total litter weight was decreased 2% and 11% at the 0.03 and 0.1 mg/ml dose levels vs control. It is noted that for male and female pups in the F_{2a} litter, mean pup weight gain was decreased by 14% at the 0.1 mg/ml dose level vs control for days 1-22 post partum. Such an effect was not observed in the F_{1a} litter.

3.Necropsy results

a. Organ weights:

Data on organ weights were presented in Tables 38-39, pages 143-146 of the report. This consisted only of the weight of the testes and epididymis in male rats. In the F_{1a} litter, testes and epididymis weight were decreased by 8% at the 0.1 mg/ml dose. In the F_{2a} litter, only the testes showed a decrease in weight, a decrease of 9% vs control.

b. Pathology

i. Macroscopic examination:

Summary incidence of gross observations in F_{1a} and F_{2a} pups was provided in Tables 34-35, pages 135-138 of the report for pups found dead up to 18 days of age, and in Tables 44-45, pages 159-168 for terminal kill pups. There did not appear to be any treatment-related increases in the incidence of macroscopic abnormalities in male or female pups of either generation. However, there was an apparent decrease in the incidence of renal pelvic dilatation in both male and female pups of the F_{2a} litter. For males, the incidence was 14/54, 11/57, 5/60, and 4/56 for the control, 0.01, 0.03, and 0.1 mg/ml dose groups. For females, the incidence was 4/54, 4/56, 3/59, and 1/56 for the same dose groups. There was no explanation of this phenomenon in the report.

ii. Microscopic Observations

The summary incidence of microscopic observations for F_{1a} and F_{2a} pups was presented in Tables 46-47, pages 168-170 of the report. The data reported appeared limited to reporting of eye abnormalities and nasal cavity abnormalities in F_{1a} pups. Bilateral anophthalmia was observed in one high dose female. The isolated incidence was considered to be of no toxicological significance. According to the report, "minor degenerative and inflammatory changes were detected in the respiratory mucosa of the majority of pups examined..." These lesions consisted of rhinitis and degeneration of the respiratory epithelium, but were not significantly different between control and treated pups.

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III. DISCUSSION

A. Investigators' conclusions

The conclusions of the registrant are appended to this review.

B. Reviewer's discussion

In the present study, the reproductive toxicity of metam sodium was assessed in male and female Sprague-Dawley rats. Groups of 30 male and female rats selected as the F_0 generation were given metam sodium in the drinking water at levels of 0, 0.01, 0.03, and 0.1 mg/ml nominal concentration (actual concentration was less; see executive summary). Administration of metam sodium in the drinking water was continuous throughout the study. After approximately 10 weeks of treatment, F_0 rats were mated to produce the F_1 litter. Groups of 30 male and 30 female rats (when possible) were selected from the F_1 litter at random as F_1 parents to produce the F_2 offspring. Test chemical was administered until weaning of the F2 litter.

The effect of metam sodium administration on body weight, body weight gain, and food consumption of both F_0 and F_1 parental rats was minor even at the highest dose level. Most effects at the high dose did not result in decreases over 10% from control. In a few specific cases (namely, food consumption during gestation and lactation in F_1 females) the decrease was 10% from control, but only in these instances.

In terms of the dose received by the rats in this study, the stability of metam sodium in drinking water was taken into consideration. Average measurement of stability showed 93% of nominal at the low dose, 80% of nominal at the mid dose, and 94% of nominal at the high dose. In addition, for each sex and generation, the intake of metam sodium was slightly different (page 14 of this review). Thus, after correction for stability, the lowest intake for a given dose level will be considered as the intake level of metam sodium for that dose. As a result, the following dose levels are used: at the 0.01 mg/ml dose level, **1.2 mg/kg/day** (males) and **1.8 mg/kg/day** (females); at the 0.03 mg/ml dose level, **3.2 mg/kg/day** (males) and **3.9 mg/kg/day** (females); at the 0.1 mg/ml dose level, **11.5 mg/kg/day** (males), and **13.5 mg/kg/day** (females).

The effects on reproductive performance in the F_0 and F_1 generations from administration of metam sodium were few. Specifically, the only observation of significance was a decrease in mean pup weight of 14% vs control on day 22 for the F_1 parents. Of note is the observation that the total number of litters with all pups surviving to day 22 as a percentage of the total litters was apparently low for all dose groups (~ 50%). Other pup findings included: A 16% decrease in body weight gain for male and female pups in the F_2 litter at the high dose, and decreases of 8-9% in testes and epididymis weights for male pups in the F_{1a} and F_{2a} litters at the high dose.

The most significant observation in this study were the microscopic observations in female

parental rats at the high dose level. Lesions of the nasal cavity were observed in increased incidence in female parental rats of both generations. These lesions consisted of Bowman's gland duct hypertrophy with loss of alveolar cells, degeneration/disorganization and/or atrophy of the olfactory epithelium, and dilatation of the Bowman's gland ducts. According to the report, duct hypertrophy was mainly confined to the nasal septum and dorsal arch with occasional foci on the opposing turbinates. The change in Bowman's glands was accompanied in all affected animals by degeneration, disorganization, and/or atrophy of the olfactory epithelium. This lesion comprised vacuolation and separation of cells in the basal layers of the olfactory epithelium with a few necrotic cells evident, loss of normal cellular arrangement and apical cytoplasm and reduction in number of cell layers. According to the report, no changes which could be related to treatment with metam sodium were detected in the nasal cavities of males receiving the high dose or in females receiving the 0.03 mg/ml dose of metam sodium.

In addition to the above, the report noted (as was also noted in this review) that the number of F_1 males suspected of being infertile was increased in treated groups vs. control males. However, it was stated that no lesions to account for infertility were detected in the reproductive tract of any of these animals. One control female and one at the 0.1 mg/ml dose level failed to produce litters; in both cases, an imperforate vagina or cervix was considered to be the cause from macroscopic examination.

The significance of the nasal lesions in this study is not clear except from a systemic toxicity standpoint. There is evidence to suggest that metam sodium may be a developmental toxicant in both rats and rabbits (HED document # 010693; also, Developmental and Reproductive Toxicity Peer Review of Metam Sodium, 1991), but the evidence in this study does not suggest an effect on reproduction in rats. It is quite possible that the lack of an effect could be due to the drinking water route of administration in this study vs the oral gavage route in the developmental toxicity studies, where the nature of the delivered dose would be different in the drinking water study (more continuous) than in the oral gavage study (bolus administration).

IV. CLASSIFICATION: Core minimum

This study satisfies the data requirements (§83-4) for a reproductive toxicity study in rats.

Parental Toxicity NOEL = 0.03 mg/ml (**3.2 mg/kg/day** [males] and **3.9 mg/kg/day** [females])

Parental Toxicity LEL = 0.1 mg/ml (**11.5 mg/kg/day** [males], and **13.5 mg/kg/day** [females]); nasal lesions in F_0 and F_1 female parental rats.

Reproductive Toxicity NOEL = 0.1 mg/ml

Reproductive Toxicity LEL $\geq$ 0.1 mg/ml