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

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OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Sodium N-methyldithiocarbamate (Metam Sodium): Review of a Study Submitted by the Registrant under section 6(a)(2) of FIFRA.

Toxchem No: 039003
Submission: S433168
MRID No: 426000-01

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Registrant: Metam Sodium Task Force

Action Requested: Review of a subchronic oral toxicity study in dogs with metam sodium submitted under section 6(a)(2) of FIFRA.

Conclusions:

A study entitled, "Metam Sodium:90-Day Oral Dosing Study in Dogs," was submitted by the Metam Sodium Task Force under FIFRA section 6(a)(2) for review. The results of this review are summarized in the following paragraph:

Metam sodium was administered by gelatin capsule to male and female dogs at nominal dose levels of 0, 1, 5, and 10mg/kg/day once daily for 13 weeks. Toxic effects were observed at all dose levels tested, but were primarily evident at the 5 and 10 mg/kg/day dose levels. These included decreased body weight and body weight gain in male and female dogs at 10 mg/kg/day, hematologic alterations (increased cell volume, cell hemoglobin, neutrophils, and monocytes; decreased MCHC) at 5 and 10 mg/kg/day, significant increases in plasma ALT, AST, ALK PHOS, and GGT at 5 and 10 mg/kg/day (including significantly increased ALT in female dogs at 1 mg/kg/day), increased amounts of blood, urobilinogen, bilirubin, and protein in urine at 5 and 10 mg/kg/day, and microscopic evidence of hepatitis at 5 and 10 mg/kg/day. A majority of the toxic effects observed in this study appeared dose- and time-related in treated dogs. No evidence of tumors was found in this study.

Based upon the results of this study, the systemic NOEL is < 1 mg/kg/day, and the systemic LEL is ≤ 1 mg/kg/day for female dogs, based upon the increase in plasma ALT observed in female dogs at 1 mg/kg/day and the biliary duct proliferation with inflammatory cell infiltration observed in female dogs at the 1 mg/kg/day dose level. For male dogs, the systemic NOEL is = 1 mg/kg/day and the systemic LEL = 5 mg/kg/day, based upon statistically significant increases in plasma ALT, AST, and alkaline phosphatase, as well as the increased incidence of hepatitis and bile duct proliferation.

Classification: core supplementary

This study does not satisfy the guideline requirement (§ 82-1) for a subchronic toxicity study in dogs, due to the lack of establishment of a systemic NOEL for toxicity.

Reviewed by: Timothy F. McMahon, Ph.D. 2/2/93
Section I, Toxicology Branch II (H7509C)
Secondary Reviewer: Yiannakis M. Ioannou, Ph.D. 2/2/93
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Data Evaluation Report

Study type: Subchronic Oral Toxicity - dogs
Guideline: § 82-1

EPA ID Numbers: MRID number: 426000-01
Submission: S433168
DP Barcode: D186419
PC Code: 039003

Test material: Sodium N-methyldithiocarbamate

Synonyms: Metam-sodium

Study number(s): CTL/P/3679

Sponsor: Metam Sodium Task Force

Testing Facility: ICI Central Toxicology Laboratory

Title of report: Metam Sodium: 90-Day Oral Dosing Study in Dogs

Author(s): A. Brammer

Study Completed: November 11, 1992

Conclusions: Metam sodium was administered by gelatin capsule to male and female dogs at nominal dose levels of 0, 1, 5, and 10mg/kg/day once daily for 13 weeks. Toxic effects were observed at all dose levels tested, but were primarily evident at the 5 and 10 mg/kg/day dose levels. These included decreased body weight and body weight gain in male and female dogs at 10 mg/kg/day, hematologic alterations (increased cell volume, cell hemoglobin, neutrophils, and monocytes; decreased MCHC) at 5 and 10 mg/kg/day, significant increases in plasma ALT, AST, ALK PHOS, and GGT at 5 and 10 mg/kg/day (including significantly increased ALT in female dogs at 1 mg/kg/day), increased amounts of blood, urobilinogen, bilirubin, and protein in urine at 5 and 10 mg/kg/day, and microscopic evidence of hepatitis at 5 and 10 mg/kg/day. A majority of the toxic effects observed in this study appeared dose- and time-related in treated dogs. No evidence of tumors was found in this study.

Based upon the results of this study, the systemic NOEL is < 1 mg/kg/day, and the systemic LEL is ≤ 1 mg/kg/day for female dogs, based upon the increase in plasma ALT observed in female dogs at 1 mg/kg/day and the biliary duct proliferation with inflammatory cell infiltration observed in female dogs at the 1 mg/kg/day dose level. For male dogs, the systemic NOEL is = 1 mg/kg/day and the systemic LEL = 5 mg/kg/day, based upon statistically significant increases in plasma ALT, AST, and alkaline phosphatase, as well as the increased incidence of hepatitis and bile duct proliferation.

Classification: core supplementary

This study does not satisfy the guideline requirement (§ 82-1) for a subchronic toxicity study in dogs, due to the lack of establishment of a systemic NOEL for toxicity.

I. MATERIALS AND METHODS

A. Test Material: Metam Sodium
purity: 43.15%
reference no: BAS 005 00N; CTL reference no. YO6930/008
description: yellow liquid
storage: under argon at room temperature in the dark

B. Vehicle: gelatin capsule

C. Test Animals: Species: dog, male and female beagle
Source: colony maintained at ICI Pharmaceuticals, Alderly Park, Macclesfield, Cheshire, UK
Age: approximately 4-5 months at receipt.
Weight range (week 1 of study): males, 9.9-14.0kg; females, 9.3-12.7kg
Mean: males, 11.9±1.1kg; females, 10.6±0.84kg (page 153-156 of report).

D. Animal Husbandry:

A total of 34 dogs were obtained for use in this study, 17 males and 17 females. Dogs were acclimated to the CTL doghouse for 4-5 weeks prior to study initiation. Prior to receipt, dogs were immunized against canine viral hepatitis, distemper, leptospirosis, and canine parvovirus. Dogs also received treatment for possible nematode and ear mite infestation while at both the breeding colony and at the CTL doghouse.

Upon receipt, dogs were housed in indoor pens in pairs or threes, sexes separate, for at least seven days. After this time, dogs were housed individually. Each pen consisted of a floor area measuring approximately 12 x 4 feet, and was divided into separate sleeping and exercise areas. Male dogs received 400g and female dogs 350g of Laboratory Diet A (Special Diets Services Ltd., Stepfield, Witham, Essex, UK) each day. Water was provided ad libitum. Dogs were housed under conditions of controlled temperature (19-21 ^{o}C), humidity (not stated), and lighting (12 hour light/dark cycle). Extremes of temperature (15-23 ^{o}C) were noted on occasion.

E. Experimental Design and Dosing:

Dogs used for this study were divided into randomized blocks, each block comprising 2 male and 2 female replicates. Each replicate consisted of 4 dogs, one per treatment group.

Sixteen dogs per sex were selected from those available on the basis of normal hematology, clinical chemistry and health status as determined prior to start of the experiment. Dogs were introduced to the experiment over a 2 week period according to replicate number. Assignment was made to the following control and dose groups:

Group #	Dose (mg/kg/day)[a]	Animal #s	
		male	female
1	0	1-4	5-8
2	1	9-12	13-16
3	5	17-20	21-24
4	10	25-28	29-32

Dogs were introduced into this study over a 2-week period, in which 4 replicates were introduced on October 23, and the remaining 4 introduced on October 30, 1991.

Dogs were dosed with gelatin capsules of approximately 6ml capacity. Capsules contained the appropriate amount of test chemical based upon the most recent body weight and an assumed purity of 43.15%. The 6ml capsules were placed inside a larger (9ml) capsule prior to dosing, and dogs were fed 100g of diet 30 minutes prior to dosing to minimize regurgitation seen previously with high doses of metam sodium. Control dogs received empty gelatin capsules. The rationale for dose selection was not stated.

F. Dietary Preparation and Analysis:

Dogs in this study were dosed via gelatin capsule, thus eliminating the need for dietary preparation of test material. However, no specific information was provided on the actual doses administered to dogs in this study.

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: 010028

1) **Clinical Observations and Mortality**: Dogs were observed twice daily for clinical or behavioral abnormalities and were given a thorough examination once weekly. Regurgitation following dosing was assessed each day approximately 30-60 minutes post-dose. A full clinical examination was performed on all dogs during week -1 of the study and again prior to termination by a veterinarian.

In this study, 1 male and 1 female dog at the 10 mg/kg/day dose level were sacrificed due to adverse clinical effects. In the male dog (dog # 26), appearance of jaundice was noted first during week 11 of the study, along with a slight reduction of appetite. These symptoms continued through day 6 of week 12. The dog was terminated due to poor clinical condition (continued inappetance, jaundice). In the female dog (dog # 31), signs of jaundice, thin appearance, and leaving of food were noted on day 6 of week 10 of the study. These symptoms continued with little alteration through week 11, day 3. The dog was terminated due to poor clinical condition (thin, jaundiced, no obvious distress but hepatic damage likely).

In addition to the signs observed in the 2 dogs noted above, thinness and clinical signs of jaundice were noted in male dog #25 (also at the 10 mg/kg/day dose level), and salivation was noted in 3 of the 4 males and all of the females receiving 10 mg/kg/day metam sodium from week 3 of the study until study termination.

Some signs of regurgitation were noted in male and female dogs at the 10 mg/kg/day and 5 mg/kg/day dose levels. The incidence of this was greater at 10 than at 5 mg/kg/day (Table 4A, page 38 of the report) and it appears that the occurrence was slightly higher in male than female dogs. The toxicologic effect of this clinical finding is not known with certainty, but would most likely relate to the amount of test chemical regurgitated, if any.

2) **Body Weight:** Individual body weight data were collected for all dogs weekly, before feeding, throughout the pre-experimental period, on day 1 of the study, and at weekly intervals during administration of test chemical. Group mean body weights and body weight gains in male and female dogs are summarized in the following Table (Table 1):

TABLE 1
Group Mean Body Weights in Male and Female Dogs from
13 Week Dietary Administration of Metam Sodium[a]

	Dose Groups							
	males (mg/kg/day)				females (mg/kg/day)			
Body Weight (g)	0	1	5	10	0	1	5	10
week 1	12.02 ±0.35	12.07 ±1.71	11.85 ±0.72	11.72 ±1.55	10.63 ±0.25	10.77 ±1.43	10.65 ±0.78	10.72 ±0.88

Table 1, cont.

	males (mg/kg/day)				females (mg/kg/day)			
	0	1	5	10	0	1	5	10
week 7	13.52 ±0.15	13.47 ±1.55	13.57 ±0.86	13.15 ±1.26	11.57 ±0.21	11.80 ±1.23	11.67 ±0.57	11.52 ±0.82
week 13	14.67 ±0.30	14.57 ±1.33	14.65 ±0.60	13.33** ±0.81	12.27 ±0.25	12.45 ±1.03	12.45 ±0.48	12.03 ±1.00
mean weight gain(kg) (weeks 1-13)	2.65	2.50	2.80	1.61	1.64	1.68	1.80	1.31
% of control	-	94	106	61	-	102	110	80

[a]data taken from Table 5, pages 41-42 of the registrant's report; N=4 in all dose groups except week 13 measurements in both sexes, where N=3.
*$p < 0.05$ vs control; **$p < 0.01$ vs control.

In male dogs, absolute body weight was decreased by approximately 9% at the 10 mg/kg/day dose level by week 13 of the study. Statistically significant decreases in absolute body weight were noted at the 10 mg/kg/day dose level in male dogs beginning at week 10 of the study and continuing through until study termination. As shown above, body weight gain was also affected in male dogs at the 10 mg/kg/day dose level, such that overall weight gain for weeks 1-13 was decreased by 40% vs control. No significant effects on body weight or weight gain were observed in male dogs at lower doses of test chemical.

In female dogs, no significant effects were noted in group mean absolute body weight for the study period. Body weight gain for the study period was, however, decreased by 20% at the 10 mg/kg/day dose level vs control. This decrease was not identified as statistically significant. No significant effects were noted on body weight at lower doses of test chemical in female dogs.

4) **Food Consumption:** According to the registrant (page 15), food residues were recorded prior to feeding and any residual food was discarded. These measurements were made for at least 2 weeks prior to test article administration and throughout the treatment period.

Results for food consumption (page 43 of the report) showed only food residues left by some of the dogs at the 5 and 10 mg/kg/day dose levels. According to these data, it appears that the amount of food left by three male dogs at the 10 mg/kg/day dose level increased with increasing duration of treatment. However, residue measurements were presented only from approximately week 8 until study termination. One male dog at the 5 mg/kg/day dose level showed an increasing percentage of

food left as residue on weeks 13 and 14 of the study.

In female dogs, 2 dogs at the 10 mg/kg/day dose level were noted as leaving significant percentages of administered food. However, only one was followed over a portion of the study (week 8-11). As with the male dogs at this dose level, an increasing percentage of food was left as the study progressed.

It should be noted that of the male and female dogs mentioned above, two of these were the same dogs which were sacrificed in extremis during the study due to, among other things, inappetance.

The limited data presented above suggest that test article toxicity was evident at the 10 mg/kg/day dose level, and possibly at the 5 mg/kg/day dose level. Although it is understood that only data were presented for those dogs leaving food, food consumption data for all dogs would enable a more definitive analysis of whether test article toxicity was actually the cause of the signs observed at the 10 mg/kg/day dose level.

Results of food consumption for weeks 1, 7, and 13 are provided below (Table 2):

TABLE 2
Individual Food Residues in Male and Female Dogs from
13 week Dietary Administration of Metam Sodium[a]

Dose Groups	Week 8	Week 9	Week 10	Week 11	Week 12	Week 13	Week 14
Males							
5mg/kg/day							
dog # 18						13%	34%
10 mg/kg/day							
dog # 25				9%	62%	69%	
dog # 26	15%	33%	52%	84%	99%		
dog # 28			2%	24%	39%	64%	69%
Females							
10 mg/kg/day							
dog # 29						18%	
dog # 31	14%	45%	92%	100%			

[a]Data from Table 6, page 43 of the report, expressed as % food left as residue.

5) Food Efficiency: Food efficiency was not calculated in this study.

From the available data on body weights and food consumption, it appears that test article toxicity was evident at the 10 mg/kg/day dose level. However, in the absence of complete food consumption data, it is not possible to determine if food efficiency was affected, and hence if the effects on body weight were an effect of reduced food consumption or test article toxicity.

5) **Intake of Metam Sodium:** The registrant stated (page 14) that the capsules used for dosing "contained the appropriate amount of compound based on the most recent body weight, and assuming a purity of 43.15%" No other information other than the analysis of the technical material for purity and stability (pages 105-106 of the report) was presented.

6) **Ophthalmologic Examination:** During week -1 and prior to termination, all dogs were given an ophthalmoscopic examination using indirect ophthalmoscopy. According to the registrant (page 19 of the report), no ophthalmoscopic abnormalities were seen in any animals.

7) **Clinical Pathology:**

Collection of blood was performed at a pretest interval, and at weeks 4, 8, and prior to termination. Blood was collected from the jugular vein and put into 2 tubes, one containing EDTA and the other 0.11M trisodium citrate.

a) Hematology: The following CHECKED parameters were measured:

_X_ total leucocyte count*
_X_ erythrocyte count*
_X_ hemoglobin*
_X_ hematocrit*
_X_ platelet count
_-_ packed cell volume
_-_ activated partial thromboplastin time
_X_ reticulocyte count
_-_ erythrocyte morphology
_-_ total plasma protein*
_X_ leukocyte differential*
_X_ mean corpuscular HGB
_X_ mean corpusc. HGB conc.
_X_ mean corpusc. volume
_X_ prothrombin time
_X_ Heinz bodies

A Technicon® H1 was used for measurement of most hematology parameters. Differential white count was performed by examination of a Romanowsky-stained blood film. Using the blood sample placed in trisodium citrate, a hemostatic profile was determined by kaolin-cephalin and prothrombin times, using a Coag-a-Mate (Organon Teknika).

Observed hematologic effects considered treatment-related are summarized below: (Table 3):

TABLE 3
Altered Hematology Parameters in Male and Female Dogs from
13 week Dietary Administration of Metam Sodium[a]

	Dose Groups							
	males (mg/kg/day)				females (mg/kg/day)			
	0	1	5	10	0	1	5	10
RBC (10^{12}/l)								
Week 4								
	5.93 ±0.40	6.25 ±0.56	5.81 ±0.69	5.66 ±0.48	6.75 ±0.44	6.70 ±0.40	6.29 ±0.18	6.08 ±0.93
Week 8								
	5.96 ±0.47	5.96 ±0.68	5.63 ±0.53	5.57 ±0.17	6.80 ±0.23	6.46 ±0.55	6.24 ±0.09	6.22 ±0.69
Week 13								
	6.49 ±0.25	6.59 ±0.68	6.01 ±0.35	5.90 ±0.24	6.95 ±0.51	7.00 ±0.22	6.79 ±0.41	6.52 ±0.72
MCV (fl)								
Week 4								
	66.8 ±1.7	66.0 ±2.4	68.0 ±1.4	68.3 ±1.3	65.8 ±2.5	66.3 ±2.2	66.0 ±2.7	67.0 ±2.9
Week 8								
	67.8 ±1.5	67.3 ±1.0	69.5 ±0.6	72.0** ±2.2	66.5 ±2.4	67.0 ±2.7	67.8 ±2.1	69.8** ±1.9
Week 13								
	68.5 ±1.0	68.0 ±1.4	70.8 ±1.5	73.7** ±2.5	66.5 ±1.7	67.0 ±2.2	68.5 ±3.7	70.7* ±5.7
MCH (pg)								
Week 4								
	21.8 ±0.3	22.0 ±0.3	22.4 ±0.3	22.6* ±0.7	21.6 ±0.7	22.1 ±0.8	22.0 ±0.6	22.2 ±0.8

//

	Dose Groups							
	males (mg/kg/day)				females (mg/kg/day)			
	0	1	5	10	0	1	5	10
Week 8								
	22.5 ±0.1	22.4 ±0.2	22.9 ±0.2	23.5** ±0.8	22.4 ±0.5	22.5 ±0.8	22.7 ±0.5	23.2* ±0.8
Week 13								
	22.6 ±0.1	22.6 ±0.4	23.3 ±0.3	23.5** ±0.6	22.6 ±0.7	22.6 ±0.7	22.9 ±0.9	23.2 ±1.2
MCHC (g/dl)								
Week 4								
	32.6 ±0.5	33.4* ±1.3	33.1 ±0.5	33.2 ±0.5	33.0 ±0.5	33.4 ±0.4	33.4 ±0.6	33.1 ±0.6
Week 8								
	33.3 ±0.6	33.5 ±0.2	33.0 ±0.3	32.6* ±0.5	33.8 ±0.5	33.6 ±0.1	33.5 ±0.3	33.3 ±0.4
Week 13								
	32.9 ±0.5	33.4 ±0.1	32.8 ±0.5	31.9* ±0.6	34.1 ±0.1	33.8 ±0.3	33.5* ±0.4	32.8** ±0.9
neutrophils								
(10^9/l)								
Week 4								
	6.80 ±1.31	9.30** ±2.65	7.50 ±1.12	7.27 ±1.42	7.67 ±0.95	8.30 ±2.44	8.02 ±1.09	7.80 ±0.33
Week 8								
	7.42 ±1.66	10.17** ±0.79	9.17 ±0.91	7.45 ±0.75	7.95 ±0.67	8.35 ±0.93	9.25 ±2.36	8.00 ±0.86
Week 13								
	9.40 ±1.50	10.25 ±2.15	10.07 ±2.83	11.37 ±0.57	8.13 ±1.37	8.10 ±1.73	9.50 ±1.80	10.20 0±1.06

Table 3, cont.

	Dose Groups							
	males (mg/kg/day)				females (mg/kg/day)			
	0	1	5	10	0	1	5	10
monocytes (10^9/l)								
Week 4								
	0.500 ±0.245	0.875 ±0.395	0.700 ±0.408	0.475 ±0.096	0.625 ±0.126	0.525 ±0.287	0.750 ±0.332	0.850 ±0.129
Week 8								
	0.825 ±0.330	1.050 ±0.597	1.025 ±0.359	0.725 ±0.263	0.650 ±0.173	0.500 ±0.141	0.450 ±0.289	1.075 ±0.206
Week 13								
	0.425 ±0.340	0.575 ±0.050	0.600 ±0.216	0.933** ±0.404	0.300 ±0.082	0.425 ±0.275	0.775** ±0.150	0.933** ±0.058
prothrombin time (sec)								
Week 4								
	7.5 ±0.3	7.6 ±0.3	7.5 ±0.4	7.7 ±0.2	7.1 ±0.3	7.6** ±0.2	7.4* ±0.2	7.9** ±0.3
Week 8								
	7.5 ±0.1	7.6 ±0.3	7.8 ±0.4	8.2* ±0.7	7.6 ±0.3	7.6 ±0.5	7.8 ±0.1	8.0 ±0.5
Week 13								
	7.5 ±0.3	7.5 ±0.2	8.1 ±0.5	9.7** ±1.7	7.5 ±0.2	7.6 ±0.1	7.9 ±0.5	8.4 ±0.7

a- data taken from Table 7, pages 44-57 of the report; N=4 except at the 10 mg/kg dose level for week 13, where N=3. * $p < 0.05$ vs control; ** $p < 0.01$ vs control.

A slight reduction (5-10%) in the number of red cells was noted in male and female dogs at the 5 and 10 mg/kg/day dose levels, but was not labeled as statistically significant. Mean cell volume in male and female dogs was significantly increased at the 10 mg/kg/day dose level at weeks 8 and 13. Similar changes were observed in mean cell hemoglobin, with the exception that a significant increase was not observed in female dogs at week 8 of the study. A statistically significant reduction in mean cell hemoglobin concentration was observed in male and female dogs at the 5 mg/kg/day dose level on week 13 (females only), and at the 10 mg/kg/day dose level on weeks 8 (males only)

and weeks 13 (males and females).

The white blood cell differential analysis showed time- and dose-related increases in the numbers of neutrophils and monocytes in both male and female dogs. In most cases, these changes were not labeled as statistically significant, but did show time related increases in comparison to control values, especially at the 10 mg/kg/day dose level. Statistical significance was achieved for the increase in monocytes at the 10 mg/kg/day dose level in both male and female dogs at week 13 of the study.

The changes in prothrombin time, neutrophils, and monocytes were considered treatment-related effects by the registrant. The changes in red cell parameters were considered mild and not of toxicologic significance. It is presumed that the microscopic finding of compound-induced hepatitis seen in dogs at the 5 and 10 mg/kg/day dose levels may be related to these altered hematology parameters.

b) Blood Chemistry: Blood samples were obtained for clinical chemistry measurements at the same times as those obtained for hematology analysis. Blood for clinical chemistry analysis was placed into tubes containing lithium heparin. The following CHECKED parameters were measured using a KONE specific analyzer:

_X_ glucose*	_X_ AST(SGPT)*
_X_ albumin*	_X_ ALT(SGOT)*
_X_ globulin (calculated)	_X_ alkaline phosphatase
_X_ creatinine*	_-_ creatine phosphokinase
_X_ total bilirubin*	_-_ lactate dehydrogenase
_-_ direct bilirubin	_-_ sorbitol dehydrogenase
_-_ indirect bilirubin	_X_ gamma glutamyl trans-peptidase
_X_ urea nitrogen*	_-_ uric acid
_X_ total protein*	
_X_ calcium*	_X_ triglycerides
_X_ phosphate*	_X_ cholesterol
_X_ sodium*	_X_ chloride*
_X_ potassium*	

*EPA guideline requirement "-" not examined

A summary of treatment-related changes observed in serum chemistry is shown in the following table (Table 4):

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TABLE 4
Changes in Blood Chemistry Parameters in Male and Female Dogs from 13 week Dietary Administration of Metam Sodium[a]

	Dose Groups							
	males (mg/kg/day)				females (mg/kg/day)			
	0	1	5	10	0	1	5	10
AST (IU/L)								
pre-experimental								
	14.8 ±3.4	14.3 ±4.2	15.5 ±2.6	12.5 ±1.7	17.0 ±2.7	15.0 ±3.2	16.0 ±1.4	15.3 ±2.1
Week 13								
	20.8 ±7.4	19.5 ±4.0	50.3 * ±23.5	115.3** ±72.2	21.0 ±2.9	28.3 ±24.2	30.3 ±14.4	43.7* ±15.2
ALT (IU/L)								
pre-experimental								
	17.5 ±3.5	15.8 ±3.8	19.3 ±3.3	14.8 ±4.8	21.0 ±2.0	17.5 ±6.9	20.0 ±5.6	16.5 ±3.9
Week 13								
	28.5 ±3.8	29.0 ±8.5	429.3** ±451.6	711.3** ±283.2	29.8 ±9.0	134.5* ±213.2	207.5** ±201.7	266.7** ±28.4
ALK PHOS (IU/L)								
pre-experimental								
	197 ±32	210 ±20	223 ±47	193 ±49	185 ±16	198 ±27	199 ±27	182 ±8
Week 13								
	155 ±26	160 ±10	524* ±423	1177** ±374	141 ±18	157 ±24	377 ±340	588** ±178
creatine kinase (IU/L)								
pre-experimental								
	109 ±24	126 ±38	122 ±32	110 ±8	97 ±11	100 ±12	91 ±11	97 ±26
Week 13								
	79 ±24	84 ±14	93 ±22	154** ±54	74 ±8	76 ±14	71 ±14	81 ±26

	males (mg/kg/day)				females (mg/kg/day)			
	0	1	5	10	0	1	5	10
GGT (IU/L)								
pre-experimental								
	1.0 ±1.2	0.3 ±0.5	1.0 ±0.8	1.3 ±0.5	0.5 ±0.6	1.3 ±0.5	0.5 ±0.6	2.3 ±2.1
Week 13								
	0.8 ±1.0	0.5 ±1.0	1.5 ±1.7	4.7** ±0.6	0.8 ±1.0	0.8 ±1.0	1.3 ±2.5	4.0* ±5.2

[a]data were obtained from Table 7, pages 58-81. N=4 except at the 10 mg/kg dose level for week 13, where N=3 for both sexes.

As shown above, the major changes observed from analysis of blood for clinical chemistry parameters were in AST, ALT, ALK PHOS, and GGT. A significant increase in creatine kinase was observed in male dogs at the 10 mg/kg dose level for weeks 12 and 13, but a similar change was not observed in female dogs.

For AST, significant increases were evident at the 10 mg/kg/day dose level in male dogs by week 6, and in female dogs by week 12. By week 13, AST was increased 454% vs control in male dogs, and by 108% in female dogs.

A similar profile was reported for ALT in male and female dogs. However, the increase in ALT by week 13 for male dogs at the 10 mg/kg/day dose level was far greater (2395% increase vs control) as well as for female dogs (794% increase vs control). Interestingly, ALT activity in female dogs was increased by 351% vs control at the lowest dose tested, 1mg/kg/day, by week 13 of the study.

Statistically significant increases in ALK PHOS were evident in male dogs by week 6 of the study, and in female dogs on week 4 and at weeks 8 through 13. The increases in ALK PHOS, like other enzymes, were most evident at the 10 mg/kg/day dose level. In male dogs from the 10 mg/kg/day dose level, ALK PHOS was elevated by 659% vs control at week 13, while in female dogs, ALK PHOS was elevated by 95% in comparison to control female dogs. The increase in ALK PHOS for male and female dogs appeared dose and time-related beginning at the lowest dose tested, 1mg/kg/day.

Creatine kinase was primarily changed in male dogs at the 10 mg/kg dose level during weeks 12 and 13 of the study. At these time points, creatine kinase was elevated by 64 and 95% at weeks 12 and 13, respectively for male dogs at the high dose used. There were no apparent effects on creatine kinase at lower doses in male dogs, and female dogs showed no significant increases in activity of this enzyme during treatment.

Plasma GGT showed statistically significant increases in male dogs at the 10 mg/kg/day dose level on study weeks 12 and 13, and in female dogs at the 5 and 10 mg/kg/day dose level on week 12 and at the 10 mg/kg/day dose level on week 13. In male dogs, the increase in plasma GGT was approximately 470% for weeks 12 and 13, while in female dogs, GGT at 10 mg/kg/day was increased by 187% at week 12, and by 400% on week 13 in comparison to control.

Other changes considered to be of toxicologic significance by the registrant were: statistically significant reductions in plasma glucose and cholesterol in male dogs at week 13; statistically significant increases in triglycerides in week 4 in males at the 5 and 10 mg/kg/day dose level and in females at the 5 mg/kg/day dose level; statistically significant increases in calcium in male dogs at the 5 and 10 mg/kg/day dose levels during week 4 of the study; statistically significant increases in plasma bilirubin in male dogs at the 5 and 10 mg/kg/day dose levels at weeks 12 and 13 of the study. The registrant stated (page 22 of the report) that the changes in creatine kinase as well as the decreases in urea and creatinine in males observed at 10 mg/kg/day were possibly a reflection of poor clinical condition.

8) **Urinalysis**

Urine samples were obtained by catheterization during the week prior to termination. The following parameters were measured:

specific gravity	color
protein	general appearance
glucose	sediment examination
bilirubin	
urobilinogen	
ketones	
blood	

Results of urinary analysis were presented on pages 84-86 of the report. Individual animal results were presented on pages 199-206 of the report. At the 5 mg/kg/day dose, one male dog (#19) showed high levels of blood in urine, while one male (#20) and one female (#21) showed moderate amounts of urobilinogen and bilirubin. At the 10 mg/kg/day dose level, moderate to large amounts of protein were detected in 3 male dogs (#'s 25, 26, and 28) and in one female dog (#31). High levels of bilirubin were also detected in dog #25, and high levels of urobilinogen and bilirubin were seen in dog #26, 28, and 29. Female dog #31 also showed high levels of urobilinogen and bilirubin in urine. A high amount of blood was also observed for male dog #26. Five of the eight dogs at this dose level were also observed to have abnormal urine color.

9) **Anatomic and Histologic Pathology:**

Dogs sacrificed at study termination as well as those sacrificed in extremis were killed by exsanguination under deep pentobarbital anesthesia. All dogs were given a full post-mortem examination and the following tissues removed, trimmed, and weighed: brain, liver, kidneys, thyroid with parathyroid, adrenal glands, epididymides, and testes. All tissues collected from dogs were placed in 10% neutral buffered formalin except eyes, which were fixed in Davidson's solution and skin, testes, and mammary gland, which were fixed in Bouin's solution. The list of collected tissues is shown below.

Digestive	Respiratory	Urogenital
- tongue	x trachea	x kidneys*
x salivary glands*	x lungs*	x urinary bladder*
x esophagus*	x nasal cavity	x testes*
x stomach*		x epididymides*
x duodenum*		- seminal vesicle*
x jejunum*	x aorta*	x prostate
x ileum*	x heart*	x ovaries
x cecum*	x bone marrow*	x uterus*
x colon*	x lymph nodes*	- vagina
x rectum*	x spleen*	
x liver*	x thymus*	
x pancreas*		
x spleen		
x gall bladder		

Neurologic	Glandular	Other
x brain*	x adrenals*	x bone
x peripheral nerve*	x lacrimal gland	x skeletal muscle
x spinal cord (3 levels)*	x mammary gland	x skin*
x pituitary*	x parathyroids*	x all gross lesions*
x eyes	x thyroids*	

*EPA guideline requirement "-" not examined

a) Anatomic Pathology:

i) Organ Weights

Significant observations regarding organ weights are summarized in the following Table (Table 5).

Table 5
Absolute Organ Weights (grams) in Male and Female Dogs
Administered Dietary Metam Sodium for 13 Weeks[a]

	Dose Groups							
	males (mg/kg/day)				females (mg/kg/day)			
	0	1	5	10	0	1	5	10
Kidney	58.6 ±3.8	62.7 ±4.1	62.3 ±4.1	68.6* ±7.7	56.9 ±5.1	57.7 ±4.1	56.8 ±4.0	57.1 ±8.6

Table 5, cont.

	Dose Groups							
	males (mg/kg/day)				females (mg/kg/day)			
	0	1	5	10	0	1	5	10
testes	22.8	22.5	22.6	17.4				
% chng	±2.4	±1.2	±4.4	±6.6				

a- data taken from Table 11, pages 87-92 of the report.

As noted, few changes in terminal organ weight were observed in this study. Significantly higher kidney weight was observed in male dogs at the 10 mg/kg/day dose level, and testes weight was decreased by 24% in comparison to control values for male dogs at the 10- mg/kg/day dose level. Although not obvious from group mean data, reduced weights of the epididymides were also observed in 2 of the 4 male dogs at the 10 mg/kg/day dose level. The epididymides of 2 dogs were approximately 2g in weight, while those of the affected dogs were approximately 0.95g in weight, a reduction of about 50%.

ii) Macroscopic Lesions

Results of macroscopic examination of dogs used in this study was presented in Table 12, pages 94-96 of the report. In those dogs sacrificed in extremis, a distended gall bladder was reported in the female dog, while an accentuated lobular pattern and pale appearance were reported for the livers of both the male and female dog.

In those dogs surviving to study termination, the most prominent observations made from macroscopic examination were those in the liver. In 2 of the 3 surviving male dogs at the 10 mg/kg/day dose level, an accentuated lobular pattern, depressed red area(s), and pale (yellow) appearance were noted. Depressed red area(s) were noted in 2 of the surviving 3 female dogs at this dose level, and pale appearance of the liver in 1 female dog at this dose level.

At the 5 mg/kg/day dose level, depressed red areas of the liver were noted in 1 male and 1 female dog at this dose. Livers of all dogs were reported as macroscopically normal at the 1 mg/kg/day dose level.

iii) Microscopic Lesions

In those dogs sacrificed in extremis, a marked hepatitis was present in both the male and female dog. This lesion consisted of hepatocyte necrosis and degeneration, inflammatory cell infiltration, increased pigmentation in hepatocytes and Kupffer cells, and biliary proliferation. In addition, the testes and prostate gland of the male dog appeared immature.

The following observations are noted from the registrant's report regarding microscopic abnormalities found in surviving dogs:

Table 6
Microscopic Pathology in Male and Female Dogs
Administered Dietary Metam Sodium for 13 Weeks[a]

MALE dogs	Dose Group (mg/kg/day)			
	0	1	5	10
No. dogs examined:	4	4	4	3
	Dose Group (mg/kg/day)			
	0	1	5	10
liver:				
hepatitis, moderate	0	0	2	0
hepatitis, marked	0	0	0	3
bile duct proliferation				
minimal	0	0	0	0
slight	0	0	1	0
prostate:				
immature	0	0	0	1
testes:				
immature	0	0	0	1
thymus:				
reduced cortical lymphocytes	0	0	0	1
urinary bladder:				
increased mitosis epithelium				
minimal	0	0	1	1
slight	0	0	0	1

FEMALE dogs	Dose Group (mg/kg/day)			
	0	1	5	10
No. dogs examined:	4	4	4	3

Table 6, cont.

liver:				
hepatitis, moderate	0	0	1	2
hepatitis, marked	0	0	0	1
bile duct proliferation				
minimal	0	1	1	0
slight	0	0	0	0

[a]data taken from Table 13 pages 97-104 of the report.

As shown above, microscopic lesions observed in the liver of dogs sacrificed at study termination were similar in nature to those found in those dogs sacrificed in extremis. Other lesions noted were as follows: in male dogs, immature prostate and testes were observed in 1 of 3 dogs at the 10 mg/kg/day dose level, reduced cortical lymphocytes in 1 of 3 dogs at the 10 mg/kg/day dose level, and increases in mitosis of the urinary bladder epithelium at the 5 and 10 mg/kg/day dose levels. Bile duct proliferation was evident in 1 of 4 male dogs at the 5 mg/kg/day dose level.

In female dogs, moderate hepatitis was observed in 1 of 4 dogs at the 5 mg/kg/day dose level, and in 2 of 3 dogs at the 10 mg/kg/day dose level. Bile duct proliferation with inflammatory cell infiltration was evident in 1 of 4 female dogs at the 1 mg/kg/day dose level, and in 1 of 4 dogs at the 5 mg/kg/day dose level.

III. DISCUSSION

The subchronic oral toxicity of metam sodium was investigated in male and female dogs in partial fulfillment of 40 CFR §158.340, Toxicology Data Requirements, for registration of the active ingredient. The active ingredient (purity: 43.15%) was administered to dogs by gelatin capsule once daily for 13 weeks at doses of 0, 1, 5, and 10 mg/kg/day. Observations for mortality and clinical toxicity were made twice daily. Body weight and food consumption were recorded weekly. Clinical pathology (hematology and clinical chemistry) were made at a pre-test interval, during weeks 4 and 8 of the study, and again at study termination. Anatomic and histopathologic examinations were performed at study termination on all animals. Selected organs were weighed from all dose groups of dogs including controls.

Treatment related mortality was observed in this study. One male and one female dog at the 10 mg/kg/day dose level were sacrificed during administration of test material due to poor clinical condition (appearance of jaundice, inappetance, emaciation). No mortality was observed during administration of test material at lower doses of the test chemical.

Reductions in group mean body weight were observed primarily at the 10 mg/kg/day in both male and female dogs. In male dogs, absolute body weight was decreased by 9% vs control, and a 40%

decrease in body weight gain was reported for weeks 1-13 in male dogs at this dose in comparison to control weight gain. The decreases in body weight observed at the 10 mg/kg/day dose level in males were reported statistically significant beginning at week 10 and continuing until study termination. In female dogs, absolute body weight in treated dogs was not significantly decreased in relation to control values for the treatment period, but body weight gain for the treatment period was decreased by 20% at the 10 mg/kg/day dose level. Although this was not labeled as statistically significant, it appears that this was a treatment-related effect.

Food consumption was reported as the amount of food residue left by dogs after feeding. In this respect, increased residues were reported for dogs at the 10 mg/kg/day dose level. As shown in Table 2 above, increasing amounts of food were left by dogs with the progression of treatment at the high dose. A few dogs were also affected at the 5 mg/kg/day dose level, but not to the extent as that observed at the high dose. The significance of this finding may be a direct effect of test article or indirect nauseating effect of test chemical. As food efficiency was not reported, it is difficult to ascribe the decrease in body weight and weight gain to a direct effect of treatment.

Significant treatment-related effects on mean cell volume (increased at 10 mg/kg/day in both sexes at weeks 8 and 13), mean cell hemoglobin (significant increases in males and females at 10 mg/kg/day) MCHC (significant decreases in male and female dogs at 5 and 10 mg/kg/day), neutrophils (apparent time-related increase at the high dose for both sexes), and monocytes (time and dose-related increases for both sexes) were observed in this study These effects may be effects resulting from primary liver damage caused by the test chemical, and not a direct effect of the chemical itself. There was no evidence for anemia in this study.

Alterations in serum chemistry were observed at all dose levels used in this study. Statistically and biologically significant increases in ALT, AST, ALK PHOS, and GGT were observed in both sexes at the 1, 5, and 10 mg/kg/day dose levels. These indicators of hepatic damage coincide with the observations of jaundiced appearance in dogs, and the microscopic observation of hepatitis in both male and female dogs. The dose and time-related nature of the increase in serum enzymes points to a direct effect of test article administration. This result is also supported by the dose-related increase in severity of hepatitis, especially in male dogs.

The changes in organ weights observed in this study were confined to male dogs, and consisted of increased kidney weight at the 10 mg/kg/day dose level, and decreased testicular and epididymal weight at this dose level as well. The significance of the increase in kidney weight as well as the decrease in testicular and epididymal weight is not clear, but could be related to reduction in growth as suggested by the registrant due to reduced food intake. Further data on reproductive effects of metam sodium would be required to establish whether such a relationship existed.
Microscopically, moderate to marked hepatitis was the prominent finding in the majority of male dogs at the 5 mg/kg/day dose level. Moderate hepatitis was present in 2 of 4 dogs at the 5 mg/kg/day dose level, and marked hepatitis was reported in 3 of 3 dogs at 10 mg/kg/day. In females, the incidence of this lesion appeared less (moderate hepatitis in 1 of 4 dogs at 5 mg/kg/day, 2 of 3 at 10 mg/kg/day; marked hepatitis in 1 of 3 dogs at 10 mg/kg/day), but there was still a clear relationship between dose of test chemical and the appearance of this abnormality. The minimal to slight increase in mitosis of urinary bladder epithelium observed in 3 of 3 males at 10 mg/kg/day and in 2 of 3 females at this dose represents an increased turnover of cells, as no evidence of hyperplasia was evident. Nonetheless, this lesion was considered treatment-related by the registrant.

In summary, several toxicological effects were observed in this study in male and female dogs treated with Metam Sodium at 5 and 10 mg/kg/day, including decreased body weight gain, altered

hematology, marked increased in liver enzymes, and hepatitis. The toxicologic signs observed in female dogs at the lowest dose in this study did not make it possible for the establishment of a systemic NOEL.

IV. CONCLUSIONS

Metam sodium was administered to male and female dogs at nominal dose levels of 0, 1, 5, and 10mg/kg/day once daily for 13 weeks. Toxic effects were observed at all dose levels tested, but were primarily evident at the 5 and 10 mg/kg/day dose levels. These included decreased body weight and body weight gain in male and female dogs at 10 mg/kg/day, hematologic alterations (increased cell volume, cell hemoglobin, neutrophils, and monocytes; decreased MCHC) at 5 and 10 mg/kg/day, significant increases in plasma ALT, AST, ALK PHOS, and GGT at 5 and 10 mg/kg/day (including significantly increased ALT in female dogs at 1 mg/kg/day), increased amounts of blood, urobilinogen, bilirubin, and protein in urine at 5 and 10 mg/kg/day, and microscopic evidence of hepatitis at 5 and 10 mg/kg/day. A majority of the toxic effects observed in this study appeared dose- and time-related in treated dogs. No evidence of tumors was found in this study.

Based upon the results of this study, the systemic NOEL is < 1 mg/kg/day, and the systemic LEL is ≤ 1 mg/kg/day for female dogs, based upon the increase in plasma ALT observed in female dogs at 1 mg/kg/day and the biliary duct proliferation with inflammatory cell infiltration observed in female dogs at the 1 mg/kg/day dose level. For male dogs, the systemic NOEL = 1 mg/kg/day and the LEL = 5 mg/kg/day, based on statistically significant increases in plasma ALT, AST, and alkaline phosphatase, as well as increased incidence of hepatitis and bile duct proliferation.

V. CLASSIFICATION Core supplementary

This study does not satisfy the guideline requirement (§82-1) for a subchronic oral toxicity study in dogs, due to the lack of a systemic NOEL for toxicity.

TF Review 010028 Metam Sodium

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