FILE COPY

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, DC 20460

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

February 8, 1995

MEMORANDUM

SUBJECT: Carcinogenicity Peer Review Meeting on **METAM SODIUM**

FROM: Esther Rinde, Ph.D. E. R.
Manager, Carcinogenicity Peer Review
Health Effects Division (7509c)

TO: Addressees

Attached for your review is a package on **Metam Sodium** prepared by Dr. Timothy McMahon.

A meeting to consider the carcinogenicity classification of this chemical is scheduled for **Wednesday March 01, 1995**, at **10:00 am in Room 817, CM2.**

Addressees

S. Irene
W. Burnam
K. Baetcke
M. Van Gemert
K. Dearfield
H. Pettigrew
B. Fisher
L. Brunsman
E. Doyle
M. Copley
T. McMahon
Y. Ioannou
R. Hill
Y. Woo
A. Aranda
R. Ross/L. Brennecke

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

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Issues Addressed to the Health Effects Division Carcinogenicity Peer Review Committee in Connection with the Classification of Metam Sodium as a Carcinogen.

TO: Esther Rinde, Ph.D.
Manager, Peer Review for Carcinogenicity

FROM: Timothy F. McMahon, Ph.D. 2/8/95
Pharmacologist, Review Section I
Toxicology Branch II, Health Effects Division (7509C)

THRU: Yiannakis M. Ioannou, Ph.D.
Section Head, Review Section I
Toxicology Branch II, Health Effects Division (7509C) 2/8/95

and

Marcia Van Gemert, Ph.D. 2/8/95
Chief, Toxicology Branch II
Health Effects Division (7509C)

Attached is an overview of the carcinogenic potential of Metam Sodium, including data on mutagenicity, metabolism, and developmental and reproductive toxicity. These data are based upon evaluation of studies submitted to the Agency by the Metam Sodium Task Force.

TABLE OF CONTENTS

I. Scientific Issues Considered by Toxicology Branch II, Health Effects Division, in Connection with the Classification of Metam Sodium as a Carcinogen.

A. BACKGROUND

Metam Sodium (sodium-N-methyldithiocarbamate), also known as Vapam, Metham Sodium, and SMDC is a fumigant-type pesticide used as a non-selective preplant fumigant for control of weeds, nematodes, fungi, bacteria, and insects. There are approximately 35 different products containing metam sodium in concentrations ranging from 18-42% active ingredient. Use patterns for these various formulations include agricultural preplant soil fumigation, wood preservative, slimicide, tree root killer, and aquatic weed control. Approximately 10 million pounds of active ingredient were used in 1990, with 40-45% for agricultural purposes. For control of weeds, soilborne diseases, and nematodes infesting field and vegetable crops, the pesticide is applied at least 14 to 21 days prior to planting. As a slimicide, metam sodium is sprayed inside sewer mains and drain pipes; wood preservative uses involve injection of standing utility poles to control wood-destroying insects and to arrest wood rot.

As a result of the July 14, 1991 railcar accident in which thousands of gallons of metam sodium were spilled into the Sacramento River near Dunsmuir, California, the Environmental Protection Agency negotiated a settlement with the Metam Sodium Task Force. As per the settlement agreement and for reregistration purposes, the Task Force was required to conduct several toxicology and exposure studies. The toxicology data in this memorandum are based upon these submitted studies. Metam Sodium has not been previously subjected to peer review by the Health Effects Division Carcinogenicity Peer Review Committee.

B. Evaluation of Carcinogenicity Data

1. Two Year Carcinogenicity Study in Mice (Attachment **A**)

Reference: Horner, S.A. (1994): Metam Sodium: Two Year Drinking Study in Mice. Study # PMO841. Study Conducted by Zeneca Central Toxicology Laboratory, Cheshire, UK. MRID # 432335-01

In a two year carcinogenicity study in mice, Metam Sodium technical (43.15% active ingredient) was administered in the drinking water to groups of 55 male and 55 female C57BL/10JfCD-1/Alpk mice for 104 weeks at nominal dose levels of 0mg/ml, 0.019 mg/ml (**1.6 mg/kg** in males, **2.3 mg/kg** in females) 0.074 mg/ml (**6.5 mg/kg** in males, **8.7 mg/kg** in females) and 0.23 mg/ml (**27.7 mg/kg** in males, **29.9 mg/kg** in females). Carcinogenic potential was evidenced in this study by an increase in the incidence of angiosarcoma of the liver, spleen,subcutaneous tissue, and bone marrow of the femur and spleen, as well as the presence of a transitional cell papilloma in a single high dose male mouse and a transitional cell carcinoma in a single high dose female mouse. Tumorigenic evidence observed in this study is shown in the following table as extracted from the Qualitative Risk Assessment memorandum (Table 1):

Table 1

Male Angiosarcoma Tumor Rates[+] and Exact Trend Test and Fisher's Exact Test Results (p values)

	Dose (mg/kg/day)			
	0	1.6	6.5	27.7
Liver (%)	1/52 (2)	8/52 (15)	5/55 (9)	10[a]/52 (19)
p =	0.023*	0.016*	0.116	0.004**
Spleen (%)	6/53 (11)	3/53 (6)	10/55 (18)	21[b]/53 (40)
p =	0.000**	0.244[n]	0.233	0.001**
Bone Marrow (Femur) (%)	3/53 (6)	3/53 (6)	8[c]/55 (15)	15/53 (28)
p =	0.000**	0.661	0.113	0.002**
Bone Marrow (Spine) (%)	2/53 (4)	0/53 (0)	0/55 (0)	7[d]/53 (13)
p =	0.001**	0.248[n]	0.239[n]	0.080
Subcutaneous Tissue (%)	1/53 (2)	1/53 (2)	2[e]/55 (4)	5/53 (9)
p =	0.020*	0.752	0.514	0.103
All Other Sites[#] (%)	1/53 (2)	3/53 (6)	5[f]/55 (9)	9/53 (17)
p =	0.004**	0.309	0.112	0.008**
All Sites Combined (%)	7[g]/52 (13)	12[g]/52 (23)	12[g]/55 (22)	27[g]/52 (52)
p =	0.000**	0.155	0.191	0.000**

[+]Number of tumor bearing animals/Number of animals examined, excluding those that died before week 53.

[n]Negative change from control.

[a]First liver angiosarcoma observed at week 68, dose 27.7 mg/kg/day.

[b]First spleen angiosarcoma observed at week 68, dose 27.7 mg/kg/day.

[c]First bone marrow (femur) angiosarcoma observed at week 69, dose 6.5 mg/kg/day.

[d]First bone marrow (spine) angiosarcoma observed at week 88, dose 27.7 mg/kg/day.

[e]First subcutaneous tissue angiosarcoma observed at week 71, dose 6.5 mg/kg/day.

[f]First angiosarcoma at any other site observed in the sternum at week 73, dose 6.5 mg/kg/day.

[g]Seven, six, eighteen and forty animals in the 0, 1.6, 6.5, and 27.7 mg/kg/day dose groups, respectively, had angiosarcomas at multiple sites.

#Angiosarcoma sites include: abdominal cavity, aorta (adjacent tissue), bone (femur), bone marrow (femur), bone marrow (spine), heart, limb, liver, lung, lymph node (mesenteric), mediastinum, mesentery, spinal cord, spleen, sternum, subcutaneous tissue, and thoracic cavity.

As indicated above, there were significant dose-related trends in the incidence of angiosarcoma for male mice in the liver, spleen, bone marrow (femur and spine), and subcutaneous tissue. In addition, significant trends were observed for the incidence of angiosarcoma at all <u>other</u> sites combined (see footnote), as well as for <u>all</u> tissue sites combined. Significant pair-wise comparisons in the incidence of angiosarcoma were observed for the liver at the 1.6 mg/kg/day dose, and for the liver, spleen, and bone marrow (femur) at the 27.7 mg/kg/day dose. For all <u>other</u> sites and for <u>all</u> tissue sites combined, significant pair-wise differences were observed at the 27.7 mg/kg/day dose.

Table 2

Male Angioma and Angiosarcoma Tumor Rates[+] and Exact Trend Test and Fisher's Exact Test Results (p values)

	Dose (mg/kg/day)			
	0	1.6	6.5	27.7
Angiomas[&] (%)	2[a]/53 (4)	1/53 (2)	0/55 (0)	1/53 (2)
p =	0.378	0.500[n]	0.239[n]	0.500
Angiosarcomas[#] (%)	7/52 (13)	12/52 (23)	12/55 (22)	27[b]/52 (52)
p =	0.000**	0.155	0.191	0.000**
Combined (%)	8[c]/52 (15)	13/52 (25)	12/55 (22)	28/52 (54)
p =	0.000**	0.164	0.273	0.000**

[+]Number of tumor bearing animals/Number of animals examined, excluding those that died before week 53.

[n]Negative change from control.

[a]First angioma observed at week 100, dose 0 mg/kg/day.

[b]First angiosarcoma observed at week 68, dose 27.7 mg/kg/day.

[c]One animal in the 0 mg/kg/day dose group had both an angioma and an angiosarcoma.

[&]Angioma sites include: aorta (adjacent tissue), lymph node (mesenteric), and subcutaneous tissue.

Note: Significance of trend denoted at control. Significance of pair-wise comparison with control denoted at dose level. If *, then $p < 0.05$. If **, then $p < 0.01$.

As the above table shows, the statistical significance in tumor incidence is derived from the angiosarcoma incidence and not from the angioma incidence, which was not statistically different among treated and control male mice. It is noted that a statistically significant positive trend was observed for the incidence of angiosarcoma and angioma/angiosarcoma combined in male mice, as well as a statistically significant pair-wise comparison in the incidence of angiosarcoma and angioma/angiosarcoma combined for male mice at the high dose.

Table 3

Female Angiosarcoma Tumor Rates[+] and Exact Trend Test and Fisher's Exact Test Results (p values)

	Dose (mg/kg/day)			
	0	2.3	8.7	29.9
Liver (%)	0/54 (0)	0/55 (0)	1/47 (2)	4[a]/52 (8)
p =	0.005**	1.000	0.465	0.055
Spleen (%)	0/55 (0)	2/55 (4)	4[b]/47 (9)	5/52 (10)
p =	0.028*	0.248	0.042*	0.024*
All Other Sites[#] (%)	4/55 (7)	2/55 (4)	6[c]/47 (13)	7/52 (13)
p =	0.070	0.339[n]	0.275	0.232
All Sites Combined (%)	4/54 (7)	2[d]/55 (4)	6[e]/47 (13)	10[f]/52 (19)
p =	0.008**	0.331[n]	0.286	0.065

[+]Number of tumor bearing animals/Number of animals examined, excluding those that died before week 48.

[n]Negative change from control.

[a]First liver angiosarcoma observed at week 61, dose 29.9 mg/kg/day.

[b]First spleen angiosarcoma observed at week 48, dose 8.7 mg/kg/day.

[c]First angiosarcoma at any other site observed in the uterus at week 48, dose 8.7 mg/kg/day.

[d]Two animals in the 2.3 mg/kg/day dose groups had angiosarcomas at multiple sites.

[e]Five animals in the 8.7 mg/kg/day dose group had angiosarcomas at multiple sites.
[f]Six animals in the 29.9 mg/kg/day dose group had angiosarcomas at multiple sites.
[#]Other sites include: bone marrow (femur), bone marrow (spine), ear/Zymbal's gland, ileum, limb, mediastinum, ovary, salivary gland, spinal cord, sternum, subcutaneous tissue, and uterus.

Note: Significance of trend denoted at control. Significance of pair-wise comparison with control denoted at dose level.
If *, then $p < 0.05$. If **, then $p < 0.01$.

As noted above for female mice, significant dose-related trends were noted for liver and spleen angiosarcoma, and at all tissue sites combined. Significant pair-wise comparisons were noted in the incidence of angiosarcoma for the spleen at the 8.7 and 29.9 mg/kg/day dose levels, but not for liver.

Table 4

Female Angioma and Angiosarcoma Tumor Rates[+] and Exact Trend Test and Fisher's Exact Test Results (p values)

	Dose (mg/kg/day)			
	0	2.3	8.7	29.9
Angiomas[&] (%)	1/55 (2)	0/55 (0)	2[a]/47 (4)	2/52 (4)
p =	0.156	0.500	0.441	0.479
Angiosarcomas[#] (%)	4/54 (7)	2/55 (4)	6[b]/47 (13)	10/52 (19)
p =	0.008**	0.331	0.286	0.065
Combined (%)	5/54 (9)	2/55 (4)	8/47 (17)	11[c]/52 (21)
p =	0.009**	0.211[n]	0.194	0.075

[+]Number of tumor bearing animals/Number of animals examined, excluding those that died before week 48.

[n]Negative change from control.

[a]First angioma observed at week 87, dose 8.7 mg/kg/day.
[b]First angiosarcoma observed at week 48, dose 8.7 mg/kg/day.
[c]One animal in the 29.9 mg/kg/day dose group had both an angioma and an angiosarcoma.

[&]Angioma sites include: mammary gland, subcutaneous tissue, and uterus.

[#]Angiosarcoma sites include: bone marrow (femur), bone marrow (spine), ear/Zymbal's gland, ileum, limb, liver, mediastinum, ovary, salivary gland, spinal cord, spleen, sternum, subcutaneous tissue, and uterus.

Note: Significance of trend denoted at control.
Significance of pair-wise comparison with control denoted at dose level.
If *, then $p < 0.05$. If **, then $p < 0.01$.

As for the male mice, significance was observed only for the incidence of angiosarcoma and not angioma. Statistically significant positive trends were observed for angiosarcoma at all sites combined and for angioma/angiosarcoma combined. In contrast to the male mice, statistical pair-wise significance for the incidence of angiosarcoma at all sites combined at the high dose was not achieved in female mice, although the incidence was increased from 9% in controls to 21% at the high dose.

It is noted from the tumor data in this study that for the mice sacrificed while on study and those surviving to study termination, the sites of tumorigenicity were similar. It is also noted that significant tumor sites involving the bone marrow of the femur and spine were observed in male mice, but not in female mice.

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

Overall Incidence of Mice with Angiosarcoma in Any Site

	0.0 mg/ml	0.019 mg/ml	0.074 mg/ml	0.23 mg/ml
Males	7/52	12/52	12/55	27/52
Females	4/54	2/55	6/47	10/52

In males, the incidence of angiosarcoma in controls (13%) increased to 22 and 23% at the 0.019 and 0.074 mg/ml dose levels, and to 52% at the 0.23 mg/ml dose level. In female mice, the incidence in controls (7%) was exceeded only by the incidence at 0.074 mg/ml (13%) and 0.23 mg/ml (19%). According to the report, there was no treatment-related change in tumor latency for this tumor type.

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

Non-neoplastic pathology of the urinary bladder and liver was also observed in this study at the 0.23 mg/ml dose level, and is summarized in the following table (Table 2):

Table 2

Histopathologic Findings in Metam Sodium Treated Mice[a]

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

Table 2, continued

	Males (mg/ml)				Females (mg/ml)			
	0.0	0.019	0.074	0.23	0.0	0.019	0.074	0.23
submucosal hyalinization								
total	0	0	0	45	0	0	1	26
minimal	0	0	0	5	0	0	0	10
slight	0	0	0	33	0	0	1	15
moderate	0	0	0	7	0	0	0	1
Liver								
No. examined	55	55	55	55	55	55	55	55
fat vacuolation								
total	4	2	5	20	1	0	1	6
minimal	3	1	1	1	0	0	0	2
slight	1	1	4	10	1	0	1	3
moderate	0	0	0	9	0	0	0	1

[a]data taken from Table 12B, pages 184-212 of MRID # 432335-01.

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

At the 0.23 mg/ml dose level, body weight gain in male mice was decreased by 14% vs control for weeks 1-13 of the study, and by 20% for weeks 1-104 of the study. Liver weight in male mice was increased by 35% over control at this dose level and was accompanied by an increase in fat vacuolation. The incidence of non-neoplastic pathology of the urinary bladder was also increased at the 0.23 mg/ml in male mice. In female mice, non-neoplastic pathology of the urinary bladder was increased at the 0.23 mg/ml dose level, as was the incidence of angiosarcoma when all tissue sites were combined. There were no statistically significant effects of treatment on survival in male or female mice. Based on these effects, the high dose level of 0.23 mg/ml (**27.7 mg/kg** in males, **29.9 mg/kg** in females) is considered an adequate dose for assessment of carcinogenic potential in male and female mice.

2. Two Year Carcinogenicity Study in Rats (Attachment **B**)

Reference: Rattray, N.J. (1994): Metam Sodium: Two Year Drinking Study in Rats. Study # PRO838. Conducted by Zeneca Central Toxicology Laboratory, Cheshire, UK. MRID # 432758-02.

Metam Sodium technical (43.14% active ingredient) was administered in drinking water to groups of 64 male and female Hsd/Ola: Wistar Tox rats for either 52 weeks or 104 weeks at dose levels of 0 mg/ml, 0.019 mg/ml (**1.3 mg/kg** in males, **2.3 mg/kg** in females), 0.056 mg/ml (**3.9 mg/kg** in males, **6.2 mg/kg** in females), and 0.19 mg/ml (**12.0 mg/kg** in males, **16.2 mg/kg** in females). Evaluation of tumor data by Toxicology Branch II as presented in the study demonstrated no association of metam sodium treatment with increased incidence of carcinogenicity. Evaluation of tumor data by the California Environmental Protection Agency, Department of Pesticide Regulation indicated a possible tumorigenic effect of metam sodium at the 0.056 mg/ml dose. According to this review, the incidence of hemangiosarcoma (8/64) was increased in relation to the control incidence (0/64) and the high dose incidence (3/64). The hypothesis that this could be a positive response was based upon the positive findings in mice as well as the reasoning that the increased incidence of this tumor at 0.056 mg/ml could be based upon the decreased body weight observed at the high dose in relation to other doses. Lower body weight has often been shown to be associated with lower tumor incidence in rats.

Data on liver and pituitary neoplasms as reviewed by Toxicology Branch II are summarized below.

Table 5
Neoplastic Observations in Male and Female Rats Administered Metam Sodium in Drinking Water[a]

	Males (mg/ml)				Females (mg/ml)			
	0.0	0.019	0.056	0.19	0.0	0.019	0.056	0.19
All Animals								
Liver								
No. examined	64	64	64	64	64	64	64	64
hepatocellular adenocarcinoma	3	2	4	5	0	0	2	0
hepatocellular adenoma	2	1	3	4	1	1	1	2
Pituitary								
No. examined	64	63	63	62	62	63	63	64
adenoma	28	30	**33**	**35**	51	50	53	46

[a]data taken from Tables 17a-17b, pages 400-420 of MRID # 432758-02.

Evaluation of the liver and pituitary tumor data by the Science Analysis Branch, Health Effects Division showed a statistically non-significant trend ($p = 0.119$) for pituitary adenoma in male rats, as well as statistically non-significant pair-wise comparisons between treated and control male rats ($p = 0.323$, 0.234, and 0.129 for the low, mid, and high dose groups, respectively).
For liver adenoma, a statistically non-significant trend was identified ($p = 0.246$) as well as a statistically non-significant pair-wise comparsion of adenoma incidence among treated male rats ($p = 0.651$, 0.452, and 0.36 for the low, mid and high dose groups, respectively). For liver adenocarcinoma and adenoma/adenocarcinoma combined, similar statistically non-significant trends and comparisons were observed.

Summary of male rat blood tumor rates is made below, as analyzed by the Science Analysis Branch, Health Effects Division.

Table 6
Metam Sodium-Hsd/Ola: Wistar Rat Tox Study
Male Blood Tumor Rates[+] and Peto's Prevalence Test Results (p values)

	Dose (mg/kg/day)			
	0	1.3	3.9	12.0
Hemangiomas (%)	9[a]/50 (18)	3/50 (6)	4/51 (8)	8/51 (16)
p =	0.469[n]	0.950[n]	0.899[n]	0.688[n]
Hemangiomsarcomas (%)	0/47 (18)	3/49 (6)	8[b]/50 (8)	3/51 (16)
p =	0.414	0.017*	0.004**	0.073
Combined (%)	9/50 (18)	6/50 (12)	11[c]/51 (22)	11/51 (22)
p =	0.469[n]	0.950[n]	0.899[n]	0.688[n]

[+]number of tumor-bearing animals/number of animals examined, excluding those that died before observation of the first tumor.
[a]first hemangioma observed at week 56, dose 0 mg/kg/day.

[b]first hemangiosarcoma observed at week 66, dose 3.9 mg/kg/day.
[c]one animal in the 3.9 mg/kg/day dose group had both a hemangioma and a hemangiosarcoma.

[n]negative trend or negative change from control.

Note: Significance of trend denoted at control.

Significance of pair-wise comparison with control denoted at dose level.

If *, then $p < 0.05$. If **, then $p < 0.01$.

As shown by the above data, there were no statistically significant trends in tumor rates of male rats. However, there was a significant pair-wise comparison in the incidence of hemangiosarcoma in male rats at the 1.3 and 3.9 mg/kg/day dose levels in comparison to control.

The sites of hemangioma in the present rat study included the cervical lymph node, mesenteric lymph node, thymic lymph node, and subcutaneous tissue. Sites for hemangiosarcoma included the mesenteric lymph node, subcutaneous tissue, tail, liver, lung, and uterus. However, the preponderance of tumors were observed only in male rats.

The question of whether these tumors were observed in separate rats was addressed in the review of the rat study by the California Department of Environmental Protection (Earl Meierhenry, personal communication). This review showed that of the benign hemangiomas found, one rat in the low dose group was found to have this tumor type at 2 sites (mesenteric and thymic lymph nodes). Of the malignant hemangiosarcomas found, 2 rats in the low dose group were found to have this tumor type at 2 and 3 sites (liver and lung; liver, lung, and mesenteric lymph node, respectively).

The hypothesis that increased incidence of hemangiosarcoma observed at the 0.056 mg/ml dose level vs the 0.19 mg/ml dose level may be based upon a decreased body weight in rats at the 0.19 mg/ml dose is debatable. The rats in this study were not fed a calorie-restricted diet, nor was the amount of dietary intake strictly controlled. Although a statistically decreasing trend in mortality was observed for male rats, food intake, weight gain, and food efficiency were decreased at the 0.19 mg/ml dose in both sexes of rat. In addition, a review of the time to tumor formation for the rats observed with hemangiosarcoma at all dose levels shows that the tumors were observed at approximately the same time (from weeks 93-105), with only one rat at the mid dose observed with this tumor type at an earlier time point (week 66). It has been observed that in calorie-restricted animals, not only can tumor incidence be decreased, but the time to tumor can be delayed. It cannot be proved from the data in this study that such an effect occurred at the high dose. There is no support from the mouse carcinogenicity study even though positive results were observed, as species differences in sensitivity to carcinogens is known to exist.

Systemic Toxicity:

At the 0.19 mg/ml dose level, the following were observed:

1) decreased body weight gain for weeks 1-13 (12% decrease in males, 16% decrease in females)

2) decreased body weight gain for weeks 1-105 (18% in males, 20% in females)

3) decreased food consumption, food efficiency, and water consumption in male and female rats

4) Increased incidence of liver masses (8/64 vs 4/64 in control) and fat vacuolation (11/32 vs 8/28 in control) in male rats.

5) increased incidence of voluntary muscle wasting (9/64 vs 1/64 in control) in male rats

6) increased incidence of microscopic abnormalities of the nasal cavity, voluntary muscle, and sciatic nerve, as well as decreased incidence of mineralization of the aorta in male and/or female rats.

Further details of these changes can be seen in the data evaluation record for this study, as the changes are too numerous to reproduce here.

The high dose of 0.19 mg/ml was considered adequate for testing of the carcinogenic potential of metam sodium in rats, based on the decreases in body weight gain, food efficiency, and macroscopic and microscopic pathology observed in both sexes in this study. The chronic portion of the rat chronic toxicity/carcinogenicity study was considered adequate by the Health Effects Division RfD/Peer Review Committee. This study was classified as core **minimum** data.

C. Additional Toxicology Data

1. Chronic Toxicity in Dogs

Reference: Brammer, A. (1994): Metam Sodium: 1 Year Oral Toxicity Study in Dogs. Study # PD0905. Zeneca Central Toxicology Laboratory. MRID # 432758-01.

In this study, metam sodium was administered in gelatin capsule to four male and four female beagle dogs per group at doses of 0, 0.05, 0.1 or 1.0 mg/kg/day for 52 weeks. There was no mortality or treatment-related clinical signs of toxicity. Group mean body weight was unaffected in treated dogs vs controls. Hematologically, the only significant treatment-related change was an increase in kaolin-cephalin time at the 1.0 mg/kg/day dose in male and female dogs. The significance of this change in the absence of other hematological alterations is questionable. Group mean activity of ALT at the 1.0 mg/kg/day dose in female dogs gradually increased over the course of the study until week 52, when the mean value was three times that of control. However, the difference was due to one female whose level peaked at 400 IU/l during weeks 45 and 52. At necropsy, the only treatment-related finding was in the one dog observed with increased ALT. This dog had a slight increase in hepatocyte and macrophage/Kuppfer cell pigmentation, slight mononuclear cell infiltration, slight telengiectasis and a positive reaction for hemosiderin. The systemic LOEL in males was > 1.0 mg/kg/day, and = 1.0 mg/kg/day in females. The systemic NOEL was $\geq$ 1 mg/kg/day in males, and was = 1.0 mg/kg/day in females. This study was graded as **core minimum** and satisfies the guideline requirements for a chronic toxicity study in the dog.

It is noted that the Health Effects Division RfD/Peer Review Committee, in their meeting of December 1, 1994, recommended changing the NOEL in female dogs from 0.1 mg/kg/day to 1.0 mg/kg/day, based on the questionable significance of the changes observed in female dogs at the 1.0 mg/kg/day dose.

2. Subchronic Toxicity in Dogs

Reference: Brammer, A. (1992): Metam Sodium: 90-Day Oral Dosing Study in Dogs. Study # CTL/P/3679. ICI Central Toxicology Laboratory. MRID # 426000-01

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. The systemic NOEL is < 1 mg/kg/day, and the systemic LEL is $\leq$ 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.

3. Subchronic Toxicity Study in Mice

Reference: Whiles, A.J. (1991): Metam Sodium: 90-Day Drinking Water Study in Mice with a 28-Day Interim Kill. Study # PM0808. ICI Central Toxicology Laboratory. MRID # 421173-01

Metam Sodium was administered to male and female mice in the drinking water at dose levels of 0.018 mg/ml (**2.7 mg/kg/day** for males; **3.6 mg/kg/day** for females), 0.088 mg/ml (**11.7 mg/kg/day** for males; **15.2 mg/kg/day** for females), 0.35 mg/ml (**52.4 mg/kg/day** for males; **55.4 mg/kg/day** for females) and 0.62 mg/ml (**78.7 mg/kg/day** for males; **83.8 mg/kg/day** for females) for 90 days. The systemic NOEL was 0.018 mg/ml (**2.7 mg/kg/day** for males; **3.6 mg/kg/day** for females) and the systemic LEL was 0.088 mg/ml (**11.7 mg/kg/day** for males; **15.2 mg/kg/day** for females), based on urinary bladder lesions (eosinophilic granules, cystitis and mucosal hyperplasia) in both sexes as well as decreased hemoglobin, hematocrit, and red blood cells in female mice. The Maximum Tolerated Dose appeared to be achieved at the 52.4 mg/kg/day dose in males, and the 83.8 mg/kg/day dose in females, based on decreased body weight gain at these dose levels. This study was classified as **supplementary** by the original reviewer as well as by the Health Effects Division RfD/Peer Review Committee.

4. Subchronic Toxicity in Rats

Reference: Allen, S.L.(1991): Metam Sodium: 90 Day Drinking Water Study in Rats. Study # PRO797. ICI Central Toxicology Laboratory. MRID # 421173-02.

Metam sodium was administered to male and female rats in drinking water at nominal dose levels of 0, 0.018, 0.089, and 0.443 mg/ml (1.7, 8.1, and 26.9 mg/kg/day in males; 2.5, 9.3, and 30.6 mg/kg/day in females). At the high dose in both sexes, systemic toxicity in the form of significantly decreased food and water consumption, decreased body weight gain, and histological changes in the nasal cavity olfactory epithelium were observed. At the high dose, renal tubular dilatation and basophilia, along with increases in blood, protein, and red cells in urine was also observed. In high dose males, an increased incidence of plasma cell hyperplasia in cervical lymph nodes was demonstrated as well as a significant decrease in platelet count. A significant decrease in group mean body weight was observed in female rats at the mid dose, and body weight gain was decreased 11% at this dose for the duration of the study. Significant decreases in red cell count and hematocrit were also observed at the mid dose in both male and female rats. A tentative NOEL of 1.7 mg/kg/day for males and 2.5 mg/kg/day for females was established. A tentative LEL of 8.1 mg/kg/day for males [hematological changes] and 9.3 mg/kg/day for females [decreased absolute body weight] was established.
The Tentative Maximum Tolerated Dose = 26,9 mg/kg/day (males); 30.6 mg/kg/day (females); decreased absolute body weight, body weight gain; alterations in hematology and clinical chemistry parameters; increased incidence of histopathological abnormalities.
This study was classified as **supplementary** by the original reviewer as well as by the Health Effects Division RfD/Peer Review Committee.

5. Mutagenicity

i.) Reference: Cifone, M.A. (1987): Mutagenicity Test on Metam Sodium in the Rat Primary Hepatocyte Unscheduled DNA Synthesis Assay. Study # HLA 9736-0-447. Study performed by Hazleton Laboratories America, Inc. and submitted under MRID # 403056-01.

In this study, freshly isolated hepatocytes from male Fischer 344 rat liver were incubated with metam sodium at concentrations of 0.5, 1.0, 2.5, 5.0, 10.0, 50.0, 100.0, and 250.0 nl/ml. Incubations were at 37 ^{o}C for 18-20 hours in the presence of tritiated thymidine. The 250 nl/ml dose was selected based on the results of preliminary testing showing a relative survival range of 17% at 100 nl/ml to 55.3% at 50 nl/ml. Results of the main study showed that metam sodium caused no significant changes in nuclear labeling of primary rat hepatocytes at the concentrations tested.

Classification: **acceptable**

ii) Hoorn, A.J. (1987): Mutagenicity Test on Metam Sodium in the Rec$^-$ Assay with Bacillus subtilis. Study # HBC E-9642-0-404. Study performed by Hazleton Biotechnologies Veenedal Lab, Netherlands, and submitted under MRID # 403056-02.

In this study, Bacillus subtilis strains H17 and M45 were incubated in the absence and presence of metabolic activation (rat liver S-9) with metam sodium at doses of 0.1, 1.0, 5.0, 10.0, 25.0, 50.0, 100.0, and 150.0 µl/plate. Metam sodium failed to induce recombinogenic activity in Bacillus subtilis strains H17 and M45 at the concentrations tested.

Classification: **acceptable** (HED document # 007027)

iii) Engelhardt, G. (1987): Report on the Study of Metam Sodium in the Ames Test. Study # BASF 87/0208. Study performed by BASF Aktiengeselleschaft Dept. of Toxicology, FRG and submitted under MRID # 403056-03.

In this study, metam sodium was non-mutagenic to Ames Salmonella typhimurium strains TA92, TA98, TA100, TA1535, TA1537, and TA1538 in the absence or presence of metabolic activation (rat liver S-9). Concentrations tested were: 20, 100, 500, 1000, 1500, 2000, and 2500 µg/plate in the standard plate test, and 4, 20, 100, 200, 300, 400, 500, 1000, and 2500 µg/plate, in the pre-incubation test.

Classification: **acceptable**

iv) Gelbke, H.P. (1987): In Vitro Cytogenetic Investigation in Human Lymphocytes with Metam Sodium. Study # BASF 87/0116. Study Performed by BASF Aktiengeselleschaft Dept. of Toxicology, FRG and submitted under MRID # 403056-04.

In this study, 48-hour cultures of human lymphocytes were exposed to 1, 5, 10, and 20 µg/ml metam sodium in the absence of metabolic activation and to 10, 20, and 40 µg/ml metam sodium in the presence of rat liver S-9. Incubations were for 24 hours at 37 ^{o}C. In the absence and presence of metabolic activation, metam sodium demonstrated a dose-dependent and statistically significant increase in the number of chromosomally damaged cells. There was no significant increase in the numerical chromosome abberations in treated vs solvent controls.

Classification: **acceptable**

v) Gelbke, H.P. and Engelhardt, G. (1987): Cytogenetic Study in Vivo of Metam Sodium in Chinese Hamsters, Bone Marrow Chromosome Analysis. Study # BASF 87/0238. Study performed by BASF Aktiengeselleschaft Dept. of Toxicology, FRG and submitted under MRID # 403056-05.

Metam Sodium was tested for clastogenicity in Chinese hamsters after single oral doses of 150, 300, and 600 mg/kg. Five animals per sex were sacrificed at 6, 24, and 48 hours post-dose for examination of bone marrow cells. At the dose levels tested, metam sodium was not clastogenic in Chinese hamster bone marrow.

Classification: **acceptable** (HED document # 007027)

6. Metabolism

Reference: Hawkins, D.R., Elsom, L.F., and Girkin, G. (1987): The Biokinetics and Metabolism of ^{14}C-Metam Sodium in the Rat. Study conducted by Huntingdon Research Centre, Cambridgeshire, UK and submitted under MRID # 406410-00.

Single oral doses of 10 mg/kg and 100 mg/kg ^{14}C-Metam sodium (purity > 99%) were administered to groups of male and female Sprague-Dawley rats (no. rats per group not specified). Urine and feces were collected up to 168 hours post-dose, while expired air was collected up to 72 hours post-dose. The time course of radioactivity in plasma was also investigated at the 10 and 100 mg/kg dose levels in five rats/sex/dose.

At the 10 mg/kg dose, urine was the major route of excretion, representing between 52-58% of the administered dose. Excretion through expired air represented between 32-38% of the administered dose, while between 3-4% was excreted through feces. At the 100 mg/kg dose, urinary excretion was decreased to between 37-42% of the administered dose, while excretion through expired air increased to between 47-53% of the administered dose. Fecal excretion remained low (between 1.5-1.8% of the administered dose).

At the low dose, the majority of collected radioactivity in expired air represented CO_2 (18-19% of administered dose) or COS and/or CS_2 (14-18% of the administered dose). A minor amount of MITC was observed (0.45-1.26% of the administered dose). At the high dose, the majority of collected radioactivity in expired air represented MITC (24-24.5% of the administered dose) and COS and/or CS_2 (18-21% of the administered dose), with only minor amounts of CO_2 (5.5-7.2% of the administered dose).

The time course of excretion was similar at the 10 and 100 mg/kg dose, with the shift being primarily in the percentages excreted through urine and expired air. A shift in biotransformation is indicated at the 100 mg/kg dose.

Tissue distribution at 168 hours post-dose showed the highest amounts of radioactivity in the thyroid (1.28-3.09 µg/g at 10 mg/kg; 6.24-7.55 µg/g at 100 mg/kg). Relative to other tissues, high concentrations of residual radioactivity were also observed in the liver, lung, and kidney. In general, tissue levels were higher in female rats than male rats at 168 hours.

Results of plasma time course measurements showed a T_{max} of 1.0 hours at the 10 mg/kg dose in both sexes, and a T_{max} of 0.25-1.0 hours at the 100 mg/kg dose. Half-life of elimination was unaffected by the increase in dose (60.8-74.1 hours at the 10 mg/kg dose [males and females]; 61.7-64.2 hours at 100 mg/kg [males and females]), and AUC was proportional to dose, indicating first-order kinetics at both dose levels.

The urinary and tissue profile of metam sodium metabolites was similar to that observed following dazomet administration; that is, the N-acetylcysteine conjugate of methyl isothiocyanate (MITC) was identified in urine as a major component (16.1-23.3% of the administered dose) at both dose levels, as was the glycine conjugate of MITC (5.1-8.2% of the administered dose at both dose levels). In the liver and kidney, the N-acetylcysteine conjugate of MITC was also identified as the major metabolite, as was the case for dazomet.

7. Reproductive and Developmental Toxicity

On October 15, 1991, the Health Effects Division Developmental and Reproductive Toxicity Peer Review Committee met to discuss the existing developmental and reproductive toxicity database for metam sodium. At that time, only two studies had been submitted for review: A developmental toxicity study in rats (MRID #'s 41577101, 42170101, and 92097012) and a developmental toxicity study in rabbits (MRID # 40330901 and 92097013). Several deficiencies were observed in the review of these 2 studies, but the available evidence suggested that metam sodium induced developmental toxicity. In the rat study, treatment related effects (increased incidence of skeletal variations, retardations, and anomalies) were observed at doses as low as 4.2 mg/kg/day (LDT). In addition, two fetuses from one litter at the high dose of 51 mg/kg/day were observed with meningocoele. In this study, the maternal NOEL was stated as 4.2 mg/kg/day and the developmental NOEL as $\leq$ 4.2 mg/kg/day. In the rabbit study, the maternal NOEL was established at 12.6 mg/kg/day based on reduced body weight gain, while the developmental NOEL was established at 4.2 mg/kg/day, based on an increased number of dead implantations, reduced number of fetuses, and increased post-implantation loss at the mid and high dose. At the high dose, one fetus was observed with meningocoele, while spina bifida was observed in one fetus at the high dose.

Since review of these studies by the Peer Review Committee, two developmental toxicity studies and one 2-generation reproduction study have been submitted and reviewed by Toxicology Branch II, Health Effects Division. Summaries of these studies are shown below:

A) Metam Sodium: Developmental Toxicity Study in the Rat

Reference: Tinston, D.J. (1993): Metam Sodium: Developmental Toxicity Study in the Rat. MRID # 429837-01. Conducted by Zeneca Central Toxicology Laboratory. Study # RR0624.

Wistar rats from the Barriered Animal Breeding Unit, Biological Services Section, Zeneca Central Toxicology Laboratory, Cheshire, UK received either 0, 5, 20, or 60 mg metam sodium/kg/day by oral gavage on gestation days 6 through 17 inclusive. Insemination was by natural means. Test compound (43% w/w active ingredient in aqueous solution, 525.54 g/l, batch no. BAS/005/00N) was adjusted for the above doses.

Maternal toxicity was noted at the 20 and 60 mg/kg/day dose levels in the form of decreased body weight gain during the period of treatment, and a decrease in food efficiency during test article administration. The decrease in food efficiency supports a test article related effect during the period of dosing. Therefore, the **Maternal Toxicity NOEL = 5 mg/kg/day**, and the **Maternal Toxicity LEL = 20 mg/kg/day** based on reduced body weight gain and decreased food efficiency.

Developmental toxicity was suggested at the 20 and 60 mg/kg/day dose levels in the form of an increase in total resorptions and resorptions/dam at the 60 mg/kg/day dose level, and a significant decrease in mean fetal weight at the 20 and 60 mg/kg/day dose levels. Developmental toxicity was also suggested at the 20 and 60 mg/kg/day dose levels in the form of a significant increase in the fetal and litter incidence of unossified centrum of the 4th, 5th, and 6th cervical vertebrae, an increase in the litter incidence of unossified 5th sternebrae at the 60 mg/kg/day dose level, a significant increase in the fetal incidence of unossified odontoid, centrum of the 2nd cervical vertebrum, ventral tubercle, and calcaneum at the 20 and 60 mg/kg/day dose levels. In addition, litter incidence of unossified odontoid, unossified centrum of the 2nd cervical vertebrum, and unossified ventral tubercle was also significantly increased over control at the 60 mg/kg/day dose level. Therefore, the **Developmental Toxicity NOEL = 5 mg/kg/day** and the **Developmental Toxicity LEL = 20 mg/kg/day** based on the increased incidence of skeletal observations and the increase in total resorptions and resorptions/dam.

This study is classified as Core Guideline Data and satisfies the 1984 Guideline Requirement (§ 83-3a) for a developmental toxicity (teratology) study in rats.

Although dose selection rationale for the present study was not stated, a previous study (MRID # 415771-01) in which oral doses of metam sodium of 0, 10, 40, and 120 mg/kg/day were given to Wistar rats on days 6-15 of gestation noted maternal toxicity at the 40 and 120 mg/kg/day dose levels and developmental toxicity at the 10 and 120 mg/kg/day dose levels.

B) Metam Sodium: Developmental Toxicity Study in the Rabbit

New Zealand White rabbits from Interfauna UK Limited, Huntingdon, Cambridgeshire, UK, received either 0, 5, 20, or 60 mg metam sodium/kg/day by oral gavage from gestation day 8 through 20, inclusive. The animals were received time-pregnant from the vendor. The test compound 43.14% w/w active ingredient concentration in liquid form (525.54 g/L, Batch 90/2, Y06930/007/001 and YA6930/008) was adjusted for the above doses.

Maternal toxicity was noted in the mid and high dose group in the form of increase incidence of few feces and red/orange staining on the cage tray in the 60 mg metam sodium/kg/day group compared with the control group, a treatment related decrease in body weight gain in the mid and high dose groups during the dosing period with a rebound in the high dose group following dosing. Also the dosing plus post dosing period and entire gestation period (not including gestation days 0-4) along with the corrected body weight gains for these periods, support this observation. Food consumption was reduced in the mid and high dose groups during the dosing period, with a rebound in food consumption to control levels in the high dose group following dosing. The dosing plus post dosing periods and the entire gestation period (not including gestation days 0-4). Food efficiency was reduced during the dosing period, post dosing period, entire gestation period (minus gd 0-4), and for the corrected body weight periods for the mid and high dose groups. This is evidence of toxicity and supports the body weight gain findings. Therefore, the **Maternal Toxicity NOEL = 5 mg/kg/day, and the Maternal Toxicity LOEL = 20 mg/kg/day** based on the reduced body weight gain, reduced food consumption and food efficiency.

Developmental toxicity was noted in the high dose groups in the form of increased resorptions including total litter resorptions, a decrease in the number of live fetuses and mean litter size, and an increase in post-implantation loss. There was also a decrease in mean fetal body weight noted in the high dose group. Developmental toxicity was noted in the mid dose group in the form of increased incidence of sutural bones between the parietals, misshapen hyoid, partially ossified transverse process of the cervical vertebrae, and 27 presacral vertebrae. There was an increased incidence in the high dose group in the 27 presacral vertebrae and 7 sternebrae (usually only 6 present). Therefore, the **Developmental Toxicity NOEL = 5 mg/kg/day and the Developmental Toxicity LOEL = 20 mg/kg/day** based on the increased incidence of skeletal observations.

The study is classified as Core Minimum Data and satisfies the 1984 Guideline Requirement (§ 83-3 b) for a developmental toxicity (teratology) study in rabbits.

The above findings were in general, similar to what was seen in the previous study conducted with metam-sodium (MRID# 403309-01, *Report on the Study of the Prenatal Toxicity of Metam-Sodium (aqueous solution) in rabbits after Oral Administration (gavage)*, BASF Aktiengesellschaft for BASF CORPORATION CHEMICALS DIVISION, Project No. 38R0232/8579, July 15, 1987).

C) Reproductive Toxicity of Metam Sodium in the Rat

Reference: Milburn, G.M. (1993): Metam Sodium: Multigeneration Study in the Rat. Study # RR0564/F0; RR0564/F1. Conducted by Zeneca Central Toxicology Laboratory and submitted under 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).

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) **).**

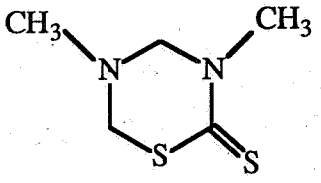
There were no apparent effects of metam sodium on reproductive performance in the F_0 or F_1 generations in this study. **The NOEL for reproductive toxicity is $\geq$ 0.1 mg/ml and the LOEL for reproductive toxicity is > 0.1 mg/ml.**

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

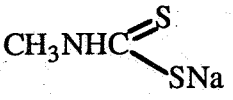
In summary, the recently submitted data on developmental and reproductive toxicity of metam sodium support the earlier conclusion of the Peer Review Committee that metam sodium is a developmental toxicant. The NOELs and LELs established in the new studies confirm the levels at which developmental toxicity was observed in the previous studies. It is noted that in the recently submitted rat study, meningocoele was observed at the high dose in one fetus from one litter, as was internal hydrocephaly in three fetuses from three litters, supporting earlier findings of neural tube defects / brain malformations from metam sodium administration at high doses.

D. Structure-Activity Considerations

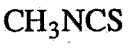
Although not structurally related, metam sodium, dazomet, and methylisothiocyanate (MITC) are related by virtue of the metabolism of all three of these chemicals to MITC or conjugates of MITC. Thiram can be considered structurally related to metam sodium as a dithiocarbamate. Structures of these chemicals are as follows:



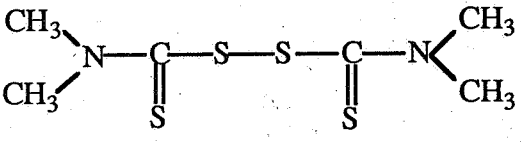
Dazomet



Metam Sodium



Methyl isothiocyanate (MITC)



Thiram

Thiram

In a 2-year feeding study in rats with Thiram (MRID # 421576-01), statistically significant positive trends were observed for development of thyroid C-cell adenomas in both male and female rats using dose levels of 0, 30, 150, and 300ppm thiram. In addition, significant positive trends were observed for development of hepatocellular adenomas in both sexes, but the incidence at the 300ppm dose was not statistically different from control incidence.

Data from IARC (Vol.12, 1976) list both the rat study mentioned above as well as human data derived from 105 Soviet workers making thiram for 3 years. These human data showed an incidence of 1 thyroid malignancy over the 3 year period for these 105 workers. A rat study in which both thiram and sodium nitrite were administered resulted in a high incidence of nasal adenomas, adenocarcinomas, olfactory carcinomas, and squamous cell carcinomas. No tumorigenic activity was observed from administration of thiram or sodium nitrite alone.

Based on these data, the conclusion of IARC with regard to thiram was that there was inadequate evidence of carcinogenicity. Thiram was assigned to risk category 3 (not classifiable).

MITC

Drinking water carcinogenicity studies have been performed for this chemical in both rats and mice, and these data have been submitted to HED for review (Accession #'s 257766 and 257759-257763). Although both studies were core graded as supplementary data, administration of MITC in drinking water did not appear to result in increased incidence of tumors in either rats or mice.However, the dose levels tested were not considered adequate for evaluation of the carcinogenic potential of MITC.

The results of these studies have also been published in *Nippon Noyaku Gakki Shi* 15(2): 297-304 (1990), which concluded that no carcinogenic activity was observed for MITC in drinking water studies with rats and mice. It appears that a final determination of the carcinogenic potential of this chemical has not been reached.

Dazomet

Dazomet has been subject to peer review through the Health Effects Division Carcinogenicity Peer Review Committee. This chemical was classified as Group D - not classifiable as to human carcinogenicity. This decision was based upon both rat and mouse studies submitted to and reviewed by Toxicology Branch II. In the submitted mouse study (MRID # 418651-01), female mice were found to have a significant dose-related trend in hepatocellular adenoma and combined adenoma/carcinoma. No significant pair-wise comparisons with control were evident, and the prevalence of this tumor type in the $B_6C_3F_1$ mouse made it difficult to assign the tumors as a treatment-related effect.

In the submitted rat study (MRID # 418650-01), there appeared to be no treatment-related effect on the incidence of tumors in male and female rats.

E. Weight-of-Evidence Considerations

The Health Effects Division Carcinogenicity Peer Revire Committee is asked to consider the following toxicology data in determining the carcinogenic potential of Metam Sodium:

1. In the mouse carcinogenicity study, administration of metam sodium technical in drinkig water for 2 years was associated with an increase in the incidence of angiosarcoma of the liver, spleen, and subcutaneous tissue, as well as the presence of a transitional cell papilloma in a single high dose male mouse and a transitional cell carcinoma in a single high dose female mouse. When considered irrespective of site of origin,the incidence of angiosarcoma in control male mice (13%) increased to 22% at the 0.019 and 0.074 mg/ml dose levels, and to 49% at the 0.23 mg/ml dose level. In female mice, the incidence in controls (7%) was exceeded only by the incidence at 0.074 mg/ml (11%) and 0.23 mg/ml (18%). According to the report, there was no treatment-related change in tumor latency for this tumor type. Angiosarcoma was considered a factor contributory to death in those mice with this tumor type at the high dose.

2. In an *in vitro* cytogenetics assay, 48-hour cultures of human lymphocytes were exposed to 1, 5, 10, and 20 µg/ml metam sodium in the absence of metabolic activation and to 10, 20, and 40 µg/ml metam sodium in the presence of rat liver S-9. Incubations were for 24 hours at 37 ^{o}C. In the absence and presence of metabolic activation, metam sodium demonstrated a dose-dependent and statistically significant increase in the number of chromosomally damaged cells. There was no significant increase in the numerical chromosome abberations in treated vs solvent controls.

Mutagenicity testing of metam sodium in an unscheduled DNA synthesis assay with primary rat hepatocytes, a Rec^{-} assay with Bacillus subtilis, an Ames Salmonella assay, and an *in vivo* cytogenetics assay with Chinese Hamster Ovary cells produced negative results in all these studies.

3. Metam sodium is structurally related to Thiram, and related to Dazomet and MITC by virtue of formation of MITC as the common end-product from metabolism of these chemicals. The experimental evidence from these other chemicals is limited, but indicates some evidence for carcinogenic potential.

4. Metam Sodium has not been previously classified for carcinogenicity by the Health Effects Division Carcinogenicity Peer Review Committee.

011139

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

JUL 29 1994

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

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

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

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

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

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

and

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

Registrant: Metam Sodium Task Force

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

Executive Summary:

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

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

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

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

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

Executive Summary:

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

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

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

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

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

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

Data Evaluation Record

Study type: Carcinogenicity - mice
Guideline: 83-2

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

Test material: Metam Sodium

Chemical name: Sodium N-methyldithiocarbamate

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

Sponsor: Metam Sodium Task Force

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

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

Author(s): S. A. Horner

Study Completed: April 20, 1994

Executive Summary:

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

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

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

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

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

I. MATERIALS AND METHODS

A. Test Material:

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

B. Test Animals

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

C. Animal Husbandry

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

D. Drinking Water Mixtures

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

D. Stability and Homogeneity

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

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

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

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

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

Table 1

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

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

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

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

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

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

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

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

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

E. Experimental Design and Dosing

The following experimental design was used for this study:

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

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

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

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

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

E. Statistical Analysis

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

F. Compliance

A signed statement of no data confidentiality claims was provided.

A signed statement of GLP compliance was provided.

A signed statement of quality assurance was provided.

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

II. OBSERVATIONS AND RESULTS

A. **Mortality and Clinical Observations**

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

TABLE 1

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

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

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

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

B. Clinical Observations

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

Table 2

Clinical Observations in Metam Sodium Treated Mice[a]

	Males (mg/ml)			
	0.0	0.019	0.074	0.23
coat greying				
no. obs.	642	762	932	398
no. of animals	17	24	25	9
hair loss				
no. obs.	164	246	67	49
no. of animals	16	20	9	3
left ear torn				
no. obs.	57	232	925	808
no. of animals	2	4	15	11
	Females (mg/ml)			
	0.0	0.019	0.074	0.23
coat greying				
no. obs.	542	403	218	476
no. of animals	14	13	9	13
hair loss				
no. obs.	557	541	245	186
no. of animals	28	27	21	16
left ear torn				
no. obs.	0	200	1134	759
no. of animals	0	3	18	13

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

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

C. **Body Weights**

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

TABLE 3

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

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

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

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

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

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

TABLE 4

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

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

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

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

C. **Food Consumption and Efficiency**

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

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

TABLE 5

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

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

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

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

TABLE 6
Group Mean Food Efficiency (%) in Male and Female Mice Given Metam Sodium in the Diet for 104 Weeks [a]

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

[a]data calculated by reviewer.

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

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

D. **Water Consumption**

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

Table 7
Water Consumption (ml/mouse/day) in Male and Female Mice Receiving Metam Sodium in Drinking Water[a]

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

Table 7, cont.

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

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

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

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

E. Intake of Metam Sodium

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

TABLE 8

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

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

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

F. Ophthalmoscopic Examination

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

G. Clinical Pathology

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

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

a) Hematology

The following CHECKED hematological parameters were examined:

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

*EPA guideline requirement

"-" not analyzed

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

H. **Macroscopic Observations**

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

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

Table 9

Macroscopic Findings in Metam Sodium Treated Mice[a]

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

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

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

H. **Organ Weights**

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

liver
kidneys
testes
adrenals
brain
epididymides

Organ / body weight ratios were also calculated.

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

Table 10

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

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

Table 10, cont.

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

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

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

I. Microscopic Observations

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

Digestive

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

Respiratory

x trachea
x lungs*
x nasal cavity

Cardiovascular

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

Urogenital

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

Neurologic

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

Glandular

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

Other

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

*EPA guideline requirement "-" not examined

1a) Non-Neoplastic Observations

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

Table 11a

Histopathologic Findings in Metam Sodium Treated Mice[a]

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

Table 11a, cont.

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

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

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

Table 11b

Histopathologic Findings in Metam Sodium Treated Mice[a]

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

Table 11b, cont.

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

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

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

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

Table 11c

Histopathologic Findings in Metam Sodium Treated Mice[a]

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

Table 11c, cont.

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

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

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

1b) Neoplastic Observations

Table 12a

Neoplastic Findings in Metam Sodium Treated Mice[a]

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

Table 12a, cont.

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

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

Table 12b

Neoplastic Findings in Metam Sodium Treated Mice[a]

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

Table 12b, cont.

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

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

Table 12c

Neoplastic Findings in Metam Sodium Treated Mice[a]

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

Table 12c, cont.

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

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

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

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

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

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

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

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

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

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

61

III. DISCUSSION

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

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

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

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

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

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

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

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

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

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

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

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

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

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

IV. Classification

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

011192

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

1

AUG 30 1994

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Metam Sodium: Review of a Chronic Toxicity / Carcinogenicity Study in Rats and Chronic Toxicity Study in Dogs Submitted by the Registrant.

P.C. Code: 039003
Submission: S468984
MRID Nos: 432758-01 and 432758-02
DP Barcode: D204958

FROM: Timothy F. McMahon, Ph.D., Pharmacologist 8/29/94
Review Section I, Toxicology Branch II
Health Effects Division (7509C)

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

THRU: Yiannakis M. Ioannou, Ph.D., Section Head Y M Ioannou 8/29/9
Review Section I, Toxicology Branch II
Health Effects Division (7509C)

and

Marcia Van Gemert, Ph.D., Branch Chief
Toxicology Branch II
Health Effects Division (7509C) Marcia Van Gemert 8/29/94

Registrant: Metam Sodium Task Force

Action Requested: Review of a chronic toxicity / carcinogenicity study conducted in rats and a chronic toxicity study conducted in dogs submitted in support of reregistration of metam sodium.

2) MRID # 432758-02

Title: Metam Sodium: Two Year Drinking Study In Rats

Summary:

In a two year combined chronic toxicity/carcinogenicity study (MRID # 432758-02), Metam Sodium technical (43.14% a.i.) was administered in drinking water to groups of 64 male and female rats for either 52 weeks or 104 weeks at dose levels of 0, 0.019, 0.056, and 0.19 ppm (**1.3 mg/kg, 3.9 mg/kg,** and **12.0 mg/kg** for male rats; **2.3 mg/kg, 6.2 mg/kg,** and **16.2 mg/kg** for female rats).

At 0.19 mg/ml, male and female rats showed decreased group mean body weight gain for weeks 1-13 (12% decrease in males, 16% decrease in females) and weeks 1-105 (18% for males, 20% for females). Decreased food consumption, food efficiency, and water consumption were significantly affected at the 0.19 mg/ml dose in both sexes. Effects on hematology (decreased red blood cells, hemoglobin, hematocrit) and clinical chemistry (decreased cholesterol and triglycerides) were also observed in both sexes at the 0.19 mg/ml dose level. Increased number of liver masses and increased incidence of fat vacuolation of the liver were observed in male rats at the 0.19 mg/ml dose, as was increased incidence of wasting of voluntary muscle. Microscopic abnormalities of the nasal cavity (increased incidence of rhinitis, hypertrophy of Bowman's ducts/glands, atrophy and adenitis of Steno's gland, and olfactory epithelium hyperplasia and degeneration), heart and aorta (decreased mineralization), voluntary muscle (increased severity of degenerative myopathy), and sciatic nerve (increased severity of degeneration) were observed in male and/or female rats at the 0.19 mg/ml dose level. **The LEL of 0.19 mg/ml is based on the changes in body weight gain, food efficiency, hematologic and clinical chemistry alterations, and macro- and microscopic abnormalities observed at this dose in both sexes. The NOEL is 0.056 mg/ml.**

Evaluation of tumor data presented in this study demonstrated that metam sodium shows no carcinogenic potential in rats.

This study is classified core **minimum** and **satisfies** the guideline requirements for §83-5, Combined Chronic Toxicity and Carcinogenicity Study in Rats.

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

Data Evaluation Record

Study type: Combined Carcinogenicity/Chronic Toxicity - rats
Guideline: 83-5

EPA ID Numbers: MRID number: 432758-02 P.C. Code: 039003

Test material: Metam Sodium

Chemical name: Sodium N-methylthiocarbamate

Project I.D. : PR0838

Sponsor: Metam Sodium Task Force

Testing Facility: Zeneca Central Toxicology Laboratory
Cheshire, UK

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

Author(s): N J Rattray

Study Completed: May 23, 1994

Executive Summary:

In a two year combined chronic toxicity/carcinogenicity study (MRID # 432758-02), Metam Sodium technical (43.14% a.i.) was administered in drinking water to groups of 64 male and female rats for either 52 weeks or 104 weeks at dose levels of 0, 0.019, 0.056, and 0.19 ppm (**1.3 mg/kg, 3.9 mg/kg,** and **12.0 mg/kg** for male rats; **2.3 mg/kg, 6.2 mg/kg,** and **16.2 mg/kg** for female rats).

At 0.19 mg/ml, **male** and female rats showed decreased group mean body weight gain for weeks 1-13 (12% decrease in males, 16% decrease in females) and weeks 1-105 (18% for males, 20% for females). Decreased food consumption, food efficiency, and water consumption were significantly affected at the 0.19 mg/ml dose in both sexes. Effects on hematology (decreased red blood cells, hemoglobin, hematocrit) and clinical chemistry (decreased cholesterol and triglycerides) were also observed in both sexes at the 0.19 mg/ml dose level. Increased number of liver masses and increased incidence of fat vacuolation of the liver were observed in male rats at the 0.19 mg/ml dose, as was increased incidence of wasting of voluntary muscle. Microscopic abnormalities of the nasal cavity (increased incidence of rhinitis,

hypertrophy of Bowman's ducts/glands, atrophy and adenitis of Steno's gland, and olfactory epithelium hyperplasia and degeneration), heart and aorta (decreased mineralization), voluntary muscle (increased severity of degenerative myopathy), and sciatic nerve (increased severity of degeneration) were observed in male and/or female rats at the 0.19 mg/ml dose level. **The LEL of 0.19 mg/ml is based on the changes in body weight gain, food efficiency, hematologic and clinical chemistry alterations, and macro- and microscopic abnormalities observed at this dose in both sexes. The NOEL is 0.056 mg/ml.**

Evaluation of tumor data presented in this study demonstrated that metam sodium shows no carcinogenic potential in rats.

Dosing was considered adequate in male and female rats based upon the decrease in body weight gain, food efficiency, changes in hematology and clinical chemistry, and microscopic pathology observed at the 0.19 mg/ml dose level.

This study is classified core **minimum** and **satisfies** the guideline requirements for §83-5, Combined Chronic Toxicity and Carcinogenicity Study in Rats.

I. MATERIALS AND METHODS

A. Test Material:

Metam Sodium technical; purity: 43.15% (written verification provided on page 426 of the report)
description: yellow colored aqueous solution
sample reference No: BAS/005/00N 90-2

B. Test Animals

Six batches of approximately 50 male and 50 female rats were delivered weekly for 6 weeks beginning in March of 1991. The strain was listed as Hsd/Ola: Wistar Tox strain obtained from Harlan Olac Ltd. Shaws Farm, Blackthorn, Bicester, Oxon, UK. Rats were delivered as weanlings (22 days old) and were placed into a single animal room for the entire study. Age: approximately 4 weeks at receipt. Acclimation period: approximately 2 weeks. Weight range (at time of dosing): males, 133-256g; females, 99-186g.

C. Animal Husbandry

Rats were housed by sex in multiple rat racks constructed of square-section aluminum. Cages were constructed of stainless steel, with solid sides, and 14 gauge wire mesh front, back, and floor. Cages were suspended over stainless steel collecting trays lined with absorbent paper sheets. Rats were initially housed not more than 6 per cage, and four per cage following assignment to experimental groups.

Food (Powdered CT1 Diet) was supplied in glass jars of approximately 300g capacity and was available *ad libitum* except during collection or urine. Drinking water was supplied in 250ml polycarbonate bottles fitted with glass nozzles and was also available *ad libitum* except during urine collection periods. Temperature during the study was designed to be maintained at 19-23 ^{o}C, with an overall range of 16-28 ^{o}C observed for the study as a whole. Humidity was designed to be maintained at 45%, with an overall recorded range of 25-86%.

D. Drinking Water Preparation

All experimental drinking water preparations were prepared daily in batches of 10 liters. For each dose level, the appropriate amount of metam sodium was added to the purified drinking water. This was then thoroughly mixed and dispensed into polycarbonate drinking bottles. This preparation supplied enough water to last each cage one day, after which bottles were removed, emptied, refilled, and replaced with drinking water from a new, freshly prepared batch.

E. Stability and Homogeneity

Amounts of metam sodium required for 10 liter batches of drinking water preparations at each dose level (corrected for purity) are summarized below (page 429 of the report):

DRINKING WATER PREPARATION

Group	Conc. of metam sodium in water (mg/ml)	Quantity of Test Substance to Prepare 10l of water (g)	Colour Code
1	0	0	Blue
2	0.019	0.43	Green
3	0.056	1.29	Yellow (Gold)
4	0.19	4.3	Red

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

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

Results of test article analysis in drinking water as well as 24 hour stability were presented in Appendices H and I, pages 439-470 of the report. A total of 30 measurements were made of drinking water concentration of metam sodium at each dose level over the course of the study. The following data are the mean analyzed concentration and mean percent of nominal at each dose.

Dose (mg/ml)	Mean conc.	Mean % Nominal
0.019	0.018	96.7
0.056	0.054	97.7
0.19	0.187	98.4

As shown, mean concentrations of metam sodium in drinking water prior to administration were close to nominal values.

Data on dose solution stability were actually the same data presented in the mouse carcinogenicity study on metam sodium (MRID # 432335-01) and are reproduced below:

Table 1

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

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

[a]data taken from Appendix H of MRID # 432335-01. [b]analyzed concentration and % nominal represent the mean of 12 measurements made at 24 hours post-dose preparation.

Appendix J, pages 471-478 of the present study, summarized the doses received by male and female rats over the course of this study, with corresponding mean values for the overall study period. The above table shows that at the low dose, degradation of approximately 12% from original concentration occurs over a 24 hour period, with lesser degradation observed at the two higher doses. Starting concentrations of test material at each dose were indicated above on page 4 of this review. The report stated the mean intake of test chemical at each dose as follows:

Males: **1.5 mg/kg** (low dose); **4.3 mg/kg** (mid dose); **12.5 mg/kg** (high dose)

Females: **2.7 mg/kg** (low dose); **6.8 mg.kg** (mid dose); **16.8 mg/kg** (high dose)

These doses can be adjusted for degradation occurring over a 24 hour period as has been the practice for calculating doses of metam sodium received in other toxicology studies submitted to the Agency:

Males: **1.3 mg/kg** (low dose); **3.9 mg/kg** (mid dose); **12.0 mg/kg** (high dose)
Males: **1.3 mg/kg** (low dose); **3.9 mg/kg** (mid dose); **12.0 mg/kg** (high dose)

Females: **2.3 mg/kg** (low dose); **6.2 mg.kg** (mid dose); **16.2 mg/kg** (high dose)

F. Experimental Design and Dosing

The following experimental design was used for this study:

Group #	Dietary Level (mg/ml)	Sacrifice Interval (weeks) 52 (Tox phase) M	52 (Tox phase) F	104 (Onco phase) M	104 (Onco phase) F
1 (Control)	0	12	12	52	52
2 (Low)	0.019	12	12	52	52
3 (Mid)	0.056	12	12	52	52
4 (High)	0.19	12	12	52	52
5 (Sentinel)	0			12	12
6 (Sentinel)	0.19			12	12

In this design, 52 animals/sex were assigned to treatment with metam sodium technical in drinking water for a period of 104 weeks, while an additional 12 rats/sex received metam sodium in drinking water for 52 weeks. Microbiological sentinels (12/sex) were given either 0 mg/ml or 0.19 mg/ml metam sodium and were housed in the same racks as the experimental animals. The duration of treatment for sentinel rats was not stated. Treatment of rats commenced between March 19, 1991 and April 25, 1991.

Dose selection for the present study was based on results of a 90-day toxicity study in rats previously performed in the same laboratory. Results of this study were not summarized in the present report.

G. Statistical Analysis

Analysis of variance was used for statistical evaluation of food and water consumption for the first 12 weeks of the study, organ weights, hematology, and clinical chemistry. Body weight was analyzed by analysis of covariance.

Differences from control were tested by comparing each treatment group least squares mean with the control least squares mean using Student's t-test based on the error mean square in the analysis.

Kaplan-Meier survival estimates were calculated separately for each sex and treatment group. Mortalities resulting from animals killed during the study or accidental deaths were considered censored observations.

Incidence of individual tumors and overall incidence of each tumor type were considered by comparing each treated group and the control group at certain time points and during selected time intervals using Fisher's Exact Test. A test for trend was conducted in addition using the Cochran-Armitage Test. Tumor analyses were conducted separately for males and females.

H. Compliance

A signed statement of no data confidentiality claims was provided.

A signed statement of GLP compliance was provided.

A signed statement of quality assurance was provided.

A signed statement of flagging studies for potential adverse effects was provided. According to the report, under the criteria of 40 CFR 158.34, this study neither meets nor exceeds any of the applicable criteria.

II. OBSERVATIONS AND RESULTS

A. **Mortality**

Rats were observed prior to study initiation to ensure that they were physically normal and that they exhibited normal activity. During the study, all rats were examined daily for changes in clinical condition and behavior. Once a week, a detailed examination of each rat was made. Any rats requiring euthanasia or found dead were given a post mortem examination. Survival in male and female rats is summarized in the following Table (Table 2), and is based upon data obtained from Table 5 of the report.

TABLE 1

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

Weeks of Study	Males (mg/ml) 0.0	0.019	0.056	0.19	Females (mg/ml) 0.0	0.019	0.056	0.19
1	64/64	64/64	64/64	64/64	64/64	64/64	64/64	64/64
% alive	100	100	100	100	100	100	100	100
13	64/64	64/64	63/64	64/64	64/64	64/64	64/64	64/64
% alive	100	100	98	100	100	100	100	100
27	64/64	63/64	63/64	63/64	63/64	64/64	64/64	63/64
% alive	100	98	98	98	98	100	100	98
53	61/64	62/64	62/64	63/64	62/64	60/64	62/64	61/64
% alive	95	97	97	98	97	94	97	95
77[b]	44/52	42/52	41/52	46/52	45/52	42/52	44/52	45/52
% alive	85	81	79	88	86	81	85	86
105[b]	11/52	15/52	20/52	16/52	27/52	25/52	23/52	29/52
% alive	21	29	38	31	52	48	44	56

[a]data taken from Table 5, pages 75-84 of the report. Numbers represent the total rats alive over the total rats in the dose group.

[b]excludes rats sacrificed at the 52 week time point (both sexes, N = 12).

* $p < 0.05$ vs control.

The data above indicate no significant effects of treatment on mortality in male and female rats. At week 105, however, mortality in control male rats appeared unacceptably low, i.e. less than 25% alive at week 105. Mortality in female rats at all dose levels was much less at week 105 in relation to male rats.

There were no historical control data provided with which to make a comparison of mortality in this strain of rat. It is of interest to note in this respect that the number of male rats found dead were 7, 3, 2, and 1 for the 0, 0.019, 0.056, and 0.19 mg/ml dose levels, respectively.

B. **Clinical Observations**

Cageside observations for indications of toxic effects were made once daily, and a detailed clinical examination performed weekly.

Clinical observations were summarized in Table 4, pages 55-72 of the report. These data indicated that treatment-related effects were observed only in male rats, and included reduced hindlimb function (observed in 5, 6, 2, and 13 control, low dose, mid dose, and high dose rats, respectively), stains around the nose (observed in 16, 19, 19, and 23 control, low dose, mid dose, and high dose rats, respectively), and thin appearance (observed in 15, 18, 15, and 31 control, low dose, mid dose, and high dose rats, respectively).

C. **Body Weights**

Body weight measurements were taken immediately prior to test article administration at study initiation, once every week for the first 14 weeks of the study, and then once every 2 weeks until study termination. Group mean body weights at selected times are presented in **Table 2.**

TABLE 2

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

Weeks of Study	Males (mg/ml) 0.0	0.019	0.056	0.19	Females (mg/ml) 0.0	0.019	0.056	0.19
1	184.9± 26.6	182.6± 23.0	183.6± 24.8	181.4± 26.8	129.6± 15.0	130.9± 14.9	129.8± 14.2	130.7± 15.8
13	440.3± 38.7	439.7± 41.4	438.6± 40.6	407.0±** 30.5	240.2± 20.3	238.3± 18.9	231.5±** 17.1	223.5±** 18.7
27	526.2± 46.4	526.6± 51.2	523.1± 52.1	479.7±** 35.7	268.0± 21.2	267.1± 21.3	259.4±** 18.8	248.7±** 19.8
53	579.7± 56.9	581.5± 63.3	577.0± 54.0	532.0±** 40.7	311.9± 33.7	308.6± 33.9	295.3±** 27.6	274.6±** 24.9
N	44	42	41	46	45	42	44	45
77	581.3± 57.9	565.3± 65.3	574.9± 59.3	526.0±** 48.2	350.4± 37.8	345.6± 48.5	332.7±* 33.6	306.5±** 29.4

Table 2, cont.

Weeks of Study	Males (mg/ml) 0.0	0.019	0.056	0.19	Females (mg/ml) 0.0	0.019	0.056	0.19
N	11	15	20	16	27	25	23	29
105	510.5± 45.0	498.3± 55.2	492.0± 40.8	448.0±** 56.0	342.9± 35.9	346.8± 47.2	326.2± 37.8	301.4±** 31.3

[a]data taken from Table 5, pages 75-84 of the report. * $p < 0.05$ vs control; ** $p < 0.01$ vs control.

Statistically significant effects were noted on group mean absolute body weight at the 0.19 mg/ml dose level for both male and female rats, and at the 0.056 mg/ml dose level in female rats. In male rats, group mean body weight was decreased by 8% vs control at week 13, while body weight in female rats was decreased by 7% vs control at this time point ($p < 0.01$). At subsequent intervals, body weight at the 0.19 mg/ml dose level was decreased by approximately 8% in male rats, and by approximately 12% in female rats. At the 0.056 mg/ml dose level, group mean body weight in female rats was decreased by 3-5% over the course of the study ($p < 0.05$).

Effects of test article treatment on group mean body weight gain in male and female rats are summarized in the following Table (**Table 3**):

TABLE 3

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

Weeks of Study	Males (mg/ml) 0.0	0.019	0.056	0.19	Females (mg/ml) 0.0	0.019	0.056	0.19
1	184.9± 26.6	182.6± 23.0	183.6± 24.8	181.4± 26.8	129.6± 15.0	130.9± 14.9	129.8± 14.2	130.7± 15.8
weight gain (g)								
1-13	255.4	257.1	255.0	225.6	110.6	107.4	101.7	92.8
% cont.	-	100	100	88	-	97	92	84
1-53	394.8	398.8	393.4	350.6	182.3	177.7	165.5	143.9
% cont.	-	101	100	89	-	97	91	79
1-105	325.6	315.7	308.4	266.6	213.3	215.9	196.4	170.7
% cont.	-	97	95	82	-	101	92	80

[a]data calculated from Table 2, above.

Effects on body weight gain were observed at the 0.19 mg/ml dose level in both male and female rats, where weight gain was decreased by 12-18% in males vs control, and by 16-20% in females vs control over the course of this study. At the 0.056 mg/ml dose level, body weight gain was unaffected in male rats, and was decreased by approximately 8-9% in female rats over the course of the study.

C. Food Consumption and Efficiency

Food consumption was measured weekly for the first 14 weeks of the study for each cage of rats. Food consumption was measured again on week 16, and thereafter every fourth week for the remainder of the study. Food efficiency was calculated for the first 12 weeks of the study.

Group mean food consumption data are presented in **Table 4** below:

TABLE 4

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

Weeks of Study	Males (mg/ml) 0.0	0.019	0.056	0.19	Females (mg/ml) 0.0	0.019	0.056	0.19
1	25.3± 1.1	25.0 0.7	24.9± 0.9	21.4±** 2.5	18.4± 0.8	18.0± 0.7	17.4±** 0.6	15.9±** 0.8
% cont.	-	99	98	84	-	98	94	86
13	26.5± 1.3	25.7* 0.9	26.0± 1.2	24.0±** 0.9	18.0± 1.0	17.8± 0.9	16.8±** 0.9	16.4±** 1.0
% cont.	-	97	98	90	-	99	93	91
Mean 1-13	26.9	26.4	26.4	24.3	18.5	18.4	17.5	16.7
% cont.	-	98	98	90	-	100	94	90
52	25.9± 1.8	25.3± 1.0	24.8± 3.1	24.5* 1.3	19.4± 1.5	19.0± 1.0	17.7±** 1.0	16.5±** 1.3
% cont.	-	100	96	96	-	98	91	85
104	24.2± 3.2	24.1± 2.6	25.6± 4.2	21.4±* 2.4	18.0± 2.5	18.3± 3.2	17.8± 2.9	17.1± 1.3
% cont.	-	100	105	88	-	102	99	95

[a]data from Table 7, pages 101-106 of the report.

In both male and female rats, group mean food consumption values (measured by cage) were decreased by 10% relative to control for weeks 1-13 of the study. At weeks 52 and 104, decreases were also observed in both sexes at the 0.19 mg/ml dose level, ranging from 4-15% below control values. The comparison of food consumption values at the 0.056 and 0.19 mg/ml dose levels appears to indicate a dose-related effect in both sexes.

Food efficiency calculations were performed by the registrant and are shown in the following table, taken from page 107 of the report:

TABLE 5

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

		Conc. of metam sodium in water (mg/ml)			
		0(Control)	0.019	0.056	0.19
Males					
Weeks 1-4	MEAN	18.19	18.62	18.32	17.76
	S.D.	1.70	1.34	1.64	1.84
	N	16	16	16	16
Weeks 5-8	MEAN	9.61	9.93	9.88	9.45
	S.D.	0.63	0.75	0.56	0.58
	N	16	16	16	16
Weeks 9-12	MEAN	6.25	6.18	6.42	6.15
	S.D.	0.67	0.65	0.42	0.41
	N	16	16	16	16
Overall (Weeks 1-12)	MEAN	11.31	11.54	11.49	11.04*
	S.D.	0.82	0.73	0.70	0.73
	N	16	16	16	16
Females					
Weeks 1-4	MEAN	12.47	12.09	11.98	11.28**
	S.D.	1.66	1.40	1.37	1.89
	N	16	16	16	16
Weeks 5-8	MEAN	5.42	5.44	5.51	5.36
	S.D.	0.80	0.79	0.74	0.98
	N	16	16	15	16
Weeks 9-12	MEAN	3.27	3.19	3.10	3.27
	S.D.	0.39	0.46	0.77	0.54
	N	15	16	16	16
Overall (Weeks 1-12)	MEAN	7.12	6.93	6.85	6.61**
	S.D.	0.71	0.72	0.66	0.98
	N	15	16	15	16

[a] data taken from Table 7a, page 107 of the report.

Efficiency of food utilization was decreased in male rats at the high dose for weeks 1-12 of the study. While this was labeled as statistically significant, this represented a decrease of only 3% from control. In female rats, larger decreases in food efficiency were observed, and at the additional time of weeks 1-4 of the study in contrast to males. For this time period, efficiency was decreased by almost 10% at the high dose vs control. For the 1-12 week study period, efficiency in female rats at the high dose was decreased by 7%.

Weight gain decreases in male rats at the 0.19 mg/ml dose level for weeks 1-13 of the study (12%) were only slightly in excess of the decreases in food consumption at this dose (10%), which might explain the slight decrease in food efficiency at the 0.19 mg/ml dose for the period of 1-12 weeks. Females, however, showed a weight gain decrease of 16% for weeks 1-13 of the study at the 0.19 mg/ml dose, and a food consumption decrease of only 10%. These observations taken together would indicate test article related toxicity, but are somewhat mild in terms of effect.

D. Intake of Metam Sodium

Mean intake values for metam sodium (in mg/kg) are shown below, based upon the evaluation of test article stability and decomposition observed in this study and summarized on pages 4 and 5 of this review.

TABLE 6

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

Dose Group (mg/ml)	Average Intake (weeks 1-104) (mg/kg/day) males	females
0.0	-	-
0.019	1.3	2.3
0.056	3.9	6.2
0.19	12.0	16.2

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

E. Water Consumption

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

Table 7
Water Consumption (ml/rat/day) in Male and Female Rats Receiving Metam Sodium in Drinking Water[a]

Weeks of Study	Males (mg/ml) 0.0	0.019	0.056	0.19	Females (mg/ml) 0.0	0.019	0.056	0.19
week 1	35.0± 6.5	32.3± 5.4	30.0±** 3.5	22.3±** 1.4	29.7± 3.7	29.2± 3.5	25.2±** 4.2	17.3±** 1.3
week 13	39.1± 4.8	36.5± 4.9	37.1± 5.6	25.8±** 1.5	45.2± 6.4	40.1±** 6.3	31.0±** 4.9	20.5±** 1.7
weeks 1-13	42.4± 3.2	40.6± 3.5	38.3± 3.0	26.3± 1.53	43.7± 5.0	41.6± 4.5	33.2± 3.0	20.0± 1.3
week 26	35.3± 4.0	33.3± 4.2	33.7± 3.4	25.7±** 1.5	43.9± 5.5	36.2±** 6.2	30.7±** 6.0	20.4±** 1.5
week 52	33.7± 3.9	31.2± 3.1	31.0± 6.1	26.0±** 1.3	44.2± 3.8	37.6±** 5.5	33.2±** 5.8	22.8±** 2.7
week 78	40.6± 8.2	38.2± 7.1	36.7± 7.4	32.9±** 4.5	40.0± 6.9	41.7± 8.9	34.6±* 4.3	24.6±** 2.3
week 104	53.8± 8.0	53.3± 11.8	56.7± 15.2	41.8±* 11.8	38.8± 7.4	44.1± 18.1	33.9± 8.3	27.8±* 6.4

[a]data taken from Table 6, pages 85-100 of the report. *p < 0.05 vs control; **p < 0.01 vs control.

The above data show significant decreases in water consumption in both male and female rats at the 0.056 and 0.19 mg/ml dose levels. Female rats appeared to be affected in a greater manner than male rats at these two dose levels. For example, mean water consumption for weeks 1-13 of the study was decreased in treated male rats by 4.2%, 9.6%, and 37.9% from control at the 0.019, 0.056, and 0.19 mg/ml dose levels, respectively. In females, the corresponding decreases were 4.8%, 24.0%, and 54.2%. Thus, at a given dose level, the decrease in water consumption appeared greater for female rats, and further, significant decreases in water consumption were observed at dose levels in female rats where there was no significant effect in male rats (weeks 26, 52, and 78 above, for example). It is worth noting that such large decreases in water consumption for both sexes at the high dose could have potentially adverse effects on normal physiology, as in many instances, the decrease in water consumption approached or exceeded 50% vs control.

F. Ophthalmoscopic Examination

An indirect ophthalmoscopic examination was performed on the eyes of all animals from the control and high dose groups prior to treatment and again at 52 weeks of the study. The eyes of control and high dose females were examined during the week prior to scheduled termination.

According to the data presented in the report (Tables 8, pages 109-111), there did not appear to be any significant relationship between treatment with metam sodium and ocular abnormalities. It is, however, mentioned that examination at pre-study (52 males and 51 females examined) showed focal opacities in 2 female rats assigned to the high dose group, and none in male rats. At week 52 (examination of 52 males and 49 females), focal opacities were observed in 5 high dose females vs 2 in control, and linear opacities were observed in 3 high dose females vs 1 in controls. At terminal sacrifice, there were no ophthalmoscopic abnormalities observed in treated animals.

F. Clinical Pathology

Blood samples for hematology and serum chemistry were obtained at weeks 14, 27, 53, and 79 from the tail vein of 13 designated male and 13 designated female rats per main study group. Any designated rat which died or was killed prior to sampling time was replaced, if considered necessary, by an alternative animal in order to maintain acceptable group size. Blood was obtained by cardiac puncture from interim kill and main study animals at termination. Samples (1ml) were introduced into tubes containing EDTA for hematology measurements and into tubes containing lithium heparin for clinical chemistry. Blood films were prepared from all animals and a differential white cell count done with an assessment of red cell morphology on control and high dose animals. Bone marrow smears were taken from interim and main study animals at termination. Reticulocyte counts were done on all animals found to be anemic.

a) **Hematology**

The following CHECKED hematological parameters were examined:

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

*EPA guideline requirement "-" not analyzed

Hematological findings were summarized in Table 9, pages 112-139 of the report. Significant observations are summarized below (Table 8):

Table 8
Hematological Findings in Male and Female Rats Receiving Metam Sodium in Drinking Water[a]

Weeks of Study	Males (mg/ml) 0.0	0.019	0.056	0.19	Females (mg/ml) 0.0	0.019	0.056	0.19
week 14								
HGB (g/dl)	15.9± 0.5	16.2±* 0.6	15.6± 0.5	15.4±* 0.5	15.1± 0.7	15.5± 0.4	15.2± 0.5	14.9± 0.6
HCT	0.491± 0.021	0.504± 0.022	0.485± 0.020	0.480± 0.032	0.474± 0.023	0.476± 0.020	0.472± 0.027	0.460±* 0.027
RBC (10^{12}/l)	8.36± 0.38	8.50± 0.46	8.35± 0.41	8.14± 0.63	7.53± 0.50	7.55± 0.46	7.52± 0.48	7.23±* 0.49
week 27								
HGB	15.2± 0.5	15.3± 0.6	15.0± 0.4	14.8±* 0.4	14.7± 0.3	14.7± 0.4	14.4±* 0.5	14.2±** 0.4
HCT	0.443± 0.015	0.447± 0.016	0.437± 0.014	0.431±* 0.014	0.418± 0.013	0.416± 0.014	0.408± 0.016	0.405±* 0.015
RBC	9.58± 0.47	9.60± 0.46	9.59± 0.33	9.33± 0.41	8.37± 0.21	8.41± 0.28	8.22± 0.35	8.07±** 0.31
week 53								
HGB	15.0± 0.5	14.9± 0.6	14.8± 0.5	14.5±* 0.3	14.4± 0.4	14.5± 0.4	14.3± 0.7	14.0± 0.7
HCT	0.446± 0.016	0.443± 0.015	0.439± 0.016	0.432±* 0.011	0.418± 0.015	0.423± 0.017	0.419± 0.023	0.405± 0.019
RBC	9.45± 0.42	9.21± 0.41	9.37± 0.36	9.07±** 0.24	8.14± 0.27	8.25± 0.25	8.12± 0.47	7.79±* 0.41

Table 8, cont.

Weeks of Study	Males (mg/ml) 0.0	0.019	0.056	0.19	Females (mg/ml) 0.0	0.019	0.056	0.19
week 79								
HGB	14.8± 0.4	14.4± 0.9	14.4± 0.7	14.2±* 0.7	14.6± 0.3	14.6± 0.5	14.4± 0.8	14.1± 0.5
HCT	0.454± 0.012	0.440± 0.026	0.442± 0.021	0.434±* 0.024	0.433± 0.010	0.439± 0.016	0.433± 0.027	0.422± 0.017
RBC	9.26± 0.29	8.83± 0.65	9.03± 0.51	8.81±* 0.24	8.31± 0.32	8.26± 0.23	8.19± 0.48	7.86±** 0.34
week 105								
HGB	14.4± 2.2	13.3± 1.2	11.9±** 1.9	12.6±** 1.1	13.9± 1.3	13.8± 0.7	13.5± 0.8	13.2±* 1.0
HCT	0.450± 0.072	0.419± 0.043	0.382±** 0.055	0.401±* 0.039	0.434± 0.038	0.432± 0.022	0.423± 0.026	0.415±* 0.032
RBC	8.71± 1.12	8.20± 0.85	7.31±** 1.30	7.80±* 0.96	8.17± 0.85	8.04± 0.45	7.86± 0.46	7.52±** 0.64

[a]data taken from Table 9 of the report, pages 112-139. *p < 0.05 vs control. **p < 0.01 vs control.

The most consistent changes observed in this study were changes in hemoglobin (HGB), hematocrit (HCT), and red blood cells (RBC). At the 0.19 mg/ml dose level, both male and female rats showed a consistent decrease of 3 to 4% from control in mean HGB and RBC throughout the study. Mean HCT was decreased as well, but not always in both sexes and not always at all times. The largest decreases observed in these parameters occurred at week 105, where HGB was decreased 12% in high dose males and 5% in high dose females, with HCT and RBC following a similar pattern. Although the changes shown above achieved statistical significance, the degree of change was small (~ 3-5%). Thus, the toxicological significance of these findings is debatable.

b) Clinical Chemistry:

The following CHECKED parameters were measured:

- x glucose*
- x albumin*
- - A/G ratio (calculated)
- x creatinine
- x total bilirubin*
- - direct bilirubin
- - indirect bilirubin
- x urea nitrogen*
- x total protein*
- x cholesterol*
- x triglycerides
- - electrophoretic protein fractions

- x calcium*
- x inorganic phosphate*
- x sodium*
- x potassium*
- x chloride*

- x AST(SGPT)*
- x ALT(SGOT)*
- x alkaline phosphatase
- x creatine kinase*
- - lactate dehydrogenase
- - sorbitol dehydrogenase
- - gamma glutamyl transpeptidase
- - ornithine carbamyl transferase

- - plasma ChE
- - red cell ChE
- x urea

*EPA guideline requirement

"-" not examined

A summary of findings in blood chemistry measurements were presented in Table 10, 140-73 of the report.

Early in the treatment period (weeks 14 and 27), both alanine and aspartate aminotransferase were decreased at the high dose in female rats. At week 14, alanine and aspartate aminotransferase were decreased by 15% and 11% respectively, and at week 27, by 27% and 32% respectively. At week 53 and beyond, there were no significant differences from control.

At weeks 79 and 105, both plasma cholesterol and triglycerides were decreased in female and male rats at the 0.19 mg/ml dose level. For cholesterol, the decreases ranged from 4-10% in males, and 17-19% in females. For triglycerides, the decrease ranged from 22-43% in females, and 18-32% in males. There were no corresponding decreases in total plasma protein (only a 3% decrease observed in high dose females at week 27).

c) **Urinalysis:**

During weeks 13, 26, 52, and 78, individual urine samples were collected over a 16-18 hour period from 13 designated male and 13 designated female rats per dose group. At study termination, urine was collected from the designated female rats, but from all surviving male rats. During the collection period, rats were housed in individual metabolism cages and denied access to food and water.

The following CHECKED parameters were examined:

x appearance*	x glucose*
x volume*	x pH
x specific gravity*	- bilirubin*
x protein*	x urobilinogen
x ketone*	- nitrite
x blood*	- total reducing substances
x sediment analysis*	

*EPA guideline requirement "-" not examined

Results of urinalysis were presented in Table 11 of the report, pages 174-183. Qualitative tests were summarized in Table 12.1, pages 185-186, and sediment analysis presented in Table 12.2, pages 188-211. Significant findings are summarized in the following Table (Table 9):

Table 9
Urinalysis in Male and Female Rats Administered Metam Sodium in Drinking Water for 104 Weeks[a]

	Males (mg/ml)				Females (mg/ml)			
	0.0	0.019	0.056	0.19	0.0	0.019	0.056	0.19
volume								
week 52	7.38± 2.61	7.83± 2.57	6.85± 2.34	5.47±* 1.74	7.48± 1.65	6.69± 2.77	5.09±* 1.61	5.24±* 1.95
week 78	10.49± 3.43	10.54± 2.78	10.03± 2.77	8.65± 3.24	8.75± 2.41	8.05± 2.28	8.13± 2.95	6.21±* 1.82

Table 9, cont.

	Males (mg/ml)				Females (mg/ml)			
	0.0	0.019	0.056	0.19	0.0	0.019	0.056	0.19
urine pH								
week 13	6.58± 0.14	6.50± 0.20	6.47± 0.19	6.31±** 0.12	6.15± 0.24	6.06± 0.17	6.10± 0.23	6.01± 0.22
week 26	6.56± 0.21	6.44± 0.22	6.49± 0.10	6.33±** 0.14	6.17± 0.20	6.10± 0.12	6.09± 0.16	6.09± 0.10
urine protein								
week 26	32.82± 15.56	29.12± 10.29	28.24± 11.71	22.81±* 6.80	2.02± 1.76	1.24± 0.24	1.27± 0.43	1.47± 0.96
week 52	113.2± 52.39	88.43± 41.41	82.92± 35.30	70.41±* 26.68	19.85± 21.38	11.50± 8.80	4.08±** 1.12	6.08±** 3.56
week 78	220.9± 95.07	221.17± 94.00	209.51± 87.77	146.54±* 62.46	64.46± 65.00	37.48± 23.34	14.80±** 8.52	18.84±** 12.92

[a]data taken from Table 11, pages 174-183. *p < 0.05 vs control; ** p < 0.01 vs control.

Changes in urine volume during weeks 52 and 78 were observed, as well as changes in urine pH (decreased during weeks 13 and 26 in males at 0.19 mg/ml) and protein (decreased in males and females during weeks 26, 52, and 78). The decreases in urine protein, which appeared dramatic at the 0.19 mg/ml dose level, were explained in the report to be the result of abnormally high control values. When these were removed (as appears to be the case for the data presented on pages 182-183 of the report), statistical significance was observed in male and female rats at week 78 at the 0.19 mg/ml dose level (34% reduction in males, 33% reduction in females).

Qualitative testing of urine showed a trend towards the presence of blood in urine with increasing dose of test chemical, as evidenced by the increase in the number of animals with more prominent grading for blood in urine. The results of this analysis are shown below, taken from pages 185 and 186 of the report: [Qualitative grading was based on a positive arbitrary scale of increasing presence of a urinary parameter (+, ++, or +++)]:

GROUP URINE QUALITATIVE TESTS

MALES

		CONTROL					0.019mg/ml					0.056mg/ml					0.19mg/ml				
	WEEK	13	26	52	78	TERM	13	26	52	78	TERM	13	26	52	78	TERM	13	26	52	78	TERM
BLOOD	-VE	13	13	13	13	16	11	13	12	12	18	12	12	12	12	23	12	13	12	13	23
	TRACE	-	-	-	-	-	-	-	1	1	-	-	-	-	1	-	-	-	-	-	-
	+	-	-	-	-	-	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	++	-	-	-	-	-	1	-	-	-	-	-	1	-	-	-	-	-	-	-	1
	+++	-	-	-	-	-	-	-	-	-	-	1	-	1	-	-	1	-	1	-	1

NML = NORMAL CDY = CLOUDY BOP = BLOOD PRESENT VISUALLY URO/GEN = UROBILINOGEN

FEMALES

		CONTROL					0.019mg/ml					0.056mg/ml					0.19mg/ml				
	WEEK	13	26	52	78	104	13	26	52	78	104	13	26	52	78	104	13	26	52	78	104
BLOOD	-VE	13	13	12	13	13	13	13	12	13	13	13	13	13	13	12	12	12	11	11	11
	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1
	++	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1	-	-	-
	+++	-	-	-	-	-	-	-	1	-	-	-	-	-	-	-	-	-	2	2	1

NML = NORMAL BOP = BLOOD PRESENT VISUALLY URO/GEN = UROBILINOGEN

The report stated that the finding of blood in urine was low in incidence and not considered of biological significance. However, there is an apparent relationship to dose of metam sodium, and thus it could be considered an effect of treatment.

Urine was also analyzed qualitatively for the presence of crystals, renal epithelial cells, bacteria, mucus, mixed cell casts, white blood cells, yeast cells, wax casts, squamous epithelial cells, granular casts, and sperm. There did not appear to be any effect of treatment on the incidence or severity of any of these in male or female rat urine.

G. Macroscopic Observations

Sacrifice of animals was performed on 12 rats/sex/group after 52 weeks of treatment (during week 53) and on all surviving animals after 104 weeks of treatment. All animals found dead or sacrificed in extremis during the study were subjected to a full post mortem examination as soon as possible after death and always within 24 hours. Rats were weighed, anesthetized with halothane, and exsanguinated.

Summary of macroscopic observations was presented in the report (Tables 14A-14B, pages 222-282). Table 14A summarized data for unscheduled deaths and the interim sacrifice, while Table 14B summarized macroscopic findings in all animals combined.

A summary of apparent treatment-related findings is made below (Table 9):

Table 9a

Macroscopic Findings in Metam Sodium Treated Rats[a]

	Males (mg/ml)				Females (mg/ml)			
	0.0	0.019	0.056	0.19	0.0	0.019	0.056	0.19
Intercurrent Deaths								
Liver								
No. examined	42	37	33	36	28	28	29	23
mass	2	1	2	6	0	0	1	0
enlarged	0	3	2	6	0	0	0	0
pale spots	3	3	6	13	0	0	0	1
Lung								
No. examined	42	37	33	36	28	28	29	23
pale	1	0	2	3	0	0	0	0
Pituitary								
No. examined	42	37	33	36	28	28	29	23
mass	5	2	2	3	17	15	17	9
Voluntary muscle								
No. examined	42	37	33	36	28	28	29	23
wasted	1	1	0	9	0	0	1	1

[a]data taken from Table 14A, pages 222-241 of the report.

For those animals dying or sacrificed during the study, male rats at the 0.19 mg/ml dose level showed an increased incidence of abormal liver pathology (mass, pale spots, enlarged) and increased incidence of animals with wasted voluntary muscle. There was an apparent decrease in the incidence of animals with pituitary masses for both sexes.

In female rats, there were none of the effects observed in males.

The following table (Table 9b) shows the incidence of macroscopic observations in all animals on study, as the deviations shown above were not observed in increased incidence in those rats surviving to study termination:

Table 9b

Macroscopic Findings in Metam Sodium Treated Rats[a]

	Males (mg/ml)				Females (mg/ml)			
	0.0	0.019	0.056	0.19	0.0	0.019	0.056	0.19
				All Animals				
Adrenal gland								
No. examined	64	64	64	64	64	64	64	64
speckled	4	4	4	6	8	7	2	10
Ears								
No. examined	3	1	1	3	0	1	3	0
traumatized pinna[b]	0	3	3	5	1	0	4	3
Eye								
No. examined	64	63	64	64	64	63	64	64
pale	8	5	12	11	1	0	2	1
Liver								
No. examined	64	64	64	64	64	64	64	64
mass	4	1	4	8	0	2	3	2
enlarged	0	5	7	7	1	0	2	1
pale spots	3	3	8	15	0	0	0	1
mottled	1	2	4	4	1	0	1	1
Lung								
No. examined	64	64	64	64	64	64	64	64
pale	1	1	2	5	0	0	0	0
Pituitary								
No. examined	64	64	64	64	64	64	64	64
mass	7	3	4	3	33	36	34	25
Voluntary muscle								
No. examined	64	64	64	64	64	64	64	64
wasted	1	2	0	9	0	0	1	1

[a]data taken from Table 14B, pages 261-282 of the report.

[b]number with findings exceeded the number examined; no explanation given.

For all animals considered together, deviations in control incidence of macroscopic pathology occurred primarily in male rats at the 0.19 mg/ml dose level, and included eye effects (pale), liver effects (enlarged, mass, pale spots), lung effects (pale), and voluntary muscle effects (wasting). The only lesion which appeared to occur in both sexes was a slight increase in the incidence of traumatized pinnae, occurring at the high dose.
The incidence of pituitary masses as observed macroscopically appeared decreased at the high dose in both sexes compared to control incidence.

H. Organ Weights

Organ weights were recorded in the 12 rats/sex/dose sacrificed at week 53, and in those rats surviving to study termination. The weight of the liver, kidneys, adrenals, brain, and testes were recorded. Organ / body weight ratios were also calculated.

Results were presented in Tables 13.1 for interim kill animals and in Table 13.2 for terminal kill animals. Significant findings are summarized below:

Table 10

Organ Weights at 52 and 104 Weeks in Metam Sodium Treated Rats[a]

	Males (mg/ml)				Females (mg/ml)			
	0.0	0.019	0.056	0.19	0.0	0.019	0.056	0.19
No. examined	11	12	11	12	10	11	12	12
52 Weeks								
adrenals	0.061± 0.018	0.059± 0.016	0.057± 0.009	0.055± 0.005	0.064± 0.012	0.068± 0.012	0.063± 0.010	0.087± 0.105
% cont.	-	97	93	90	-	106	98	136
adrenal/ b.w.	0.010	0.009	0.010	0.010	0.020	0.021	0.021	0.031
kidneys	3.71± 0.59	3.66± 0.29	3.61± 0.38	3.26±** 0.18	2.22± 0.22	2.20± 0.39	2.06± 0.16	2.29± 0.26
% cont.	-	99	97	88	-	99	93	103
kidney/ b.w.	0 62	0.58	0.61	0.61	0.69	0.67	0.69	0.83

Table 10, cont.

	Males (mg/ml)				Females (mg/ml)			
	0.0	0.019	0.056	0.19	0.0	0.019	0.056	0.19
No. examined	11	15	20	16	26	25	23	29
104 Weeks								
adrenals	0.071± 0.014	0.069± 0.013	0.205± 0.563	0.086± 0.089	0.080± 0.036	0.085± 0.018	0.105± 0.149	0.077± 0.025
% cont.	-	97	288	121	-	106	131	96
adrenal/ b.w.	0.014	0.014	0.043	0.021	0.023	0.025	0.034	0.026
kidneys	5.36± 1.25	5.31± 1.47	5.76± 1.72	4.69± 1.03	2.88± 0.60	2.79± 0.45	2.82± 0.53	2.65± 0.54
% cont.	-	99	107	88	-	97	98	92
kidney/ b.w.	1.07	1.10	1.20	1.08	0.84	0.81	0.87	0.88

[a]data taken from Tables 13.1 and 13.2, pages 212-221 of the report.
*$p < 0.05$ vs control.

At both the interim sacrifice time point as well as the terminal kill time point, the only changes noted in organ weights were those of the adrenal glands and kidneys. However, the effects on organ weight were not consistent between sexes. For example, adrenal weight in male rats at the 0.19 mg/ml dose level from the interim sacrifice group was decreased by 10% from control, while adrenal weight in female rats at the same dose level and time point was increased by 36% from control. A fairly strong dose-response relationship could be observed in both cases. At the terminal sacrifice point, no significant changes were observed in adrenal weight

Kidney weight was noted to be decreased significantly in male rats at the 0.19 mg/ml dose level from the interim sacrifice time point (decrease of 12% from control), but no effects were observed in female rats. At the terminal sacrifice time point, the same percentage decrease was observed in male rats at the 0.19 mg/ml dose level, but was not considered statistically significant by the study author.

I. Microscopic Observations

Samples of the following tissues were preserved in 10% buffered formalin, except skin, testis, epididymis, and mammary gland, which were placed in Davidson's fixative, and eye and Harderian gland, which were placed in Davidson's solution.

Digestive

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

Respiratory

x trachea
x lungs*
x nasal cavity

Cardiovascular

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

Urogenital

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

Neurologic

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

Glandular

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

Other

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

*EPA guideline requirement "-" not examined

The above tissues were prepared for microscopic examination by dehydration and embedding in paraffin wax, cutting thin sections, and staining with hematoxylin and eosin. Special stains were used as appropriate.

1) Non-Neoplastic Observations

A number of observations were recorded for animals in the interim sacrifice, unscheduled sacrifice, and terminal sacrifice groups. Because findings were numerous but similar, the observations for intercurrent deaths, terminal sacrifice, and animals surviving to termination are combined in one table (Table 11):

Table 11

Non-Neoplastic Microscopic Findings in Metam Sodium Treated Rats[a]

All Animals

	Males (mg/ml)				Females (mg/ml)			
	0.0	0.019	0.056	0.19	0.0	0.019	0.056	0.19
adrenal gland								
No. examined	64	64	64	64	64	64	64	64
vascular ectasia								
total	4	6	7	12	54	48	50	44
minimal	3	5	7	9	13	12	9	8
slight	1	1	0	2	25	29	28	23
moderate	0	0	0	1	14	7	13	12
marked	0	0	0	0	2	0	0	1
aorta								
No. examined	64	63	64	64	62	64	64	64
mineralization								
total	15	14	7	2	0	0	0	0
slight	6	2	4	0				
moderate	7	6	2	2				
marked	2	6	1	0				
Eye								
No. examined	64	63	64	64	63	63	64	64
cataractous change								
total	6	6	7	8	17	15	14	10
minimal	4	4	6	8	10	7	9	7
slight	1	0	1	0	5	5	4	1
moderate	0	0	0	0	2	2	1	1
marked	1	0	0	0	0	1	0	1

Table 11, cont.

	Males (mg/ml)				Females (mg/ml)			
	0.0	0.019	0.056	0.19	0.0	0.019	0.056	0.19
Harderian gland								
No. examined	64	63	64	64	63	63	64	64
increased porphyrin								
total	35	21	29	30	10	15	17	14
minimal	29	13	15	12	1	**12**	**9**	**9**
slight	6	8	**14**	**18**	9	3	8	5
Heart								
No. examined	64	64	64	64	64	64	64	64
vascular mineralization								
total	11	4	2	2	0	0	0	0
minimal	0	0	1	0				
slight	5	2	0	1				
moderate	5	1	1	1				
marked	1	1	0	0				
Liver								
No. examined	64	64	64	64	64	64	64	64
fat vacuolation								
total	28	26	**31**	**32**	6	5	8	7
minimal	8	9	**14**	**11**	3	4	3	4
slight	9	4	4	**10**	1	1	2	2
moderate	6	6	7	6	0	0	2	1
marked	5	7	6	5	2	0	1	0
spongiosis/peliosis hepatis with altered hepatocytes								
total	7	5	**15**	**13**	1	0	3	2
minimal	0	3	6	1	0	0	3	0
slight	5	1	7	**12**	1	0	0	2
moderate	2	1	2	0	0	0	0	0

Table 11, cont.

	Males (mg/ml)				Females (mg/ml)			
	0.0	0.019	0.056	0.19	0.0	0.019	0.056	0.19
Nasal cavity								
No. examined	63	64	64	64	64	64	64	64
rhinitis								
total	1	4	2	9	1	3	4	4
minimal	0	2	2	2	0	2	1	2
slight	1	2	0	5	0	1	3	1
moderate	0	0	0	2				
hypertrophy of Bowman's ducts/ glands								
total	0	0	2	**39**	0	0	0	**43**
minimal	0	0	2	**13**	0	0	0	**29**
slight	0	0	0	**12**	0	0	0	**13**
moderate	0	0	0	**14**	0	0	0	**1**
olfactory epithelium hyperplasia								
total	0	0	0	**7**	0	0	0	**2**
minimal	0	0	0	**5**				
slight	0	0	0	**2**				
olfactory epithelium degeneration								
total	1	0	0	**28**	0	0	1	**5**
minimal	1	0	0	**8**	0	0	1	**3**
slight	0	0	0	**18**	0	0	0	**2**
moderate	0	0	0	**2**				
Steno's gland atrophy								
total	11	12	15	**49**	13	14	17	**43**
minimal	8	9	11	**34**	12	14	14	**31**
slight	3	3	4	**14**	1	0	3	**12**
moderate	0	0	0	**1**				

Table 11, cont.

	Males (mg/ml)				Females (mg/ml)			
	0.0	0.019	0.056	0.19	0.0	0.019	0.056	0.19
Steno's gland adenitis								
total	14	4	13	**23**	1	1	**10**	**9**
minimal	12	3	13	**21**	1	1	**7**	**9**
slight	0	1	0	**2**	0	0	3	0
moderate	2	0	0	0				
Sciatic Nerve No. examined	64	64	64	64	63	64	64	63
degeneration								
total	47	42	45	47	37	34	36	39
minimal	28	25	24	13	24	20	22	19
slight	15	6	15	**20**	13	14	12	17
moderate	1	8	4	**11**	0	0	2	3
marked	3	3	2	3	0	0	0	0
Spleen No. examined	64	64	64	64	64	64	64	64
increased hemosiderin								
total	2	2	2	**8**	10	6	8	**20**
slight	2	2	2	**8**	10	6	8	**20**
Voluntary muscle No. examined	64	64	64	64	64	64	64	64
degenerative myopathy								
total	37	39	36	44	24	17	15	27
minimal	26	27	23	9	24	16	13	18
slight	7	7	7	**10**	0	1	1	**5**
moderate	2	3	5	**15**	0	0	1	**3**
marked	2	2	1	**10**	0	0	0	1

[a]data taken from Tables 15a and 15b, pages 283-395 of the report.

In those animals killed or dying during the study period as well as in those surviving to study termination, microscopic abnormalities were observed at the 0.19 mg/ml dose level in the **adrenal gland** (increased vascular ectasia), **aorta and heart** (decreased mineralization), **eye** (cataractous change), **nasal cavity** (rhinitis, hypertrophy of Bowman's ducts/glands, olfactory epithelium hyperplasia and degeneration), **liver** (spongiosis/peliosis hepatis with altered hepatocytes), Steno's gland atrophy, adenitis), **spleen** (hemosiderin), **sciatic nerve** (degeneration), and **voluntary muscle** (degenerative myopathy). The changes observed in the adrenal gland, aorta, heart, and liver were confined primarily to male rats, while the remaining changes were observed in both sexes. According to the report, the lesion in Bowman's ducts and glands was characterized by cellular hypertrophy and in some animals, degeneration of the olfactory epithelium was observed, which consisted of vacuolation, reduction in the number of sensory cells, pyknotic sensory cells, focal loss of apical cytoplasm, and occasional pigmented cells.

The incidence of rhinitis, increased in males given 0.19 mg/ml, was not considered to be treatment-related, but could have exacerbated the changes in Bowman's glands. However, there were several animals with moderate hypertrophy of Bowman's glands/ducts without rhinitis.

The incidence of degenerative myopathy overall was not increased in treated male rats, but the severity of this change was increased at the 0.19 mg/ml dose level, and the most marked cases correlated with the wasted muscle observed macroscopically (Table 9a).

According to the report, there were no microscopic correlates to the enlarged livers or pale spots observed macroscopically. However, increased incidence of fat vacuolation and spongiosis/peliosis hepatis with altered hepatocytes was observed in male rats at the 0.19 mg/ml dose level.

In the interim sacrifice rats of both sexes, the only change of note was in atrophy of Steno's gland, which was graded as slight and was increased in both high dose males and females.

Those animals surviving to study termination showed similar effects in the nasal cavity at the 0.19 mg/ml dose as those which died during the study. However, there was one change noted in those rats surviving to termination which was not evident in any other format, and this was the observation of bile duct proliferation. In just this sub group, the incidence of this lesion graded as 'slight' increased from 7/11 in control to 16/20 at the 0.56 mg/ml dose level and 13/15 at the 0.19 mg/ml dose level.

2) Neoplastic Observations

Separate summaries are provided for neoplastic observations in those animals sacrificed during the study, those surviving to study termination, interim sacrifice animals, and all animals combined (Table 12):

Table 12
Neoplastic Observations in Male and Female Rats Administered Metam Sodium in Drinking Water[a]

	Males (mg/ml)				Females (mg/ml)			
	0.0	0.019	0.056	0.19	0.0	0.019	0.056	0.19
Intercurrent								
Liver								
No. examined	42	37	33	36	28	28	29	23
hepatocellular adenocarcinoma	2	2	2	5	0	0	1	0
Interim Sacrifice								
Pituitary gland								
No. examined	11	11	10	12	8	10	11	12
adenoma	2	1	2	5	3	5	6	3
Terminal Sacrifice								
Pituitary gland								
No. examined	11	15	20	15	26	25	23	29
adenoma	6	10	16	12	24	25	22	25
All Animals								
Liver								
No. examined	64	64	64	64	64	64	64	64
hepatocellular adenocarcinoma	3	2	4	5	0	0	2	0
hepatocellular adenoma	2	1	3	4	1	1	1	2
Pituitary								
No. examined	64	63	63	62	62	63	63	64
adenoma	28	30	33	35	51	50	53	46

[a]data taken from Tables 17a-17b, pages 400-420 of the report.

In addition to the above data, hemangioma and hemangiosarcoma were considered in all animals irrespective of site, as was performed in the mouse carcinogenicity study (MRID # 432335-01). The sites of hemangioma in the present rat study included the cervical lymph node, mesenteric lymph node, thymic lymph node, and subcutaneous tissue. Sites for hemangiosarcoma included the mesenteric lymph node, subcutaneous tissue, tail, liver, lung, and uterus. However, the preponderance of tumors were observed only in male rats.

Hemangioma (all sites, male rats)

Control - 9/64 animals
0.019 mg/ml dose - 4/64 animals
0.056 mg/ml dose - 4/64 animals
0.19 mg/ml dose - 8/64 animals

Hemangiosarcoma (all sites, male rats)

Control - 0/64 animals
0.019 mg/ml dose - 3/64 animals
0.056 mg/ml dose - 7/64 animals
0.19 mg/ml dose - 3/64 animals

The question of whether these tumors were observed in separate rats was addressed in the review of this study by the California Department of Environmental Protection (Earl Meierhenry, personal communication). This review showed that of the benign hemangiomas found, one rat in the low dose group was found to have this tumor type at 2 sites (mesenteric and thymic lymph nodes). Of the malignant hemangiosarcomas found, 2 rats in the low dose group were found to have this tumor type at 2 and 3 sites (liver and lung; liver, lung, and mesenteric lymph node, respectively).

The only other observations of tumorigenicity in this study involved the liver (adenocarcinoma) and pituitary (adenoma), both of which appeared slightly increased in male rats at the 0.19 mg/ml dose level. However, this did not appear to be a strong dose-response relationship.

III. DISCUSSION

In the present study, the chronic toxicity and carcinogenicity of Metam Sodium technical was examined in male and female Hsd/Ola: Wistar Tox rats. Test chemical was administered in the drinking water at nominal doses of 0, 0.019, 0.056, and 0.19 mg/ml for either 52 weeks (interim sacrifice group) or 104 weeks (terminal sacrifice group). When corrected for decomposition of test material, doses of metam sodium received by male rats were calculated as **1.3 mg/kg** (low dose); **3.9 mg/kg** (mid dose); and **12.0 mg/kg** (high dose). For female rats, these doses were calculated as **2.3 mg/kg** (low dose); **6.2 mg.kg** (mid dose); **16.2 mg/kg** (high dose). Standard measurements on body weight, food consumption, clinical pathology, ophthalmology, urinalysis, and histopathology were performed as appropriate for this study.

There were no apparent detrimental effects of treatment with metam sodium on survival in male and female rats at any dose level used in this study, although survival in control male rats was below an acceptable level at study termination (i.e. < 25% alive). However, the occurrence of this at such a late time point (post 78-weeks) is not thought to compromise the conclusions of the study. Clinical signs observed in the present study were confined to male rats, where the incidence of reduced hindlimb function, staining around the nose, and thin appearance were increased at the 0.19 mg/ml dose level.

Statistically significant effects were noted on group mean absolute body weight at the 0.19 mg/ml dose level for both male and female rats, and at the 0.056 mg/ml dose level in female rats. Group mean body weight gain for weeks 1-13 was decreased by 12% in male rats and 16% in female rats at the 0.19 mg/ml dose level, but was not significantly affected at lower doses. For weeks 1-53, a similar effect was noted, with decreases of 11% in males and 21% in females at the 0.19 mg/ml dose level. For the study period as a whole, body weight gain was decreased 18% in male rats and 20% in female rats at the 0.19 mg/ml dose level.

Decreases in food consumption were also observed in this study, with a decrease from control of 10% in male and female rats at the 0.19 mg/ml dose level during weeks 1-13. Larger or smaller decreases were observed subsequent to this time point. Food efficiency was also reported as significantly decreased in male and female rats for weeks 1-12 of the study. The decrease in food consumption for male rats for weeks 1-13 of the study at the 0.19 mg/ml dose (10%) is approximately equal to the decrease in weight gain (12%), but for females, the decrease in weight gain (16%) exceeds the decrease in food consumption (10%). Based on the combined observations of body weight gain, food consumption, and food efficiency, a mild toxic effect of metam sodium could be inferred at the 0.19 mg/ml dose level. Water consumption was also measured in this study and was found to be significantly affected at the 0.19 mg/ml dose level for both sexes, and at the 0.056 mg/ml dose level for females. The decrease was dose-related, and equaled or exceeded 50% of control values at the 0.19 mg/ml dose level. The significance of such a dramatic decrease in water consumption on toxicity of metam sodium (as related to effects on normal physiology) was not addressed in this study.

Ophthalmological examination at pre-study (52 males and 51 females examined) showed focal opacities in 2 female rats assigned to the high dose group, and none in male rats. At week 52 (examination of 52 males and 49 females), focal opacities were observed in 5 high dose females vs 2 in control, and linear opacities were observed in 3 high dose females vs 1 in controls. At terminal sacrifice, there were no ophthalmoscopic abnormalities observed in treated animals.

Hematological examinations showed effects on red blood cells (RBC), hematocrit (HCT), and hemoglobin (HGB) at the 0.19 mg/ml dose level. These effects consisted of decreases in these parameters of from 3-5% vs control, and were observed up to week 79 of the study, usually in both sexes. At week 105, the decreases in these parameters were slightly greater in high dose males vs high dose females (HGB: 12% in males, 5% in females; HCT: 11% in males, 4% in females; RBC: 10% in males, 8% in females). The increased hemosiderin observed in the spleen of high dose males and females could be coupled to the decrease in RBC, HCT, and HGB and be interpreted as a mild hemolytic anemia at this dose.

Treatment with metam sodium produced effects on the clinical chemistry parameters of cholesterol (decreases of 10% and 17% in high dose males and females at week 105; decreases of 4% and 19% in high dose males and females at week 79), triglycerides (decrease of 18% and 22% in high dose males and females at week 79; decrease of 32% and 43% in high dose males and females at week 105), alanine transaminase (decrease of 15% in high dose females at week 14; decrease of 27% and 24% in high dose and mid dose females at week 27), and aspartate transaminase (decrease of 11% in high dose females at week 14; decrease of 32% in high dose females at week 27). There was also an effect on glucose in mid- and high dose females at week 105 (increases of 16% and 14%, respectively), but this was not observed at earlier time points. The most significant effects appeared to be on cholesterol and triglycerides.

Urinalysis showed a decreased volume in high dose males and females at week 52 (decreases of 25% and 30%, respectively), and week 78 (29% decrease in high dose females). Specific gravity was increased slightly (0.5%) in high dose females at week 52, but increased by 6% over control in high dose females at week 78. The qualitative analysis of urine showed that in both sexes, the presence of blood appeared to increase in prominence as the dose of metam sodium was increased. Both the number of animals displaying this symptom as well as the severity of the symptom appeared increased at the high dose, and some dose-response relationship was apparent.

Macroscopic examination of rats in this study (all animals combined) showed an increase in liver masses in male rats at the high dose (8 recorded vs 4 in control). Of the eight recorded masses, four were identified as adenocarcinomas, three identified as adenomas, and one identified as an hepatoblastoma. The incidence of enlarged liver as well as pale spots was also increased at both the mid and high dose for male rats, although there were no definitive microscopic correlates. Fat vacuolation was, however, increased at the high dose, possibly providing some correlate for the enlarged liver appearance at the high dose. Wasting of voluntary muscle was observed to be increased at the high dose in male rats, and could be correlated with an increase in the severity and incidence of degenerative myopathy. The severity (but not incidence) of sciatic nerve degeneration was also shown to be increased at the high dose in male rats.

Significant microscopic findings were observed in the nasal cavity of high dose male and female rats in this study.The changes observed included rhinitis, hypertrophy of Bowman's ducts/glands, atrophy and adenitis of Steno's gland, and olfactory epithelium hyperplasia and degeneration. Insofar as the incidence was so greatly increased at the high dose, this is considered an effect of treatment. As stated in the report, the lesions observed are indicative of a systemic effect due to the posterior location of Bowman's and Steno's glands in the nasal passage, and because both glands are metabolically active (meaning presumably the capacity to biotransform the parent chemical). Of interest is the observation of decreased mineralization of the aorta and heart observed in high dose males vs control.

Based on examination of the tumor data presented in this study, there is no evidence for tumorigenicity of metam sodium in rats.

Based upon the decrease in body weight gain and food efficiency in both sexes, as well as the observed hematological, clinical chemistry, and microscopic pathology changes, the **LEL is considered to be 0.19 mg/ml. The NOEL is considered to be 0.056 mg/ml.**

Dosing was considered adequate in male and female rats based upon the decrease in body weight gain, food efficiency, changes in hematology and clinical chemistry, and microscopic pathology observed at the 0.19 mg/ml dose level.

IV. Classification

This study is classified **core minimum** and satisfies the guideline requirement for §83-5, Combined Chronic Toxicity and Carcinogenicity Study in Rats.

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

FEB 1 1995

MEMORANDUM

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

SUBJECT: Metam Sodium Qualitative Risk Assessment Based On Hsd/Ola: Wistar Tox Rat and C57BL/10JfCD-1/Alpk Mouse Drinking Studies

Caswell No. 780

TO: Timothy F. McMahon, Toxicologist
Review Section I
Toxicology Branch II
Health Effects Division (7509C)

FROM: Lori L. Brunsman, Statistician
Statistics Section
Science Analysis Branch
Health Effects Division (7509C)

Lori L. Brunsman

THROUGH: Hugh M. Pettigrew, Section Head
Statistics Section
Science Analysis Branch
Health Effects Division (7509C)

Hugh M. Pettigrew

Summary

This qualitative risk assessment of Metam Sodium was based upon two chronic drinking studies conducted in Hsd/Ola: Wistar Tox rats and C57BL/10JfCD-1/Alpk mice. The rats received 0, 0.019, 0.056, or 0.19 mg/ml of Metam Sodium in drinking water (0, 1.3, 3.9, or 12.0 mg/kg/day for males; 0, 2.3, 6.2, or 16.2 mg/kg/day for females) for 105 weeks. The mice received 0, 0.019, 0.074, or 0.23 mg/ml of Metam Sodium in drinking water (0, 1.6, 6.5, or 27.7 mg/kg/day for males; 0, 2.3, 8.7, or 29.9 mg/kg/day for females) for 105 weeks.

The statistical evaluation of mortality indicated a significant decreasing trend with increasing doses of Metam Sodium in male rats. Female rats showed no significant incremental changes in mortality with increasing doses of Metam Sodium.

There were no statistically significant increasing trends in the tumor rates of male rats. However, there were significant differences in the pair-wise comparisons of the 1.3 and 3.9 mg/kg/day dose groups with the controls for hemangiosarcomas.

There were no significant compound-related tumors observed in female rats.

The statistical evaluation of mortality indicated no significant incremental changes with increasing doses of Metam Sodium in male or female mice.

Male mice had significant dose-related increasing trends in liver, spleen, bone marrow (femur), bone marrow (spine), and subcutaneous tissue angiosarcomas, angiosarcomas at all other sites, angiosarcomas at all sites combined, and angiomas and/or angiosarcomas combined. There was a significant difference in the pair-wise comparison of the 1.6 mg/kg/day dose group with the controls for liver angiosarcomas. There were significant differences in the pair-wise comparisons of the 27.7 mg/kg/day dose group with the controls for liver, spleen, and bone marrow (femur) angiosarcomas, angiosarcomas at all other sites, angiosarcomas at all sites combined, and angiomas and/or angiosarcomas combined.

Female mice had significant dose-related increasing trends in liver angiosarcomas, spleen angiosarcomas, angiosarcomas at all sites combined, and angiomas and/or angiosarcomas combined. There were significant differences in the pair-wise comparisons of the 8.7 and 29.9 mg/kg/day dose groups with the controls for spleen angiosarcomas.

Background

A chronic toxicity and carcinogenicity study in Harlan Olac Limited Shaws Farm Hsd/Ola: Wistar Tox rats was conducted by Zeneca Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, United Kingdom, for the Metam Sodium Task Force, and dated May 23, 1994 (Report No. CTL/P/4139; Study No. PR0838; MRID No. 432758-02).

The study design allocated groups of 52 rats per sex to dose levels of 0, 0.019, 0.056, or 0.19 mg/ml of Metam Sodium in drinking water (0, 1.3, 3.9, or 12.0 mg/kg/day for males; 0, 2.3, 6.2, or 16.2 mg/kg/day for females) for 105 weeks. An additional 12 rats per sex per dose were designated for interim sacrifice at week 53.

A chronic carcinogenicity study in C57BL/10JfCD-1/Alpk mice received from the SPF Barriered Animal Breeding Unit of Zeneca Pharmaceuticals was conducted by Zeneca Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, United Kingdom, for the Metam Sodium Task Force, and dated April 20, 1994 (Report No. CTL/P/4095; Study No. PM0841; MRID No. 432335-01).

The study design allocated groups of 55 mice per sex to dose levels of 0, 0.019, 0.074, or 0.23 mg/ml of Metam Sodium in drinking water (0, 1.6, 6.5, or 27.7 mg/kg/day for males; 0, 2.3, 8.7, or 29.9 mg/kg/day for females) for 105 weeks.

Survival Analyses

The statistical evaluation of mortality indicated a significant decreasing trend with increasing doses of Metam Sodium in male rats. There were no significant incremental changes in mortality with increasing doses of Metam Sodium in female rats or male or female mice. See Tables 1 and 2 for rat mortality test results. See Tables 4 and 5 for mouse mortality test results.

The statistical evaluation of mortality was based upon the Thomas, Breslow and Gart computer program.

Tumor Analyses

There were no statistically significant increasing trends in the tumor rates of male rats. However, there were significant differences in the pair-wise comparisons of the 1.3 and 3.9 mg/kg/day dose groups with the controls for hemangiosarcomas, with significance at $p < 0.05$ for the 1.3 mg/kg/day dose group and at $p < 0.01$ for the 3.9 mg/kg/day dose group.

There were no significant compound-related tumors observed in female rats.

Male mice had significant increasing trends, in addition to significant differences in the pair-wise comparisons of the 27.7 mg/kg/day dose group with the controls, for spleen and bone marrow (femur) angiosarcomas, angiosarcomas at all other sites, angiosarcomas at all sites combined, and angiomas and/or angiosarcomas combined, all at $p < 0.01$. Male mice also had significant increasing trends in liver and subcutaneous tissue angiosarcomas at $p < 0.05$ and in bone marrow (spine) angiosarcomas at $p < 0.01$. There were significant differences in the pair-wise comparisons of the 1.6 and 27.7 mg/kg/day dose groups with the controls for liver angiosarcomas at $p < 0.05$ for the 1.6 mg/kg/day dose group and at $p < 0.01$ for the 27.7 mg/kg/day dose group.

Female mice had significant increasing trends in liver angiosarcomas, angiosarcomas at all sites combined, and angiomas and/or angiosarcomas combined, all at $p < 0.01$. Female mice also had a significant increasing trend, in addition to significant differences in the pair-wise comparisons of the 8.7 and 29.9 mg/kg/day dose groups with the controls, for spleen angiosarcomas, all at $p < 0.05$.

The statistical analyses of the male rats were based upon Peto's prevalence test since there was a statistically significant negative trend for mortality in male rats with increasing doses of Metam Sodium. The statistical analyses of the male and female mice were based upon the Exact trend test and the Fisher's Exact test for pair-wise comparisons. See Table 3 for rat tumor analysis results, and Tables 6, 7, 8 and 9 for mouse tumor analysis results.

Table 1. Metam Sodium - Hsd/Ola: Wistar Tox Rat Study

Male Mortality Rates[+] and Cox or Generalized K/W Test Results

	Weeks					
Dose (mg/kg/day)	1-26	27-52	53[i]	53-78	79-105[f]	Total
0	0/64	3/64	11/61	8/50	31/42	42/53 (79)*[n]
1.3	1/64	1/63	12/62	9/50	26/41	37/52 (71)
3.9	1/64	1/63	11/62	11/51	20/40	33/53 (62)
12.0	1/64	0/63	12/63	5/51	30/46	36/52 (69)*[n]

[+]Number of animals that died during interval/Number of animals alive at the beginning of the interval.

[i]Interim sacrifice at week 53.

[f]Final sacrifice at week 105.

[n]Negative trend or negative change from control.

( )Percent.

Note: Time intervals were selected for display purposes only.

Significance of trend denoted at control.

Significance of pair-wise comparison with control denoted at dose level.

If *, then $p < 0.05$. If **, then $p < 0.01$.

Table 2. Metam Sodium - Hsd/Ola: Wistar Tox Rat Study

Female Mortality Rates[+] and Cox or Generalized K/W Test Results

Dose (mg/kg/day)	Weeks 1-26	27-52	53[i]	53-78	79-105[f]	Total
0	1/64	1/63	10/62	7/52	19/45	28/54 (52)
2.3	0/64	4/64	11/60	8/49	16/41	28/53 (53)
6.2	0/64	2/64	12/62	6/50	21/44	29/52 (56)
16.2	1/64	2/63	12/61	4/49	16/45	23/52 (44)

[+]Number of animals that died during interval/Number of animals alive at the beginning of the interval.

[i]Interim sacrifice at week 53.

[f]Final sacrifice at week 105.

( )Percent.

Note: Time intervals were selected for display purposes only.

Significance of trend denoted at control.

Significance of pair-wise comparison with control denoted at dose level.

If *, then $p < 0.05$. If **, then $p < 0.01$.

Table 3. Metam Sodium - Hsd/Ola: Wistar Tox Rat Study

Male Blood Tumor Rates[+] and Peto's Prevalence Test Results (p values)

	Dose (mg/kg/day)			
	0	1.3	3.9	12.0
Hemangiomas (%)	9[a]/50 (18)	3/50 (6)	4/51 (8)	8/51 (16)
p =	0.469[n]	0.950[n]	0.899[n]	0.688[n]
Hemangiosarcomas (%)	0/47 (0)	3/49 (6)	8[b]/50 (16)	3/51 (6)
p =	0.414	0.017*	0.004**	0.073
Combined (%)	9/50 (18)	6/50 (12)	11[c]/51 (22)	11/51 (22)
p =	0.375	0.713[n]	0.389	0.438

[+]Number of tumor bearing animals/Number of animals examined, excluding those that died before observation of the first tumor.

[a]First hemangioma observed at week 56, dose 0 mg/kg/day.

[b]First hemangiosarcoma observed at week 66, dose 3.9 mg/kg/day.

[c]One animal in the 3.9 mg/kg/day dose group had both a hemangioma and a hemangiosarcoma.

[n]Negative trend or negative change from control.

Note: Significance of trend denoted at control.

Significance of pair-wise comparison with control denoted at dose level.

If *, then $p < 0.05$. If **, then $p < 0.01$.

Table 4. Metam Sodium - C57BL/10JfCD-1/Alpk Mouse Study

Male Mortality Rates[+] and Cox or Generalized K/W Test Results

	Weeks				
Dose (mg/kg/day)	1-26	27-52	53-78	79-105[f]	Total
0	1/55	1/54	8/53	24/45	34/55 (62)
1.6	1/55	1/54	8/53	25/45	35/55 (64)
6.5	0/55	0/55	7/55	21/48	28/55 (51)
27.7	1/55	1/54	8/53	25/45	35/55 (64)

[+]Number of animals that died during interval/Number of animals alive at the beginning of the interval.

[f]Final sacrifice at week 105.

( )Percent.

Note: Time intervals were selected for display purposes only.

Significance of trend denoted at control.

Significance of pair-wise comparison with control denoted at dose level.

If *, then $p < 0.05$. If **, then $p < 0.01$.

Table 5. Metam Sodium - C57BL/10JfCD-1/Alpk Mouse Study

Female Mortality Rates[+] and Cox or Generalized K/W Test Results

Dose (mg/kg/day)	Weeks 1-26	27-52	53-78	79-105[f]	Total
0	0/55	0/55	5/55	22/50	27/55 (49)
2.3	0/55	0/55	10/55	20/45	30/55 (55)
8.7	8/55	1/47	5/46	22/41	36/55 (65)
29.9	3/55	0/52	5/52	25/47	33/55 (60)

[+]Number of animals that died during interval/Number of animals alive at the beginning of the interval.

[f]Final sacrifice at week 105.

( )Percent.

Note: Time intervals were selected for display purposes only.

Significance of trend denoted at control.

Significance of pair-wise comparison with control denoted at dose level.

If *, then $p < 0.05$. If **, then $p < 0.01$.

Table 6. Metam Sodium - C57BL/10JfCD-1/Alpk Mouse Study
Male Angiosarcoma Tumor Rates[+] and Exact
Trend Test and Fisher's Exact Test Results (p values)

	Dose (mg/kg/day)			
	0	1.6	6.5	27.7
Liver	1/52	8/52	5/55	10[a]/52
(%)	(2)	(15)	(9)	(19)
p =	0.023*	0.016*	0.116	0.004**
Spleen	6/53	3/53	10/55	21[b]/53
(%)	(11)	(6)	(18)	(40)
p =	0.000**	0.244[n]	0.233	0.001**
Bone Marrow	3/53	3/53	8[c]/55	15/53
(Femur) (%)	(6)	(6)	(15)	(28)
p =	0.000**	0.661	0.113	0.002**
Bone Marrow	2/53	0/53	0/55	7[d]/53
(Spine) (%)	(4)	(0)	(0)	(13)
p =	0.001**	0.248[n]	0.239[n]	0.080
Subcutaneous	1/53	1/53	2[e]/55	5/53
Tissue (%)	(2)	(2)	(4)	(9)
p =	0.020*	0.752	0.514	0.103
All Other Sites[#]	1/53	3/53	5[f]/55	9/53
(%)	(2)	(6)	(9)	(17)
p =	0.004**	0.309	0.112	0.008**
All Sites	7[g]/52	12[g]/52	12[g]/55	27[g]/52
Combined (%)	(13)	(23)	(22)	(52)
p =	0.000**	0.155	0.191	0.000**

[+]Number of tumor bearing animals/Number of animals examined, excluding those that died before week 53.
[n]Negative change from control.
[a]First liver angiosarcoma observed at week 68, dose 27.7 mg/kg/day.
[b]First spleen angiosarcoma observed at week 68, dose 27.7 mg/kg/day.
[c]First bone marrow (femur) angiosarcoma observed at week 69, dose 6.5 mg/kg/day.
[d]First bone marrow (spine) angiosarcoma observed at week 88, dose 27.7 mg/kg/day.
[e]First subcutaneous tissue angiosarcoma observed at week 71, dose 6.5 mg/kg/day.
[f]First angiosarcoma at any other site observed in the sternum at week 73, dose 6.5 mg/kg/day.
[g]Seven, six, eighteen and forty animals in the 0, 1.6, 6.5, and 27.7 mg/kg/day dose groups, respectively, had angiosarcomas at multiple sites.
[#]Other sites include: abdominal cavity, aorta (adjacent tissue), bone (femur), heart, limb, lung, lymph node (mesenteric), mediastinum, mesentery, spinal cord, sternum, and thoracic cavity.

Note: Significance of trend denoted at control.
Significance of pair-wise comparison with control denoted at dose level.
If *, then $p < 0.05$. If **, then $p < 0.01$.

Table 7. Metam Sodium - C57BL/10JfCD-1/Alpk Mouse Study

Male Angioma and Angiosarcoma Tumor Rates[+] and Exact Trend Test and Fisher's Exact Test Results (p values)

	Dose (mg/kg/day)			
	0	1.6	6.5	27.7
Angiomas[&] (%)	2[a]/53 (4)	1/53 (2)	0/55 (0)	1/53 (2)
p =	0.378	0.500[n]	0.239[n]	0.500
Angiosarcomas[#] (%)	7/52 (13)	12/52 (23)	12/55 (22)	27[b]/52 (52)
p =	0.000**	0.155	0.191	0.000**
Combined (%)	8[c]/52 (15)	13/52 (25)	12/55 (22)	28/52 (54)
p =	0.000**	0.164	0.273	0.000**

[+]Number of tumor bearing animals/Number of animals examined, excluding those that died before week 53.

[n]Negative change from control.

[a]First angioma observed at week 100, dose 0 mg/kg/day.
[b]First angiosarcoma observed at week 68, dose 27.7 mg/kg/day.
[c]One animal in the 0 mg/kg/day dose group had both an angioma and an angiosarcoma.

[&]Angioma sites include: aorta (adjacent tissue), lymph node (mesenteric), and subcutaneous tissue.

[#]Angiosarcoma sites include: abdominal cavity, aorta (adjacent tissue), bone (femur), bone marrow (femur), bone marrow (spine), heart, limb, liver, lung, lymph node (mesenteric), mediastinum, mesentery, spinal cord, spleen, sternum, subcutaneous tissue, and thoracic cavity.

Note: Significance of trend denoted at control.
Significance of pair-wise comparison with control denoted at dose level.
If *, then $p < 0.05$. If **, then $p < 0.01$.

Table 8. Metam Sodium - C57BL/10JfCD-1/Alpk Mouse Study

Female Angiosarcoma Tumor Rates[+] and Exact Trend Test and Fisher's Exact Test Results (p values)

	Dose (mg/kg/day)			
	0	2.3	8.7	29.9
Liver	0/54	0/55	1/47	4[a]/52
(%)	(0)	(0)	(2)	(8)
p =	0.005**	1.000	0.465	0.055
Spleen	0/55	2/55	4[b]/47	5/52
(%)	(0)	(4)	(9)	(10)
p =	0.028*	0.248	0.042*	0.024*
All Other Sites[#]	4/55	2/55	6[c]/47	7/52
(%)	(7)	(4)	(13)	(13)
p =	0.070	0.339[n]	0.275	0.232
All Sites Combined	4/54	2[d]/55	6[e]/47	10[f]/52
(%)	(7)	(4)	(13)	(19)
p =	0.008**	0.331[n]	0.286	0.065

[+]Number of tumor bearing animals/Number of animals examined, excluding those that died before week 48.
[n]Negative change from control.
[a]First liver angiosarcoma observed at week 61, dose 29.9 mg/kg/day.
[b]First spleen angiosarcoma observed at week 48, dose 8.7 mg/kg/day.
[c]First angiosarcoma at any other site observed in the uterus at week 48, dose 8.7 mg/kg/day.
[d]Two animals in the 2.3 mg/kg/day dose groups had angiosarcomas at multiple sites.
[e]Five animals in the 8.7 mg/kg/day dose group had angiosarcomas at multiple sites.
[f]Six animals in the 29.9 mg/kg/day dose group had angiosarcomas at multiple sites.
[#]Other sites include: bone marrow (femur), bone marrow (spine), ear/Zymbal's gland, ileum, limb, mediastinum, ovary, salivary gland, spinal cord, sternum, subcutaneous tissue, and uterus.

Note: Significance of trend denoted at control.
Significance of pair-wise comparison with control denoted at dose level.
If *, then $p < 0.05$. If **, then $p < 0.01$.

Table 9. Metam Sodium - C57BL/10JfCD-1/Alpk Mouse St

Female Angioma and Angiosarcoma Tumor Rates[+] and Exact Trend Test and Fisher's Exact Test Results (p values)

	Dose (mg/kg/day)			
	0	2.3	8.7	29.9
Angiomas[&] (%)	1/55 (2)	0/55 (0)	2[a]/47 (4)	2/52 (4)
p =	0.156	0.500	0.441	0.479
Angiosarcomas[#] (%)	4/54 (7)	2/55 (4)	6[b]/47 (13)	10/52 (19)
p =	0.008**	0.331	0.286	0.065
Combined (%)	5/54 (9)	2/55 (4)	8/47 (17)	11[c]/52 (21)
p =	0.009**	0.211[n]	0.194	0.075

[+]Number of tumor bearing animals/Number of animals examined, excluding those that died before week 48.

[n]Negative change from control.

[a]First angioma observed at week 87, dose 8.7 mg/kg/day.
[b]First angiosarcoma observed at week 48, dose 8.7 mg/kg/day.
[c]One animal in the 29.9 mg/kg/day dose group had both an angioma and an angiosarcoma.

[&]Angioma sites include: mammary gland, subcutaneous tissue, and uterus.

[#]Angiosarcoma sites include: bone marrow (femur), bone marrow (spine), ear/Zymbal's gland, ileum, limb, liver, mediastinum, ovary, salivary gland, spinal cord, spleen, sternum, subcutaneous tissue, and uterus.

Note: Significance of trend denoted at control.
Significance of pair-wise comparison with control denoted at dose level.
If *, then $p < 0.05$. If **, then $p < 0.01$.

References

Armitage, P. (1955) Tests for Linear Trends in Proportions and Frequencies. Biometrics 11, 375-386.

Cochran, W.G. (1954) Some Methods for Strengthening the Common X^2 Test. Biometrics 10, 417-451.

Cox, D.R. (1972) Regression Models and Life Tables (with discussion). J. Royal Stat. Soc. Ser. B. 34, 187-220.

Gart, J.J., D. Krewski, P.N. Lee, R.E. Tarone, and J. Wahrendorf (1986) The Design and Analysis of Long-Term Animal Experiments. In: Statistical Methods in Cancer Research, Volume III. IARC Scientific Publications No. 79. Lyon, France: International Agency for Research on Cancer, p. 18.

Peto, R., M. Pike, N. Day, R. Gray, P. Lee, S. Parish, J. Peto, S. Richard, and J. Wahrendorf (1980) Guidelines for Simple, Sensitive, Significant Tests for Carcinogenic Effects in Long-Term Animal Experiments. In: Monographs on the long-term and short-term screening assays for carcinogens: a critical appraisal. IARC Monographs, Supplement 2. Lyon, France: International Agency for Research on Cancer, pp. 311-426.

Thomas, D.G., N. Breslow, and J.J. Gart (1977) Trend and Homogeneity Analyses of Proportions and Life Table Data. Computers and Biomedical Research 10, 373-381.

U.S. ENVIRONMENTAL PROTECTION AGENCY
OFFICE OF PESTICIDES/HED/TB-1
TOX ONELINERS

CASWELL#: 780
CAS-REG#: 6734-80-1

P.C. CODE 039003- Sodium methyldithiocarbamate FILE LAST PRINTED: 11/01/94

CITATION	MATERIAL	ACCESSION/ MRID NO.	RESULTS	TOX CAT	COREGRADE/ DOCUMENT#
83-3(a) Developmental Toxicity Study Species: rat BASF 87/0128; 3/87	Metam-Sodium, 42.2% a.i	415771-01 420686-01	An aqueous solution of Metam-sodium was admin. at: 0, 10, 40, and 120 mg/kg/day by gavage to pregnant Wistar rats days 6-15 of gestation. Maternal toxicity was observed at the 40 and 120 mg/kg levels as significantly decreased body weight gain during the dosing period. There was a significant increase in post-implantation loss, and a significant decrease in the % of live fetuses/dam at 10 and 120 mg/kg. Fetal weights were significantly reduced at 120 mg/kg. Examination of the viscera of fetuses that underwent skeletal examination revealed a significant increase in variations at the 40 mg/kg level. Skeletal examination revealed findings in the 40 and 120 mg/kg groups. The administration of 120 mg/kg in the main study and 240 mg/kg in the dose-range finding study resulted in meningocoele. Based upon deficiencies, this study can not be upgraded. Maternal NOEL = 10 mg/kg. Maternal LOEL = 40 mg/kg. Developmental Tox. NOEL = not determined. Developmental LOEL = 10 mg/kg. Addendum: Deficiencies not resolved - Date: 01/09/22.		Supplementary 008520 Supplementary 009030
83-3(a) Developmental Toxicity Study Species: rat ZENECA Central Tox. Lab RR0624; 10/93	Metam Sodium (43% a.i.)	429837-01	Administration of Metam Sodium to pregnant rats at doses of: 0, 5, 20, or 60 mg/kg/d on gestation days 6-17 inclusive resulted in signs of maternal toxicity at the 20 and 60 mg/kg/d dose levels (decr. body wt. gain, decr. food efficiency). Examination of cesarean section data showed an increase in total resorptions at the 60 mg/kg/d dose level & resorptions/dam, while mean fetal weight waas significantly decreased at the 20 & 60 mg/kg/day dose levels. Developmental toxicity was present at the 20 & 60 mg/kg/d dose levels & consisted of a significant incerease in the fetal and litter incidence of unossified centrum of the 4th, 5th, and 6th cervical vertebrae, and increase in the litter incidence of unossified 5th sternebrae at the 60 mg/kg/day dose level, a significant increase in the fetal incidence of unossified odontoid, centrum of the 2nd cervical vertebrum, ventral tubercle, and calcaneum at the 20 & 60 mg/kg/day dose levels. In addition, litter incidence of unossified odontoid, unossified centrum of the 2nd cervical vertebrum, and unossified ventral tubercle was also significantly increased over the control at the 60 mg/kg/day dose level. Maternal NOEL = 5 mg/kg/d. Maternal LOEL = 20 mg/kg/d (decr. body wt. gain, decr. food efficiency). Developmental NOEL = 5 mg/kg/d. Developmental LOEL = 20 mg/kg (incr. fetal and litter incid. of minor skeletal defects & variants).		Guideline 010693

U.S. ENVIRONMENTAL PROTECTION AGENCY
OFFICE OF PESTICIDES/HED/TB-1
TOX ONELINERS

.C. CODE 039003- Sodium methyldithiocarbamate FILE LAST PRINTED: 11/01/94

CITATION	MATERIAL	ACCESSION/ MRID NO.	RESULTS	TOX CAT	COREGRADE/ DOCUMENT#
-3(b) velopmental Toxicity Study ecies: rabbit SF R0232/8579; 7/15/87	Metam-Sodium, 42.2% aq. sol.	403309-01 420686-01	Maternal Tox. NOEL = 10 mg/kg/day. Maternal LOEL = 30 mg/kg/day, based on reduced body weight gains, reduced food consumption, increased number of dead implantations & reduced numbers of fetuses, and increased post-implantation loss in either mid or high dose group or both. Develpmental Toxicity was apparent in the mid and high dose in the form of increased number of dead implantations and reduced numbers of fetuses, and increased post-implanation loss. One observation each of meningocoele and spina bifida were noted in the high dose, a defect noted in the rat teratology study with metam-sodium. These observations were not reported in provided historical control data; however the Developmental Toxicity NOEL and LOEL can not be determined with available data; additional information is required. Dose levels tested: 10, 30, and 100 mg/kg by gavage from gestation days 6 through 18 in Himalayan rabbits. Addendum - Deficiencies not resolved - Date: 01/07/92.		Supplementary 008520 Supplementary 009030
3-3(b) evelopmental Toxicity Study pecies: rabbit ENECA Central Tox. Lab TL/P/4035; RB0623; 09/06/93	Metam-Sodium 43.14% w/w 525.54 g/L; batch 90/2, Y06930/007/001, & YA6930/008	429631-01	Maternal Tox. NOEL = 5 mg/kg/d. Maternal Tox. LOEL = 20 mg/kg/d based on reduced body weight gain, reduced food consumption & food efficiency. Developmental Tox. NOEL = 5 mg/kg/d. Develop. Tox. LOEL = 20 mg/kg/d based on the incr. incid. of skeletal observations. In the high dose there was an increase in resorptions, decrease in litter size, increased post-implantation loss & decreased mean fetal body weight. Rabbits of the NZW strain from Interfauna UK Limited, Huntingdon, Cambridgeshire, UK, received either 0, 5, 20 or 60 mg metam sodium/kg/day by oral gavage from gestation day 8 through 20, inclusive. The animals were received time-pregnant from the vendor. The test compound 43.14% w/w active ingred. conc. in liquid from (525.54 g/L, Batch 90/2, Y06930/007/001 and YA6930/008) was adjusted for the above doses.		Minimum 010693

U.S. ENVIRONMENTAL PROTECTION AGENCY
OFFICE OF PESTICIDES/HED/TB-1
TOX ONELINERS

P.C. CODE 039003- Sodium methyldithiocarbamate FILE LAST PRINTED: 11/01/94

CITATION	MATERIAL	ACCESSION/ MRID NO.	RESULTS	TOX CAT	COREGRADE/ DOCUMENT#
3-4 eproduction-2 generation pecies: rat ENECA Central Tox. Lab RO564/FO;RR0564F1; 12/23/93	Metam Sodium	431361-01	Metam sodium was admin. in drinking water to male and female SD rats at 0.01 mg/mL (1.2 mg/kg/d (M); 1.8 mg/kg/d (F)), 0.03 mg/mL (3.2 mg/kg/d (M); 3.9 mg/kg/d (F)) and 0.1 mg/mL (11.5 mg/kg/d (M); 13.5 mg/kg/d (F)). Test drinking water was admin continuously throughout the study. Systemic toxicity was observed at the 0.1 mg/mL dose in adult female rats of the Fo and F1 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 Bowman's gland ducts. Ths 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 & observed mainly at the high dose. These consisted of a decrease in mean pup wt. of 14% vs control on day 22 for the F1 parents, a 16% decrease in body wt. gain for male & female pups in the F2 litter at the high dose, & a decr. of 8-9% in testes and epididymis wts for male pups in the F1 and F2a litters at the high dose. There was no apparent effects of metam sodium on reproductive performance in the Fo or F1 generations. Sys. NOEL = 0.03 mg/mL (3.2 mg/kg/d (M); 3.9 mg/kg/d (F)). Sys LOEL = 0.1 mg/mL (11.5 mg/kg/d (M); 13.5 mg/kg/d (F)). NOEL for reprod. toxicity = 0.1 mg/mL; Reprod. LOEL is => 0.1 mg/mL.		Minimum 010928
Subchronic Feeding Species: rat ICI Central Tox. Lab. PRO 797; 10/26/91	Metam-sodium 45.13%	421173-02	Metam sodium was administered to male & female rats in drinking water at nominal dose levels of 0, 0.018, 0.089, & 0.443 mg/mL (1.7, 8.1 & 26.9 mg/kg/day in males; 2.5, 9.3 and 30.6 mg/kg/d (F). At the high dose in both sexes, systemic toxicity in the form of significantly decreased food & water consumption, decr. body wt. gain, & histological changes in the nasal cavity olfactory epithelium were observed. Renal tubular dilatation and basophilia, along with increases in blood, protein, and red cells in urine was also observed at the hgih dose. In high dose males, an increased incidence of plasma cell hyperplasia in cervical lymph nodes was demonstrated as well as a significant decrease in platelet count. A significant decrease in group mean body wt. was observed in female rats at the mid dose, and body wt. gain was decreased 11% at this dose for the duration of the study. Significant decreases in red cell count and hematocrit were observed at the mid dose in both male & female rats. Tentative NOEL = 1.7 mg/kg/d (M); 2.5 mg/kg/d (F). Tentative LOEL = 8.1 mg/kg/d (M; hematological changes); 9.3 mg/kg/d (F; decr. absolute body wt.). Tentative Maximum Tolerated Dose = 26.9 mg/kg/day (M); 30.6 mg/kg/d (F); decr. absolute body weight gain; alterations in hematology and clinical chemistry parameters; incr. incidence of histopathological abnormalities.		Supplementary 010180

U.S. ENVIRONMENTAL PROTECTION AGENCY
OFFICE OF PESTICIDES/HED/TB-1
TOX ONELINERS

P.C. CODE 039003- Sodium methyldithiocarbamate FILE LAST PRINTED: 11/01/94

CITATION	MATERIAL	ACCESSION/ MRID NO.	RESULTS	TOX CAT	COREGRADE/ DOCUMENT#
31-8 Acute oral neurotoxicity Species: rat Wil Research Lab 188009; 09/1993	Metam sodium...42.15% a.i	429778-01 429778-02	The acute neurotoxicity of metam sodium technical was investigated in male & female Sprague-Dawley rats at single oral doses of 50 mg/kg, 750 mg/kg (12 rats/sex/dose), and 1500 mg/kg (16 rats/sex/dose; [actual doses based on % active ingred. were: 0, 22, 324, and 647 mg/kg. Viability, clinical signs, body weights, functional observational battery and motor activity evaluations were performed. Mortality was observed at the 1500 mg/kg (647 mg/kg actual dose) dose level, where a total of 5 males and 3 females were found dead during the course of the study. Signs of systemic toxicity were observed at the 750 and 1500 mg/kg dose level, and included alterations in posture and palpebral closure, increased lacrimation and salivation, alterations in respiratory rate, decr. arousal, decr. rearing activity, increased time to first step, lack of approach, olfactory, and pupil responses, absent or reduced tail pinch response, reduced hindlimb strength, and decr. body temperature and body weight. Reductions in mean ambulatory and total motor activity were observed at the 50 mg/kg dose level and above. Inhibition of plasma and red cell cholinesterase was observed at the 1500 mg/kg dose level in male & female rats 24 hrs. post-dose. The LOEL of 22 mg/kg is based on reduced ambulatory and total motor activity observed in male & female rats. The NOEL < 22 mg/kg and was not achieved in this study.		Minimum 010828 Supplementary 011050
82-1(a) 90 day oral Species: mice ICI Central Tox. Lab. PM0808; 09/26/91	Metam sodium 45.13% a.i.	421173-01	Metam sodium was administered to male & female C57 mice in drinking water at dose levels of 0, 0.018, 0.088, 0.35 and 0.62 mg/mL, equivalent to: 2.7, 11.7, 52.4 and 78.7 mg/kg/day for males & 3.6, 15.2, 55.4 & 83.8 mg/kg/day (F). The systemic NOEL = 0.018 mg/mL in both sexes. The LOEL = 0.088 mg/mL, based on urinary bladder lesions (eosinophilic granules, cystitis, mucosal hyperplasia) in both sexes and decr. HGB, RBC and HCT in female mice. Based on body weight gain decrements, the MTD appears to have been achieved at 0.35 mg/mL in males and 0.62 mg/mL in females.		Supplementary 009501
82-1(b) Feeding-13 week Species: dog ICI Central Tox. Lab. CTL/P/3679; 11/11/92	Metam sodium, 43.15% a.i.	426000-01	Metam sodium (43.15%) was administered to male & female dogs at nominal dose levels of 0, 1, 5, and 10 mg/kg/day once daily for 13 weeks. Toxic effects were observed at all dose levels tested, but were primarily evident at the 5 & 10 mg/kg/d dose levels. These included decr. body wt. & body wt. gain in male & female dogs at 10 mg/kg/d, hematologic alterations (incr. cell volume, cell hemoglobin, neutrophils, & monocytes; decr MCHC) at 5 & 10 mg/kg/d, significant increase in plasma ALT, AST, ALK PHOS, and GGT at 5 & 10 mg/kg/d (including significantly increased ALT in female dogs at 1 mg/kg/d), incr. amounts of blood, urobilinogen, bilirubin, & protein in urine at 5 & 10 mg/kg/d, & microscopic evidence of hepatitis at 5 & 10 mg/kg/d. A majority of the toxic effects in this study appearewd dose and time-related in treated dogs. No evidence of tumors was found in this study. Systemic NOEL < 1 mg/kg/d (female dogs, not achieved); = 1 mg/kg/d (M). Systemioc LOEL <= 1 mg/kg/d (female dogs, incr. ALT and bile duct prolif-		Supplementary 010028

eration); = 5 mg/kg/day (male dogs; incr. AST, ALT. ALK PHOS, & incr. incidence of hepatitis and bile duct proliferation).

U.S. ENVIRONMENTAL PROTECTION AGENCY
OFFICE OF PESTICIDES/HED/TB-1
TOX ONELINERS

P.C. CODE 039003- Sodium methyldithiocarbamate FILE LAST PRINTED: 11/01/94

CITATION	MATERIAL	ACCESSION/ MRID NO.	RESULTS	TOX CAT	COREGRADE/ DOCUMENT#
84-2(a) Mutagenic-Ames Species: salmonella BASF Aktiengesellschaft 87/0208; 6/5/87	Metam-sodium, Batch# 2H130585; 42.2% pure	403056-03	Not a mutagen up to 2500 ug/plate for TA92, TA98, TA100, TA1535, TA1537, and TA1538 strain of Salmonella typh in the standard plate test and in the preincubation test either with or without metabolic activation at the concentrations tested: Standard plate test: 20, 100, 500, 1000, 1500, 2000 and 2500 ug/plate. Preincubation test: 4, 20, 100, 200, 300, 400 500, 1000 and 2500 ug/plate.		Acceptable 006570
84-2(b) Mutagenic-rec assay and rever. Species: B. subtilis Hazleton Lab., Madison Wisc. HBCE-9642-0-404; 3/27/87	Metam-Sodium (batch 2H130 585; 42.2% purity)	9-0201A 403056-02	Not a recombinogenic agent (ie damage of DNA) to B. subtilis strains H17 and M45 at the conc. tested. Concentrations: 0.1, 1, 5, 10, 25, 50 100 and 150 ul/well.		Unacceptable 006570 Acceptable 007027
84-2(b) Mutagenic- in vitro cytogen. Species: human lymphocytes BASF Aktiengesellschaft 87/0116; 3/9/87	Metam-Sodium (Batch 2H130585), 42.2% purity	403056-04	Positive response in the cultured human lymphocytes either at 20 ug/ml without metabolic activation or at 20 and 40 ug/ml with metabolic activation. Concentrations tested: 1., 5, 10 and 20 ug/ml without S9 mix; 10, 20, and 40 ug/ml with S9 mix.		Acceptable 006570
84-2(b) Mutagenic-in vivo cytogenetic Species: Chinese Hamster BASF Aktiengesellschaft 87/0238; 6/30/87	Metam-Sodium (Batch 2H130 585; 42.2% purity)	9-0201A 403056-05	Negative response in the chinese hamster bone marrow cytogenetic assay at the conc. tested. Concentrations tested: 150, 300, & 600 mg/kg.		Unacceptable 006570 Acceptable 007027
84-4 Mutagenic-unscheduled DNA synt Species: rat hepatocytes Hazleton Lab America HLA 9736-0-447; 7/1/87	Metam-Sodium (Batch 2H130585; 42.2% purity	403056-01	Inactive in the UDS in primary rat hepatocytes at the dose levels tested. Doses tested: 0.5, 1, 2.5, 5, 10, 50, 100 and 250 nl/ml.		Acceptable 006570
Immunotoxicity Species: Buckman Lab. Int. 11/07/91	Metam Sodium		Summary data provided in two abstracts supplied by Buckman lab Int. indicated that Metam Sodium (and other dithiocarbamates) are possible immunotoxic agents. Final conclusions will ensue after receipt of the two immunotoxicity studies.		008805
85-1 Pharmacokinetics Species: rat Huntingdon Res. Centre, Eng. 455/617/8875	Dazomet 99.3%	406410-00	Doses were 10 and 100 mg/kg. Group B: Single, oral low dose, 14C-labeled (Acceptable). Group C: 14 consecutive daily doses with non-labeled followed by labeled compound on day 15 with low dose (not performed). Group D: Single oral high dose, 14C-labeled (Acceptable)		Acceptable 010977

U.S. ENVIRONMENTAL PROTECTION AGENCY
OFFICE OF PESTICIDES/HED/TB-1
TOX ONELINERS

P.C. CODE 039003- Sodium methyldithiocarbamate FILE LAST PRINTED: 11/01/94

CITATION	MATERIAL	ACCESSION/ MRID NO.	RESULTS	TOX CAT	COREGRADE/ DOCUMENT#
5-1 harmacokinetics pecies: rat untingdon Res. Centre, Eng. 55/617/8875	Metam Sodium 99%	406410-00	Doses were 10 and 100 mg/kg. Group B: Single, oral low dose, 14C-labeled (Acceptable). Group C 14 consecutive daily doses with non-labeled followed by a single 14C-labeled dose on day 15, low dose. Group D: Single, oral high dose, 14C-labeled.		Acceptable 010977
5-1 harmacokinetics pecies: rat luntingdon Res. Centre, Eng. 55/617/8875	Methyl isothiocyanate (MTIC) 95%	406410-00	Doses were 44 and 33 mg/kg. Group B: Single oral low dose, 14C-labeled Group C: 14 consecutive oral daily low doses with non-labeled followed by a 14C-labeled low dose on day 15 (not performed). Group D: Single, oral high dose, 14C-labeled. The studies with dazomet and MITC support the pharmacokinetic and metabolism data for metam sodium. There are evidently similarities in absorption from the G.I. tract, products of metabolism, excretion, organ distribution and retention of all three compounds. The data appear convincing that both dazomet and metam sodium are converted to MITC in the early stages of metabolism within rats. Metabolic profiles detected in urine, liver and kidneys were basically qualitatively similar for the three compounds, but there were some differences, mainly quantitative in nature (DER 010977 - 9/30/88).		Acceptable 010977

Submission: S468984 File Last Updated no idea Current Date: 8/25/94

Study/Lab/Study #/Date
83-5 chronic toxicity/carcinogenicity
43.148% purity
species: rats
PRO838
Zeneca Central Tox Lab.
5/23/94

MRID # 432758-02; P.C. Code 039003
Test material: metam sodium, aq. soln, of

Doses of of 0, 0.019, 0.056, and 0.19 mg/ml metam sodium administered in drinking water to groups of 64 male and female Wistar rats for either 52 weeks (12/sex/dose) or 104 weeks (52/sex/dose). Actual doses received were **1.3 mg/kg, 3.9 mg/kg,** and **12.0 mg/kg** for male rats; **2.3 mg/kg, 6.2 mg/kg,** and **16.2 mg/kg** for female rats.

At 0.19 mg/ml, the following effects were noted: decreased body weight gain in male and female rats (12-18% vs control for males; 16-20% vs control for females; weeks 1-104 inclusive); decreased food efficiency for weeks 1-12 in both sexes; decreased red blood cells, hemoglobin, and hematocrit in both sexes; decreased cholesterol and triglycerides in both sexes; increased incidence of liver masses, fat vacuolation, and wasting of voluntary muscle in male rats; microscopic pathology of the nasal cavity (increased incidence of rhinitis, hypertrophy of Bowman's ducts/glands, atrophy and adenitis of Steno's gland, and olfactory epithelium hyperplasia and degeneration), heart and aorta (decreased mineralization), voluntary muscle (degenerative myopathy), and sciatic nerve (increased severity of degeneration).

Evaluation of tumor data showed no evidence for a carcinogenic effect of metam sodium in this study.

Dosing was considered adequate in male and female rats based upon the systemic effects observed at the 0.19 mg/ml dose level.

Systemic LEL = 0.19 mg/ml (decreased body weight gain; changes in hematology, clinical chemistry, macroscopic pathology, and microscopic pathology in both sexes).

Systemic NOEL = 0.056 mg/ml

Classification: core minimum

Submission: S467006 File Last Updated no idea Current Date: 7/28/94

Study/Lab/Study #/Date
83-2 carcinogenicity
species: mouse
PMO841
Zeneca Central Tox Lab.
4/20/94

MRID # 432335-01; P.C. Code 039003
Test material: metam sodium, aq. soln, of 43.148% purity

Doses of of 0, 0.019, 0.074, and 0.23 mg/ml metam sodium administered in drinking water to groups of 55 C57BL male and female mice for 104 weeks **(1.6 mg/kg, 6.5 mg/kg, and 27.7 mg/kg** for male mice and **2.3 mg/kg, 8.7 mg/kg, and 29.9** mg/kg for female mice).

At 0.074 and 0.23 mg/ml, liver weight was significantly increased by 11-35% in male and female mice over control. At 0.23 mg/ml, decreased body weight gain in male mice (14% for weeks 1-13, 20% for weeks 1-104) was observed. Increased incidence of macroscopic pathology also seen in liver (accentuated lobular pattern, pale appearance) and urinary bladder (wall thickening). Non-neoplastic pathology present at 0.23 mg/ml, and included increases in extramedullary hemopoiesis of the spleen and several alterations in the urinary bladder, including epithelial hyperplasia, eosinophilic/hyaline cytoplasmic inclusions, increased submucosal connective tissue, and submucosal hyalinization. Fat vacuolation in the liver was also observed in both sexes at this dose.

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

Systemic LEL = 0.074 mg/ml (increased liver weight [males and females; decreased body weight gain in males])

Systemic NOEL = 0.019 mg/ml

Classification: core minimum

Citation	Material	MRID No.	Results	Tox Cat	Coregrade
83-1 Chronic Toxicity Species: dog (Zeneca Central Toxicology Lab PID0905: 5/23/94	Technical metam sodium (43.148 %, a.i.)	432758-01	Metam sodium was administered in gelatin capsules to four male and four female beagle dogs per group at dosages of 0, 0.05, 0.1 or 1.0 mg/kg/day for 52 weeks. There were no deaths or treatment-related clinical signs of toxicity. Group mean body weights of the treated animals were comparable to the control groups over the course of the study. The group mean ALT levels in the 1.0 mg/kg/day group females gradually increased over the course of the study until week 52 when the value was three times that of the control level. However, the difference was due to one female whose level peaked at 400 IU/l during weeks 45 and 52. This animal also had a slight increase in AST. The only treatment-related finding on necropsy was on microscopic examination of the liver of the female from the 1.0 mg/kg/day group with the ALT elevation. This animal had a slight increase in hepatocyte and macrophage/Kupffer cell pigmentation, slight mononuclear cell infiltration, slight telangiectasis and a positive reaction for hemosiderin. LOEL - males > 1 mg/kg/day; females = 1 mg/kg/day NOEL - males ≥ 1 mg/kg/day; females = 0.1 mg/kg/day		Minimum