Microfiche

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

1

019693

DEC 8 1993

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Metam Sodium: Review of a Rat Developmental Toxicity Study Submitted by the Registrant under FIFRA Section 6(a)(2) and Review of a Rabbit Developmental Toxicity Study Submitted by the Registrant

P.C. Code: 039003
Submissions: S453310 and S451460
MRID Nos: 429837-01 and 429631-01
DP Barcodes: D196731 and D196100

FROM: Timothy F. McMahon, Ph.D., Toxicologist 12/7/93
Review Section I, Toxicology Branch II
Health Effects Division (7509C)

TO: Linda Deluise / PM 51
Special Review and Reregistration Division (7508W)

THRU: Yiannakis M. Ioannou, Ph.D., Section Head J.M. Ioannou 12/7/93
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) 12/8/93

Registrant: Metam Sodium Task Force

Action Requested: Review of rat and rabbit developmental toxicity studies submitted in support of reregistration of metam sodium.

1 of 48

010693

Data Summary:

1) Metam Sodium: Developmental Toxicity Study in the Rat

In a developmental toxicity (teratology) study, rats of the Wistar strain 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.

2) Metam Sodium: Developmental Toxicity Study in the Rabbit

In a developmental toxicity (teratology) study, rabbits of the New Zealand White 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 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. Therefor 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).

Reviewed by: Timothy F. McMahon, Ph.D 12/7/93
Pharmacologist, Section I, Toxicology Branch II (7509C)
Secondary Reviewer: Stephen C. Dapson, Ph.D. 12/7/93
Senior Pharmacologist, Section I, Toxicology Branch II (7509C)

Data Evaluation Report

Study type: Developmental Toxicity- Teratology
Species: rat
Guideline: 83-3

EPA ID Numbers: Submission: S453310
DP Barcode: D196731
MRID number: 429837-01
Caswell No: 780
PC Code: 039003

Test material: sodium methyldithiocarbamate

Synonyms: metam sodium

Study number(s): RR0624

Testing Facility: Zeneca Central Toxicology Laboratory
Cheshire, UK

Sponsor: Metam Sodium Task Force

Title of report: Metam Sodium Developmental Toxicity Study in the Rat

Author(s): D.J. Tinston

Study Completed: October 5, 1993

Executive Summary: In a developmental toxicity (teratology) study, rats of the Wistar strain 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 level 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.

5

I. MATERIALS and METHODS

A. Test Material: Metam sodium
purity: 525.54 g/l (43% a.i.)
batch number: BAS/005/00N
description: yellow aqueous solution

B. Vehicle: deionized water

C. Dose Solution Preparation,Stability and Homogeneity: For each dose level, the concentration of metam sodium was adjusted to give a constant volume of 1ml/100g body weight. A weighed amount of test substance (adjusted for purity) was diluted with deionized water to give the appropriate test material concentration. Each preparation was thoroughly mixed before being subdivided into aliquots. Aliquots were stored at room temperature and fresh aliquots were used each day of the study.

A sample of each preparation was analyzed prior to the start of dosing to verify concentration in the dose solutions. In addition, stability of the stock solution itself was investigated over the course of the study. Results of stock solution stability were presented in Appendix B, page 66 of the report. These data show that over a period of three years, there was no significant degradation of the metam sodium stock solution (measurements ranging from 487-526 g/l).

According to the report (page 15), "chemical stability of metam sodium at the 0.5 mg/ml level was determined by re-analysis of the dosing formulation over an interval of up to 6 days. Metam sodium was shown to be stable in deionized water for up to 7 days at concentrations of 5 mg/ml and 60 mg/ml in a concurrent study."

Data on dose solution stability and concentration were presented in Tables 2, 3, and 4, pages 33-37 of the report. In Table 2, achieved dose solution concentrations for the doses used in this study (0, 5, 20, and 60 mg/kg) were found to be between 90-108% of nominal over the duration of this study. Table 3 presented a summary of the data for dose solutions, showing that average achieved concentrations were 98% of nominal for all dose groups. In Table 4, the concentration of dose solutions prepared at the 5 mg/kg and 60 mg/kg doses were shown to be stable for up to 7 days post-preparation, as concentrations did not decrease to below 90% of nominal from day 0 at either concentration of test article.

D. Test Animals: Species: Wistar rats, virgin female, Alpk:APfSD)
Source: Barriered Animal Breeding Unit, Biological Services Section, Alderly Park, Cheshire, UK
Age: 10-12 weeks on arrival.
Male rats (from the same source) were used for natural insemination of females.
Weight range (mean, day 1 of gestation): control, 223-320g; low dose, 230-311g; mid dose, 167-306g; high dose, 198-281g.

Note: it appears that for the control, low dose, and mid dose group, body weight of one rat per group is outside the recommended range of ± 2 S.D.

E. Animal Husbandry:

A total of 96 female rats,supplied over a two week period, were used in this study. Twelve female rats were supplied on each of eight days. Following transfer to the SPF Barriered Unit at Zeneca Toxicology Laboratory, personnel access was restricted as a quarantine procedure. Rats were housed singly in cage racks constructed of aluminum, with 20 cages each suspended over stainless steel collecting trays lined with absorbent paper. Backs and fronts of cages were constructed of 14 standard wire gauge stainless steel mesh. Rats were housed under conditions of constant temperature (18-24 ^{o}C) and humidity (31-60%) with a 12 hour light/ 12 hour dark cycle. Food (CT1 diet, SDS Limited, Essex, UK) and filtered (0.2 µm) tap water was made available on an ad libitum basis. The room in which this study was done contained animals from this study only.

F. Experimental Design and Dosing:

Metam Sodium Technical was administered by gavage in deionized water at a dose volume of 10 ml/kg to female rats on gestation days 7 through 16 inclusive in order to assess developmental toxicity of this chemical. There was no background information provided on dose selection rationale. However, in a previous teratology study (MRID # 415771-01) with metam sodium in rats at doses of 0, 10, 40, and 120 mg/kg/day, maternal toxicity was observed at the 40 and 120 mg/kg/day dose levels, while there was evidence of developmental toxicity at 10 and 120 mg/kg/day. Doses for this study were 0, 5, 20, and 60 mg/kg.

Female rabbits were assigned to the following dose groups for the main study according to computer-generated randomization:

Dose Group	Dose Level(mg/kg/day)	No. rats assigned
1	0 mg/kg/day	24
2	5 mg/kg/day	24
3	20 mg/kg/day	24
4	60 mg/kg/day	24

G. Mating

After an acclimation period of at least 10 days in the laboratory setting, female rats were paired overnight with males of the same strain (ratio of females: males not stated). On the following morning, vaginal smears were examined for the presence of sperm. Detection of sperm was designated as day 1 of gestation.

H. Statistical Analysis:

Animals which were non-pregnant or in which litters were totally resorbed were excluded from statitstical analysis.

Body weights were analyzed by analysis of covariance using day 7 as the initial body weight. Food consumption, number of implantations and live fetuses per dam, gravid uterus weight, litter weight, mean fetal liver weights per litter and mean manus and pes scores per litter were analyzed by analysis of variance. Maternal performance data, proportion of litters and fetuses with defects, and the proportion of fetuses with each individual manus and pes score were analyzed using Fischer's Exact Test. Pre- and post-implantation loss, intrauterine deaths, defects, variants, and male/female sex ratio were analyzed by analysis of variance following the double arcsine transformation of Freeman and Tukey, while the proportion of fetuses affected and the proportion of litters affected (with the exception of male fetuses) by Fischer's Exact Test.

I. Compliance:

A signed statement of Compliance with Good Laboratory Practice Standards (40 CFR Part 160; 40 CFR part 792; OECD GLP; Japanese Ministry of Agriculture, Forestry, and Fisheries) was provided.

A signed statement of No Data Confidentiality Claims was provided. No claim of confidentiality is made for any information contained in this study on the basis of its falling within the scope of FIFRA § 10(d)(1)(A), (B), or (C). The Metam Sodium Task Force does not waive any protection or right involving this material that would have been claimed confidential by the Metam Sodium Task Force if this material had not been submitted to the EPA.

A signed statement of Quality Assurance was provided.

A signed statement of Flagging of Studies for Potential Adverse Effects was provided for this study. This study neither meets nor exceeds the criteria of 40 CFR 158.34 for potential adverse effects, in contrast to a previous letter submitted by the registrant claiming potential adverse effects under FIFRA section 6(a)(2).

II. OBSERVATIONS and RESULTS:

A. Maternal Toxicity

1. Mortality and Clinical Toxicity

All rats were observed upon arrival for normal physical appearance, and were subsequently observed at least twice each day.

There was no mortality among treated and control dams during the study. Clinical observations considered treatment-related are summarized as follows:

Table 1

Clinical Observations in Dams Treated with Metam Sodium[a]

Sign	Dose level (mg/kg) 0	5	20	60
discharge from eye	0/24	0/24	0/24	3/24
piloerection	0/24	0/24	0/24	10/24
salivation	0/24	0/24	10/24	24/24
subdued	0/24	0/24	0/24	6/24
urinary incontinence	0/24	0/24	1/24	10/24
vaginal bleeding	0/24	1/24	3/24	3/24

[a]data taken from Table 6, pages 40-42 of the report.

As shown, increased incidence of discharge from the eye, salivation, piloerection, subdued behavior and urinary incontinence was observed at the 60 mg/kg/day dose level. In addition to the increased number of dams observed with these signs, signs of salivation and urinary incontinence were also observed for a longer time period in high dose dams vs mid dose dams. Salivation was observed from days 10-16 at the mid dose and from days 7-16 at the high dose, while urinary incontinence was observed only on day 16 in 1 dam at the mid dose, but from days 7-22 in 10 dams at the high dose.

2. Body Weight:

Body weight of each animal was recorded upon arrival and again on study days 4, 7-16 inclusive, and days 19 and 22 of gestation. Group mean body weight gain is shown in **Table 2**, below.

TABLE 2

Group Mean Body Weight Gains (g) in Metam Sodium Treated Pregnant Rats[a]

Study Interval (days)	Dose groups (mg/kg/day) 0	5	20	60
1-7	32.5	30.9	38.3	31.8
8-16	47.4	43.7	36.4	29.3
16-22	75.9	80.6	78.7	77.7
8-22	123.3	124.3	115.1	107.0
1-22	159.3	156.4	152.9	132.4

Animals which were non-pregnant are not included. [a]Data taken from Table 7, pages 44-45 of the report.

No significant differences in group mean body weight gain were observed during the pre-treatment period among pregnant dams. During the period of treatment (days 7-16 of gestation), decreases of 23% and 38% were observed in group mean body weight gain at the 20 and 60 mg/kg/day dose levels, respectively. For the treatment and post-treatment period (days 8-22), a decrease of 13% in body weight gain was observed at the 60 mg/kg/day dose level, while for the overall study period (days 1-22), a decrease of 16% was observed at the 60 mg/kg/day dose level. With the exception of effects observed during days 8-16, body weight gain was affected only at the 60 mg/kg/day dose level.

3. Food consumption

Food consumption in each animal was determined by giving a weighed quantity of food contained in a glass jar on days 1, 4, 7, 10, 13, 16, and 19 and calculating the amount consumed from the residue on days 4, 7, 10, 13, 16, 19, and 22, respectively. Summary data are shown below (Table 3):

11

TABLE 3

Group Mean Food Consumption (g/day) in Metam Sodium Treated Pregnant Rats[a]

METAM SODIUM: DEVELOPMENTAL TOXICITY STUDY IN THE RAT
TABLE 8
INTERGROUP COMPARISON OF MATERNAL FOOD CONSUMPTION (g/DAY)

		0(Cor...	...of Metam Sodium (mg/kg/day) 5	20	60
PRE-DOSING					
Days 1-4	MEAN	23.7	23.9	25.1	23.8
	S.D.	3.2	2.0	1.7	2.6
	N	24	24	23	21
Days 4-7	MEAN	27.2	26.8	27.4	26.3
	S.D.	1.8	2.3	2.0	1.6
		24	24	23	21
DURING DOSING					
Days 7-10	MEAN	29.1	27.0**	25.2**	19.2**
	S.D.	3.2	3.1	2.6	2.5
	N	24	24	23	21
Days 10-13	MEAN	31.3	29.8*	26.2**	24.8**
	S.D.	2.7	2.8	2.7	1.8
	N	24	24	23	21
Days 13-16	MEAN	33.5	31.4*	29.0**	25.8**
	S.D.	3.1	2.7	2.5	2.6
	N	24	24	23	21
POST DOSING					
Days 16-19	MEAN	35.0	34.5	33.5	29.5**
	S.D.	3.0	3.7	2.7	2.7
	N	24	24	23	21
Days 19-22	MEAN	34.9	34.2	32.9*	31.0**
	S.D.	2.9	3.2	3.3	3.5
	N	24	24	23	21

Animals which were non-pregnant were excluded from analysis.

[a]Data taken from Table 8, page 46 of the report.

Food consumption prior to dosing was unaffected in control and test article treated rats. During the period of dosing, a dose-related decrease in food consumption was observed in treated groups of pregnant dams. While statistical significance was achieved at the lowest dose level, the decrease from control at this dose level was between 5-7%. Decreases of greater than 10% (between 13-16%) were observed at the 20 mg/kg/day dose level for the period of dosing, while decreases of between 23-34% were observed at the 60 mg/kg/day dose level for the period of dosing. Post dosing, decreases of between 11-15% were present at the 60 mg/kg/day dose level. Effects of treatment on food consumption were similar to those effects of treatment on body weight gain, but food consumption showed a more definite relation to intake of test chemical than body weight, in that clear dose-related effect could be observed on food consumption.

4. Food Efficiency

Food efficiency was not calculated in this study, but data are provided below, based on calculations made by the reviewer. Data were taken from Appendices 2 and 3, pages 126-134 of the report.

TABLE 4

Group Mean Food Efficiency (%) in Metam Sodium Treated Pregnant Rats[a]

Study Interval (days)	Dose groups (mg/kg/day)			
	0	5	20	60
1-7	21.3	20.3	24.3	21.1
7-16	18.0	16.9	14.8	11.0
16-22	36.1	39.1	39.5	42.7
1-22	24.7	25.1	25.5	24.5

As shown, food efficiency was affected primarily during the period of test article administration, where efficiency of food utilization appeared decreased in a dose related fashion. For the post-dosing period and the overall period of the study, food efficiency was not significantly affected. Thus, the decrease in body weight gain during the period of dosing appears to be test article related, as shown by decreased food efficiency during this period. Decreases in body weight gain during other periods appears to be based on reduced food intake, as food efficiency was not affected at other times during the study.

5. Gross Pathology

On day 22 of gestation, all dams were sacrificed by over-exposure to halothane vapor. Following sacrifice of the dams, necropsy and gross pathological assessment was performed. The uterus from any animal without clear evidence of implantation was removed and stained with ammonium polysulphide to determine whether or not implantation had occurred. For pregnant animals, the intact gravid uterus was removed and weighed. Following examination of the ovaries and uterus, the number of corpora lutea, live fetuses, intrauterine deaths, individual fetal weights, and pre- and post-inplantation loss was recorded.

Each fetus was examined externally for abnormalities. Each fetus was then examined internally for visceral abnormalities, sexed, eviscerated and fixed in methanol. After 24 hours, the head of each fetus was cut along the fronto-parietal suture line and the brain examined for macroscopic abnormalities. Carcasses were then returned to methanol for subsequent processing and staining with Alizarin Red S. Stained fetal skeletons were examined for abnormalities and the degree of ossification assessed. The manus and pes were also assessed.

i) Gross Observations

Gross findings in dams were limited to an increase in the number of dams with pelvic dilatation of the kidney at the 60 mg/kg/day dose level (4/24 vs 0/24 in control).

ii) Histopathologic Observations

Histopathologic observations were not performed on dams in this study.

iii) Organ Weights

The mean weight of the gravid uterus was provided (Table 10, page 48 of the report). According to these data, there were no significant differences in mean gravid uterus weight among the groups of treated and control dams (78.1-82.0 grams).

iv) Cesarean Section Observations

Observations recorded by the registrant at cesarean section are listed in the following table (Table 5):

Table 5: Cesarean Section Observations[a]

Dose (mg/kg/day):	0	5	20	50
#Animals Assigned	24	24	24	24
#Animals Pregnant	24	24	23	22
Pregnancy Rate (%)	100	100	96	92
Maternal Wastage				
#Died	0	0	0	0
#Died/pregnant	0	0	0	0
#Non pregnant	0	0	1	2
#Aborted	0	0	0	0
#Premature Delivery	0	0	0	0
Whole Litter Resorptions	0	0	0	1
Total # of litters	24	24	23	21
Total Corpora Lutea[b]	346	351	339	316
Corpora Lutea/dam	14.4	14.6	14.7	15.0
Total Implantations[c]	278	293	292	284
Implantations/Dam	11.6	12.2	12.7	13.5*
Total Live Fetuses[d]	261	273	276	261
Live Fetuses/Dam	10.9	11.4	12.0	12.4
Total Resorptions[e]	17	20	16	23
Early	13	17	14	18

Table 5, cont.

Dose (mg/kg/day):	0	5	20	60
Late	4	3	2	5
Resorptions/Dam	0.7	0.8	0.7	1.1
Total Dead Fetuses	0	0	0	0
Dead Fetuses/Dam	0	0	0	0
Mean Fetal Weight (gm)[f] (M + F)	5.0	5.0	4.8**	4.3**
Preimplantation Loss (mean %)	19.7	16.5	13.9	10.1*
Postimplantation Loss (mean %)	6.1	6.8	5.5	8.1
Sex Ratio (mean % M/F)	59/41	52/48	50/50	52/48

---

[a]Data taken from Table 10, page 48, and Appendix 5, pages 230-233 of the report.

b, c, [e]calculated to include all pregnant dams.

d, [f]excludes dams which died or aborted during the study.

*$p < 0.05$ vs control.

Cesarean section data were unremarkable with the exception of increased total resorptions and decreased mean fetal weights at the 20 and 60 mg/kg/day dose levels, where mean weight was decreased by 4% and 14% vs control, respectively.

2. Developmental Toxicity

According to the report, all fetuses were examined for both visceral and skeletal abnormalities. Summary of findings is made below (Table 6):

TABLE 6

Developmental Toxicity of Metam Sodium in Rats[a]

Dose group (mg/kg/day)	0	5	20	60
Observations[a]				
#pups(litters) examined	261(24)	273 (24)	276(23)	261(21)
external examination				
[#litters(pups) affected]				
major defects	1(1)	0(0)	1(1)	4(4)[b]
minor defects	2(4)	4(5)	1(1)	3(3)
variants	7(13)	4(6)	8(15)	3(6)
skeletal				
[#litters(pups) affected]				
major defects	0(0)	2(2)	1(1)	3(3)
minor defects	16(30)	18(45)	21(47)	19(88)**
variants	24(182)	24(205)	23(235)**	21(257)**

[a] Data taken from Table 11, pages 50-51 of the report.
* $p < 0.05$ vs control; ** $p < 0.01$ vs control.
[b] the report lists 5 fetuses as having major defects at the 60 mg/kg dose in Table 12.

a. Major Defects

Summary incidence of major defects was given in the report in Table 12, page 52. Specific findings are summarized in the following table (Table 7):

TABLE 7

Major Defects in Metam Sodium Treated Rats[a]

Dose group (mg/kg/day)	0	5	20	60
Observations[a]				
external/visceral				
meningocoele	0(0)	0(0)	0(0)	1(1)
upper jaw shortened	0(0)	0(0)	0(0)	1(1)
cleft lip	0(0)	0(0)	0(0)	1(1)
microphthalmia	1(1)	0(0)	0(0)	2(2)
internal hydrocephaly	0(0)	0(0)	0(0)	3(3)
skeletal				
2nd cervical vertebrae-arch not ossified	0(0)	0(0)	0(0)	1(1)
3rd cervical vertebrae-arch not ossified	0(0)	0(0)	0(0)	1(1)
4th cervical vertebrae-arch not ossified	0(0)	0(0)	0(0)	1(1)

[a]data taken from Table 13, pages 54-57 of the report. Numbers in parentheses represent the litter incidence for each observation.

As shown, the fetal and litter incidence of several external/visceral observations were increased slightly at the high dose level. The incidence of non-ossification of the arches of the 2nd, 3rd, and 4th cervical vertebrae was also slightly increased at the high dose level.

b. Minor defects

The incidence of minor external/visceral defects was not significantly different in the fetuses of treated rats vs control. Summary of minor skeletal defects is made below:

TABLE 8

Minor Skeletal Defects in Metam Sodium Treated Rats[a]

Dose group (mg/kg/day)	0	5	20	60
Observations[a]				
cervical vertebrae				
5th, arch partially ossified	1(1)	2(2)	3(2)	7(6)
4th, centrum not ossified	4(3)	5(3)	8(7)	27**(13)**
5th, centrum not ossified	2(2)	3(2)	3(2)	14**(8)*
6th, centrum not ossified	1(1)	0(0)	2(2)	9*(5)
12th, centrum partially ossified	0(0)	3(2)	0(0)	5(5)*
sternebrae				
5th, not ossified	2(2)	2(2)	8(5)	10(9)*
4th, slightly misaligned	6(5)	6(5)	6(5)	11(6)
5th, slightly misaligned	7(6)	4(4)	7(7)	13(10)

[a]data taken from Table 13, pages 56-62 of the report. Numbers in parentheses represent the litter incidence for each observation.
* $p < 0.05$ vs control; ** $p < 0.01$ vs control.

The data as presented show a statistically significant increase in the fetal and litter incidence of unossified centrum of the 4th, 5th, and 6th cervical vertebrae, as well as an increase in the litter incidence of unossified 5th sternebrae at the 60 mg/kg/day dose level. Other indications of a treatment effect at the 60 mg/kg/day dose level include: increase in the incidence of partial ossification of the arch of the 5th cervical vertebrae and the centrum of the 12th cervical vertebrae; and an increase in the incidence of slight misalignment of the 4th and 5th sternebrae.

Skeletal variants observed in this study are summarized below (Table 9):

TABLE 9

Skeletal Variants in Metam Sodium Treated Rats[a]

Dose group (mg/kg/day)	0	5	20	60
odontoid				
not ossified	24(13)	35(14)	56**(18)	118**(21)**
cervical vertebrae				
2nd centrum not ossified	44(17)	68*(19)	109**(20)	185**(21)*
3rd centrum not ossified	10(6)	12(6)	18(13)	60(18)**
7th transverse process partially ossified	30(15)	31(15)	17*(9)	15*(7)
ventral tubercle not ossified	10(6)	12(9)	26*(9)	22*(13)*
sternebrae				
5th, partially ossified	76(20)	70(21)	80(22)	107**(20)
calcaneum				
not ossified	113(22)	155**(21)	186**(22)	245**(21)

[a]data taken from Table 13, pages 56-63 of the report. Numbers in parentheses represent the litter incidence for each observation. * $p < 0.05$ vs control; ** $p < 0.01$ vs control.

As shown, the fetal incidence of unossified odontoid, centrum of the 2nd cervical vertebrum, ventral tubercle, and calcaneum was significantly increased 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. Interestingly, at the lowest dose, there was a significant increase in the fetal incidence of unossified calcaneum, and there appeared to be a dose-related trend for this effect.

To ascertain whether the effects seen at the low dose (non-ossification of the centrum of the 2nd cervical vertebra, non-ossification of the calcaneum) were related to treatment, the individual litter incidence of each of these abnormalities was calculated for each dose group and statistically analyzed.

Results of manus and pes assessment are shown in the following table (Table 10). It is noted that in the assessment of the degree of ossification, the observations were converted to a six-point scale from good (1) to poor (6).

HEXIM SODIUM: DEVELOPMENTAL TOXICITY STUDY IN THE RAT
TABLE 14
INTERGROUP COMPARISON OF MANUS/PES ASSESSMENT

		Dose Level of Hexim Sodium (mg/kg/day) 0(Control)	5	20	60
MANUS SCORES					
Prop. with score 3		8 (3.1%)	3 (1.1%)	3 (1.1%)	2 (0.9%)
Prop. with score 4		194 (74.3%)	221 (81.0%)	201 (72.8%)	122** (46.7%)
Prop. with score 5		59 (22.6%)	49 (17.9%)	71 (25.7%)	134** (51.3%)
Prop. with score 6		0 (0.0%)	0 (0.0%)	1 (0.4%)	3 (1.1%)
Mean manus score per litter	MEAN	4.21	4.16	4.26	4.54**
	S.D.	0.25	0.19	0.23	0.34
	N	24	24	23	21
PES SCORES					
Prop. with score 4		31 (11.9%)	34 (12.5%)	26 (9.4%)	6** (2.3%)
Prop. with score 5		229 (87.7%)	239 (87.5%)	249 (90.2%)	250** (95.8%)
Prop. with score 6		1 (0.4%)	0 (0.0%)	1 (0.4%)	5 (1.9%)
Mean pes score per litter	MEAN	4.87	4.86	4.91	5.00**
	S.D.	0.16	0.19	0.18	0.12
	N	24	24	23	21

The above table shows that for fetuses in the 60 mg/kg/day dose group, there was an increase in the number of fetuses with higher scores for the manus and pes, indicating that the degree of ossification was poorer at this dose. The differences at this dose level were also significantly different from control.

III. DISCUSSION

Developmental toxicity of metam sodium technical was assessed in pregnant Wistar rats through administration of test chemical on gestation days 7 through 16 inclusive. Indices of maternal toxicity were made through measurement of changes in body weight, food consumption, clinical signs, mortality, gravid uterine weight, and gross necropsy. In addition, complete cesarean section data were provided as additional evidence of maternal toxicity. In fetuses, examination was made of external surfaces, viscera, and skeletons as appropriate.

Mortality in pregnant dams was unaffected in this study, but the incidence of certain clinical signs was increased at the 60 mg/kg/day dose level (discharge from eye, piloerection, salivation, subdued behavior, urinary incontinence). Body weight gain in pregnant dams was decreased during the period of dosing at the 20 and 60 mg/kg/day dose levels. At 20 mg/kg/day, body weight gain was decreased 23% vs control and at 60 mg/kg/day, was decreased 38% vs control for days 8-16 of the study. Food consumption and food efficiency were also found to be decreased at the 20 and 60 mg/kg/day dose levels during the period of dosing, indicating a toxic effect of test article during the period of its administration. Following administration of test article, neither body weight gain nor food consumption was significantly affected. Thus, the primary effects of metam sodium on maternal weight gain were manifest during the period of its administration, and were reversed upon its discontinuation.

Cesarean section data showed an increase in resorptions and resorptions/dam at the 60 mg/kg/day dose level, as well as a significant decrease in mean fetal weight at the 20 and 60 mg/kg/day dose levels. Gross pathological findings and gravid uterine weights were not significantly different among treated dams vs controls.

Examination of the fetuses for external, visceral, and skeletal abnormalities showed the following:

1) a statistically significant increase in the incidence of minor skeletal defects at the 60 mg/kg/day dose level and variants at the 20 and 60 mg/kg/day dose levels, which can be broken down as follows:

a) A statistically significant increase in the fetal and litter incidence of unossified centrum of the 4th, 5th, and 6th cervical vertebrae, as well as an increase in the litter incidence of unossified 5th sternebrae at the 60 mg/kg/day dose level.

b) 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. Interestingly, at the lowest dose, there was a significant increase in the fetal incidence of unossified calcaneum, and there appeared to be a dose-related trend for this effect.

Statstical analysis of the individual litter incidence of the effects observed at the lowest dose (non-ossified centrum of the 2nd cervical vertebra, non-ossification of the calcaneum) revealed that on a per litter basis, there was no significant difference from control in the incidence of these 2 defects at the low dose, but that significant differences did exist at the mid and high dose levels vs control. In addition, the report provided data (Appendix I, page 77) which demonstrated that the incidence observed at the low dose for these variants was within historical control range. Thus, a no effect level can be defined at the 5 mg/kg/day dose for developmental toxicity, while the 20 mg/kg/day dose level can be considered the low effect level.

III. CONCLUSIONS

Administration of Metam Sodium technical to pregnant rats at doses of 0, 5, 20, and 60 mg/kg/day on gestation days 6 through 17 inclusive resulted in signs of maternal toxicity at the 20 and 60 mg/kg/day dose levels (decreased body weight gain, decreased food efficiency). Examination of cesarean section data showed an increase in total resorptions at the 60 mg/kg/day dose level and resorptions/dam, while mean fetal weight was significantly decreased at the 20 and 60 mg/kg/day dose levels. Developmental toxicity was present at the 20 and 60 mg/kg/day dose levels and consisted 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.

Maternal NOEL = 5 mg/kg/day
Maternal LEL= 20 mg/kg/day (decreased body weight gain, decreased food efficiency)

Developmental toxicity NOEL = 5 mg/kg/day
Developmental toxicity LEL = 20 mg/kg/day (increased fetal and litter incidence of minor skeletal defects and variants)

IV. CLASSIFICATION Core guideline

This study satisfies the guideline requirements (§ 83-3) for a developmental toxicity study in rats.

010693

Primary Review by: Stephen C. Dapson, Ph.D. Stephen C Dapson 12/7/93
Senior Pharmacologist, Review Section 1, TB II/HED (7509C)

Secondary Review by: Yiannakis M. Ioannou, Ph.D., D.A.B.T. Y.M.I. 12/7/93
Section Head, Review Section 1, TB II/HED (7509C)

DATA EVALUATION RECORD

Study Type: Developmental Toxicity - Teratology
Species: Rabbit; Guideline: 83-3 (b)

EPA ID No.s: EPA MRID No. 429631-01
EPA Pesticide Chemical Code: 039003
Toxicology Chemical Code: 780
EPA DP Barcode D196100
EPA Submission # S451460

Test Material: Metam-Sodium (43.14% w/w, 525.54 g/L, Batch 90/2, Y06930/007/001 and YA6930/008)

Synonyms: Sodium-N-methyl-dithiocarbamate, BASF Substance No. BASF/005/00N

Sponsor: Metam Sodium Task force

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

Title of Report: Metam-Sodium: Developmental Toxicity Study in the Rabbit

Study Number(s): Report No.: CTL/P/4035, Study No.: RB0623

Author(s): M.C.E. Hodge

Report Issued: September 6, 1993

Executive Summary: In a developmental toxicity (teratology) study, rabbits of the New Zealand White 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 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

25

010693

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. Therefor 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 <u>Core Minimum Data</u> and satisfies the 1984 Guideline Requirement (§ 33-3 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).

A. Materials and Methods A copy of the "materials and methods" section from the investigators report is appended.

Test Compound: Purity: 43.14% w/w, 525.54 g/L
Density: 1.218 g/cm^3
Description: yellow liquid
Lot No.: 90/2,Y06930/007/001 and YA6930/008
Receipt date:1/6/93
Other provided information: analysis of compound
Contaminants: not provided

Vehicle(s): deionized water

Test Animal(s): Species: Rabbits
Strain: New Zealand White
Source: Interfauna UK Limited, Huntingdon, Cambridgeshire, UK
Age: not provided
Body Weight: 3743-3809 g on gd 4
Any information on males used: animals provided as timed pregnant mated with males of same strain at supplier

B. Study Design

This study was designed to assess the developmental toxicity potential of metam-sodium when administered by gavage on gestation days 6 through 20, inclusive.

Mating Procedure

Assume natural mating (day of mating as gestation day 1); however, these animals were received as *timed pregnant* from the vendor, procedure was not provided.

Animal Husbandry

Animals were kept under standard animal care conditions. Food was SDS Standard Rabbit Diet supplied by Special Diet Services, Witham, Essex, UK. The animals received the diet daily with *filter-sterilized* tap water (automatic watering system) *ad libitum*.

010693

Group Arrangement:

Test Group	Dose Level(mg/kg)	Number Assigned
Control	double distilled water	20
Low Dose	5	20
Mid Dose	20	20
High Dose	60	20

This was done by a method of randomization described in detail in the attached materials and methods.

Dose Administration:

All doses were administered in a volume of 1 ml/kg of body weight/day prepared weekly during the dosing period. The dosing solutions were analyzed for concentration and stability. Homogeneity was not determined since the compound was in a solution. Dosing was based on daily body weight.

A pilot study was not conducted since a previous study was conducted with this compound 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. The following are the conclusions from the review.

Dose Levels tested: 10, 30, and 100 mg/kg by gavage from gestation days 6 through 18 with a **42.2% aqueous solution** of metam-sodium in Himalayan rabbits.

Maternal NOEL = 10 mg/kg/day
Maternal LOEL = 30 mg/kg/day

Maternal Toxicity consisted of reduced body weight gains, reduced food consumption, increased number of dead implantations and reduced numbers of fetuses, and increased post-implantation loss in either mid or high dose group or both. Developmental 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-implantation loss; however the Developmental Toxicity NOEL and LOEL could not be determined with available data and additional information was required.

The study was classified as **Core-Supplementary Data** and did not satisfy the 1984 Pesticide Guideline Requirements (§ 83-3 b) for a developmental toxicity (teratology) study in rabbits. Additional data supplied by the registrant were not adequate to upgrade the study. The Agency requested a new teratology study in rabbits.

28

Observations

The animals were checked twice daily for *changes in behavior of clinical condition.* Individual bodyweights were *recorded on arrival and on days 4, 8-20 (inclusive) and on days 23, 26, and 30 of gestation.* Food consumption *was measured by giving a weighed quantity of food on days 4, 8, 11, 14, 17, 20, 23, and 26 and calculating the amount consumed from the amount left on days 8, 11, 14, 17, 20, 23, 26, and 30, respectively.* Dams were sacrificed on day 30 of gestation. Examinations at sacrifice consisted of: a macroscopic examination post mortem. Non-pregnant uteri were stained using ammonium polysulfide. The uterus and ovaries were removed and the gravid uterine weight was determined. The number of corpora lutea, live fetuses, early intra-uterine deaths, late intra-uterine deaths and individual fetal weights were recorded.

The fetuses were examined in the following manner: as mentioned each fetus was weighed, examined macroscopically for external findings along with the palate. All fetuses were then examined internally for visceral observations, sexed, then eviscerated and fixed in methanol for approximately 24 hours. After fixation, the head of each fetus was cut along the fronto-parietal suture line and the brain examined. The carcasses were stained with Alizarin Red S for skeletal examination.

Historical control data were provided **only** for 27 presacral vertebrae to allow comparison with concurrent controls.

Statistical analysis

The following statistical analysis methods were employed (from the investigators report):

> Data relating to animals which were non-pregnant, suffered abortions or died intercurrently were excluded from the statistical analysis. It should be noted that data were analysed with and without animals which totally resorbed their litters (see Sections 3.4, 3.5 and 3.7).
>
> Maternal bodyweight during the dosing and post-dosing periods was considered by analysis of covariance on day 8 bodyweight.
>
> Maternal food consumption during the dosing and post-dosing periods, the numbers of implantations and live foetuses per female, gravid uterus weight, litter weight, mean foetal weights per litter and mean manus and pes scores per litter were considered by analysis of variance.

29

Maternal performance data, the proportion of foetuses with each individual manus and pes score, the proportion of foetuses with each defect and the proportion of litters with each defect were considered by Fisher's Exact Test.

Pre-implantation loss, post-implantation loss, early intra-uterine deaths, late intra-uterine deaths, male foetuses, major external/visceral defects, minor external/visceral defects, external/visceral variants, major skeletal defects, minor skeletal defects and skeletal variants were analysed as follows:-

(1) Percentages were analysed by analysis of variance following the double arcsine transformation of Freeman and Tukey (1950)

(2) the proportion of foetuses affected and with the exception of male foetuses the proportion of litters affected were considered by Fisher's Exact Test.

All analyses were carried out in SAS (1989). For Fisher's Exact Test the proportion in each treated group was compared to the control group proportion. Analyses of variance and covariance allowed for the replicate structure of the study design. Least-squares means for each group were calculated using the LSMEAN option in SAS PROC GLM. Unbiased estimates of differences from control were provided by the difference between each treatment group least-squares mean and the control group least-squares mean using a Student's t-test, based on the error mean square in the analysis.

All statistical tests were two-sided.

Compliance

A signed and dated **Statement of Data Confidentiality Claim** (no confidentiality was claimed) was provided.

A signed and dated **Statement of GLP Compliance** was provided.

A signed and dated **EPA Flagging Criteria** statement was provided, according to the investigators, the study neither meets nor exceeds the applicable criteria.

A signed and dated **Quality Assurance Statement** was provided.

Results

Analysis of the Test Substance

According to the investigators: *The concentrations of individual samples were within 8% of nominal and the mean concentrations were within 3% of nominal.* Further, *Metam sodium was stable at the low and high concentration* (only ones measured) *for up to 7 days when stored at room temperature.* Data were provided to support the above claims.

Maternal Toxicity:

Mortality

There were 3 deaths, 1 in each treatment group, no cause of death could be determined. The high dose animal aborted and was sacrificed as was the mid dose animal.

Clinical Observations

The investigators stated that: An increase incidence of few feces and red/orange staining on the cage tray was seen in the 60 mg metam sodium/kg/day group compared with the control group. Data were provided to support this statement. No other clinical sign appeared related to treatment.

Body Weight

The investigators supplied the Agency with selected group mean data as well as individual animal data. The following table presents body weight gain data:

Table I: Body Weight Gains (grams)[a]

DAYS:	4-8	8-20	20-30	8-30	4-30	C8-30[1]	C4-30[2]
Control	91	310	290	600	691	64	155
LDT	106	318	270	570	676	5	111
MDT	95	222	273	495	590	-43	52
HDT	122	44	224	268	390	-103	19
HDT[3]	116	-1	314	313	429	-58	58

above values calculated by reviewer from means

[1] = corrected body wgt gain for dosing period plus post dosing period = body wgt gain for dosing period plus post dosing period minus gravid uterus wgt.
[2] = corrected body wgt gain for entire gestation period = body wgt gain for entire gestation period minus gravid uterus wgt.
[3] = including dams with total resorptions
[a] = Data extracted from Project No. CTL/P/4035, Tables 7A, 7B & 10A.

The above data indicate a treatment related decrease in body

010693

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

The investigators supplied the Agency with selected group mean data as well as individual animal data. The following table presents food consumption data:

Table II: Food Consumption Data (gm/day)[a]

DAYS:	4-8	8-20	20-30	8-30	4-30
Control	173	188	178	184	182
LDT	186	185	164	176	177
MDT	178	167	159	163	165
HDT	200	118	178	144	151
HDT[1]	191	122	197	154	159

above values calculated by reviewer from means

[1] = including dams with total resorptions

[a] = Data extracted from Project No. CTL/P/4035, Tables 8A & 8B.

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), support this observation.

Table III: Food Efficiency Data (%)[a]

DAYS:	4-8	8-20	20-30	8-30	4-30	C8-30[1]	C4-30[2]
Control	13.1	12.4	14.9	13.5	13.5	1.4	3.0
LDT	14.3	14.3	16.3	14.7	14.7	0.1	2.4
MDT	13.3	10.6	15.3	12.8	12.9	-1.1	1.1
HDT	15.3	3.1	12.6	8.5	9.9	-3.3	0.5
HDT[3]	13.1	-0.1	16.0	8.2	10.3	-1.5	1.4

above values calculated by reviewer from means

Body weight gain over a given time period expressed in grams divided by the food consumption in grams over the same time period X 100

[1] = corrected body wgt gain for dosing period plus post dosing period.

[2] = corrected body wgt gain for entire gestation period (except gd 0-4).

[3] = including dams with total resorptions

[a] = Data extracted from Project No. CTL/P/4035, above & Appendix 3.

Food efficiency was reduced during the dosing period, post dosing period (with a rebound for the high dose including dams with total resorptions),dosing plus 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.

32

Gross Pathological Observations

The investigators stated that: The incidence of findings was low and there was no evidence that any of the findings were compound-related. This was supported by the provided data (group summary and individual animal data).

Cesarean Section Observations

Table IV: Cesarean Section Observations[a]

Dose:	Control	LDT	MDT	HDT
#Animals Assigned	20	20	20	20
#Animals Pregnant	20	17	18	19
Pregnancy Rate (%)	100	85	90	95
Maternal Wastage				
#Died/sacrificed	0	1	1	1
#Died/pregnant	0	1	1	1
#Non pregnant	0	0	0	0
#Aborted	0	0	0	1
#Premature Delivery	0	0	0	0
Total Litter Resorptions	0	1	0	9**
Total # litters	20	16	17	9
Total Corpora Lutea	238	185	183	99
Corpora Lutea/dam	11.9	11.6	10.8	11.0
Total Implantations	189	165	159	87
Implantations/Dam	9.45	10.31	9.35	9.67(8.67)[1]
Total Live Fetuses	168	148	148	52
Live Fetuses/Dam	8.40	9.25	8.71	5.78(2.89**)[1]
Total Resorptions	21	17	11	35
Early	17	11	8	32**(100**)[1]
Late	4	6	3	3(4)[1]
Resorptions/Dam	1.05	1.06	0.65	3.89(5.78)[1]
Mean Fetal Weight(gm)	44.8	42.7	42.8	40.1*
Preimplantation Loss(%)	21.6	11.2*	13.6	12.3
Postimplantation Loss(%)	10.4	12.6	6.8	41.3**(70.7**)[1]
Sex Ratio (%Male)	44.0	50.2	59.1	29.7*

[1] = including total resorptions

* = $p < 0.05$; ** $p < 0.01$

[a] = Data extracted from Project No. CTL/P/4035, Tables 5, 10A, 10B & App. 5.

Toxicity was noted in the high dose group in the form of increased resorptions including total litter resorptions, a decrease in the number of live fetuses and mean litter size, an increase in post-implantation loss and a decrease in mean fetal body weight. The sex ratio was also statistically significantly decreased; however, unless the test compound specifically kills male fetuses, this observation might not be directly due to treatment, but rather to the lower number of fetuses available.

2. Developmental Toxicity

External/Visceral Observations

The investigators combined the data on external and visceral defects (and separated them by a major and minor defect division defined in the attached materials and methods).

No treatment related effects were noted in the provided external/visceral data.

Skeletal Observations

Table V: Skeletal Examinations[a]

Observations+	Control	Low Dose	Mid Dose	High Dose
#pups/litters examined	168/20	148/16	148/17	52/9
Skull:Sutural Bones - between				
Frontals and nasals	1/1[1]	5/4	1/1	0/0
Nasals	1/1	0/0	1/1	0/0
Parietals	1/1	1/1	4/3	0/0
Hyoid:				
Misshapen	3/3	3/3	5/5	1/1
Partially ossified	1/1	0/0	0/0	0/0
Cervical Vertebrae - partially ossified				
Transverse Process 7th	0/0	3/1	6*/3	1/1
Vertebral Column - Presacral Vertebrae				
27	34/13	26/9	50**/13	37**/9
28	0/0	1/1	0/0	0/0
Sternebrae - 5th				
Bipartite	4/4	2/2	1/1	0/0
Not ossified	22/9	17/6	15/8	0**/0*
Partially ossified	64/18	54/14	55/15	7**/5
Misaligned	3/2	3/2	4/4	1/1
Sternebrae:				
7 present	0/0	0/0	1/1	7**/2
Fused 2nd & 3rd	3/3	0/0	0/0	0/0
Fused 3rd & 4th	2/2	0/0	2/2	2/2
Fused 4th & 5th	2/2	0/0	1/1	2/2

+ = some observations may be grouped together
[1] = fetal/litter incidence
[a] = Data extracted from Project No. CTL/P/4035, Table 13.

Possible 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.

The utility of the high dose group was questionable due to the low numbers of litters available for comparison with the larger control and treatment groups, also the smaller litter size may have allowed more rapid maturation of the fetus as evidenced by the decreased incidence of the ossification observations mentioned above and the 5th sternebrae is an example (see above). There was an increased incidence in the high dose group in the 27 presacral vertebrae and 7 sternebrae (usually only 6 present).

The Manus and Pes were assessed in the study and the data presented do not show any specific treatment related effect. According to the investigators, the 27 presacral vertebrae incidence was within historical control. The historical control data were provided and do support this claim; however, when compared to concurrent control, there was an increase in incidence.

The investigators stated that: *Minimal fetotoxicity, indicated by changes in ossification pattern, was seen at 20 mg metam sodium/kg/day, a single change (increased incidence of 27 pre-sacral vertebrae) only, and in viable fetuses in the 60 mg metam sodium/kg/day groups .*

D. Discussion/Conclusions

a. Maternal Toxicity:

Maternal toxicity was noted in the mid and high dose groups 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 dose groups. This is evidence of toxicity and supports the body weight gain findings.

b. Developmental Toxicity:

i. Deaths/Resorptions:

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.

ii. Altered Growth:

A decrease in mean fetal body weight was noted in the high dose group.

iii. Developmental Anomalies/Malformations:

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. Too few litters were available for comparison in the high dose group; however, there was an increased incidence in the high dose group of 27 presacral vertebrae and 7 sternebrae (usually only 6 present).

E. **Study Deficiencies**:

No specific deficiencies were noted that affected the outcome of the study.

F. **Core Classification**: **Core Minimum Data**

Maternal Toxicity NOEL = 5 mg/kg/day
Maternal Toxicity LOEL = 20 mg/kg/day

Developmental Toxicity NOEL = 5 mg/kg/day
Developmental Toxicity LOEL = 20 mg/kg/day

This study satisfies the 1984 Guideline Requirement (§ 83-3 b) for a developmental toxicity (teratology) study in rabbits.

Metam Sodium

Page _____ is not included in this copy.

Pages 38 through 47 are not included in this copy.

The material not included contains the following type of information:

_____ Identity of product inert ingredients.

_____ Identity of product impurities.

_____ Description of the product manufacturing process.

_____ Description of quality control procedures.

_____ Identity of the source of product ingredients.

_____ Sales or other commercial/financial information.

_____ A draft product label.

_____ The product confidential statement of formula.

_____ Information about a pending registration action.

X FIFRA registration data.

_____ The document is a duplicate of page(s) _____.

_____ The document is not responsive to the request.

The information not included is generally considered confidential by product registrants. If you have any questions, please contact the individual who prepared the response to your request.