8-16-91

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

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

MEMORANDUM

SUBJECT: Metam Sodium - Review of Two Developmental Toxicity Studies in Rats and Rabbits Submitted by the Registrant

FROM: Yiannakis M. Ioannou, Ph.D., Section Head
Review Section I, Toxicology Branch II
Health Effects Division (H7509C)

Y.M. Ioannou 8/16/91

TO: Susan Lewis, PM 21
Herbicide-Fungicide Branch
Registration Division (H7505C)

THRU: Marcia van Gemert, Ph.D., Chief
Toxicology Branch II
Health Effects Division (H7509C)

Marcia van Gemert 8/16/91

Registrant: BASF Corporation, Rsearch Triangle Park, NC.

Action Requested: Review the two developmental toxicity studies with Metam Sodium submitted by the Registrant under FIFRA Section 6(a)(2)-Adverse Effects Data.

Toxicology Branch II has completed the review of two developmental toxicity studies with Metam Sodium titled:

1. Report on the Study of the Prenatal Toxicity of Metam Sodium in Rats After Oral Administration (Gavage).
   MRID No.: 415771-01; Study No.: 34R0232/8569

2. Report on the Study of the Prenatal Toxicity of Metam Sodium (Aqueous Solution) in Rabbits After Oral Administration (Gavage).
   MRID No.: 403309-01; Study No.: 38R0232/8579

Briefly, the conduct of these studies and the major findings were as follows:

1. Developmental Toxicity Study in Rats:

An aqueous solution of Metam Sodium was administered at 0, 10, 40, and 120 mg/kg 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 dcrease in the percent of live fetuses/dam at 10 ad 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 neural tube defect (meningocele in two fetuses in on litter and 12 fetuses in seven litters for 120 and 240 mg/kg, respctively).

Maternal NOEL = 10 mg/kg/day
Maternal LOEL = 40 mg/kg/day
Developmental NOEL = Not determined (lower than 10 mg/kg/day)
Developmental LOEL $\leq$ 10 mg/kg/day

Based on major deficiencies (see DER) this study is classified as Core-Supplementary Data and does not satisfy guideline requirements (83-3a) for a developmental toxicity study in rats.

2. Developmental Toxicity Study in Rabbits

An aqueous solution of Metam Sodium was administered to pregnant Himalayan rabbits at dose levels of 0, 10, 30 and 100 mg/kg/day during days 6-18 of gestation. Maternal toxicity was observed at the 30 and 100 mg/kg/day levels in the form of reduced body weight gains, reduced food consumption, increased number of dead implantations and reduced number of fetuses and increased post-implantation loss. Developmental toxicity was observed in the 30 and 100 mg/kg/day levels in the form of increased post-implantation loss, increased number of dead implantations, and reduced number of fetuses. The incidence of skeletal anomalies could not be determined in this study since the investigators used only an X-ray technique and not a staining technique for skeletal examinations. The administration of 100 mg/kg/day resulted in neural tube defects (meningocele in one fetus; spina bifida in one fetus).

2

3.

Maternal NOEL = 10 mg/kg/day
Maternal LOEL = 30 mg/kg/day
Developmental Toxicity NOEL and LOEL could not be established with the available data (incomplete skeletal malformation data). With the existing data, however, a TENTATIVE Developmental Toxicity NOEL of 10 mg/kg/day and a LOEL of 30 mg/kg/day can be established.

Based on major deficiencies (see DER) this study is classified as Core-Supplementary Data and does not satisfy guideline requirements (83-3b) for a developmental toxicity study in rabbits. This study can be up-graded if all deficiencies are resolved.

GUIDELINE: 83-3

Primary Review by: Karen E. Whitby, Ph.D. 8/15/91
Toxicologist, Review Section II, Toxicology Branch II/HED (H7509C)

Secondary Review by: K. Clark Swentzel 8/15/91
Section Head, Review Section II, Toxicology Branch II/HED (H7509C)

DATA EVALUATION RECORD

Study Type: Teratology - Developmental Toxicity
Species: Rat
Guideline: 83-3

EPA Identification No.s: EPA MRID (Accession) No.: 415771-01
Caswell No. 780
HED Project No. 1-1988

Test Material: Metam-Sodium (aqueous solution)

Synonyms: Sodium N-methyl-dithiocarbamate

Sponsor: BASF Corporation
Agricultural Chemicals Group
2505 Meridian Parkway
P.O. Box 13528
Research Triangle Park, NC 27709-3528

Study Number(s): 87/0128 (Project No. 34RO232/8569)

Testing Facility: BASF Aktiengesellschaft
Agricultural Research and Development
D-6703 Limburgerhof
West Germany

Title of Report: Report on the Study of the Prenatal Toxicity of Metam Sodium in Rats After Oral Administration (Gavage)

Author(s): Dr. J. Hellwig and Dr. B. Hildebrand

Report Issued: March 1987

Study Dates: January 21, 1986 - February 17, 1986 (In-life)

Conclusions:

An aqueous solution of Metam-sodium was administered at 0, 10, 40, and 120 mg/kg 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. The corrected maternal body weight gain was significantly reduced at 120 mg/kg. Although not statistically analyzed, mean maternal feed consumption was reduced during the treatment period. The greatest decrease occurred initially, days 7-8 for the 40 and 120 mg/kg group (-16 and -19% of the control, respectively). The cesarean section data indicate a significant increase in postimplantation loss, and a significant decrease in the % of live fetuses/dam at the 10 and 120 mg/kg levels. Fetal weights were significantly reduced for male and female fetuses in the 120 mg/kg group. Examination of the viscera of fetuses that underwent skeletal examination revealed a significant increase in variations at the 40 mg/kg level. There were significant increases in the % fetuses/litter with anomalies, variations, and retardations at the 40 mg/kg level, which were dose-related (except for anomalies). There were significant increases in the % fetuses/litter with variations and retardations at the 120 mg/kg level which were dose-related. The administration of Metam-sodium at high doses [120 mg/kg (HDT in the main study) and 240 mg/kg (HDT in the range finding study)] resulted in meningocele which was not reported in the historical or concurrent control. This study cannot be upgraded. The EPA Subdivision F Pesticide Assessment Guidelines (1984) state that 1/3 to 1/2 of each litter should be prepared and examined for skeletal anomalies, and the remaining part of each litter should be prepared and examined for soft tissue anomalies using appropriate methods. The current study evaluated 2/3's of each litter for skeletal changes and the remaining fetuses were evaluated for soft tissue changes via the Barrow and Taylor technique. Given that the administration of this test substance appears to result in meningocele (in two species - rat and rabbit) it is the opinion of this reviewer that examination of 2/3's of each litter for soft tissue changes as directed in the guidelines would have provided a better assessment of the potential for neural defects. Furthermore, due to the effects observed at the lowest dose tested (10 mg/kg) a NOEL has not been established. Therefore this study has been classified as supplementary.

Core Classification: Supplementary

Maternal NOEL = 10 mg/kg
Maternal LOEL = 40 mg/kg
Developmental Toxicity NOEL = not determined
Developmental Toxicity LOEL = 10 mg/kg

RANGE-FINDING STUDY

The main developmental toxicity study was preceded by a pilot study, which was performed to determine the dosage levels to be used in the main study. Doses in the range-finding study were based on an ALD_{50} value of about 1210 mg/kg in female rats. The highest dose tested 240 mg/kg, was about 1/5 of the ALD_{50}. The lower doses were 120 and 60 mg/kg. The information available on the conduct of this study appears in the protocol in the report for the main study (p. 257-260) as the justification for the selection of doses in the main study. In addition, a synopsis is presented on page 14 in the introduction as to the reasons for the selection of doses. Raw data, study dates, study number, study director, information on the test substance are not provided.

Female Wistar rats were administered Metam-sodium (aqueous solution by gavage days 6-15 of gestation. A control group which did not receive the test substance was maintained concurrently. There were 25 animals per test group.

Results

The available information indicate the body weight loss of all treated groups days 6-8 was dose-dependent. The body weight of all treated animals from day 8 until the end of the study was dose dependent and significantly below that of controls. Uterine weights of the females receiving 120 and 240 mg/kg were significantly reduced. A significant dose dependent reduction in corrected body weight (final body weight minus the uterine weight and body weight gain day 0-20 minus the uterine weight) was observed for all treated groups. There was a dose-dependent reduction in feed consumption during the dosing period. The feed consumption of these animals was reported to adjust itself to that of the controls after the withdrawal of treatment. Abbreviated tables indicate that there was a significant dose-dependent reduction in absolute and relative feed consumption of all treated groups during days 0-20. Although not measured, the consumption of water by treated animals appeared to be higher. Macroscopic exam of the dams at study termination did not reveal treatment related changes.

The number of dead implantations was significantly increased. An increase in the number of intermediate resorptions was observed at 120 and 240 mg/kg relative to the control. The mean weights of the male and female fetuses (and both sexes combined) were dose-dependently and significantly lowered in all treatment groups. Mean placental weights of female fetuses from all treatment groups were significantly reduced (no dose-response relationship). A significant reduction was also observed when the placental weights of male and female fetuses were combined.

Meningocele was observed in 12 out of 291 fetuses (4.21%) in 7 litters (29.2%) in the 240 mg/kg group, during the macroscopic exam. The report indicates that this finding does not appear in their historical control data.

The doses selected for the main study were 0, 10, 40, and 120 mg/kg, based upon the maternal toxicity observed down to the lowest dose tested (60 mg/kg) in the range-finding study.

A. Materials

A copy of the "materials and methods" section from the investigators report is appended (appendix I).

1. Test Compound:

Test Substance: Metam-Sodium (aqueous Solution)
Purity:
Description: liquid
Batch No.: Z H 130585/April 1985
Composition: formulated product
Contents of Active Ingredient: 42.2% (517.3 g/L)
Stability: Stability on storage guaranteed for the period of the study.
Storage Conditions: no special conditions
Vehicle: Doubly distilled water

Analysis of the stability of the test substance was performed in the analytical laboratory of the Department of Agricultural Research and Development of BASF Aktiengesellschaft before the start of the study. Analyses were also performed for the stability of the test substance in water, and of each preparation of the test substance for verification of the concentration.

2. Test Animal(s):

Species:	Rat
Sex:	Female
Strain:	Wistar [Chbb = THOM (SPF)]
Source:	Dr. Karl Thomae GmbH Biberach/Riss, FRG
Age:	9-11 weeks at start of study
Weight:	mean was approx. 200 g at start of study

The number of animals obtained from the breeder for the purpose of this study was not stated. The fate of animals not successfully mated was not stated. The source and total number of males used for mating was not stated.

B. Methods

1. Animal Husbandry:

Prior to the start of the study the rooms were completely disinfected ("AUTEX" fully automatic final disinfecting apparatus using formaldehyde and ammonia). Each week the walls and floor were cleaned with water containing about 0.5% Mikro-Quat (supplied by Schulke and Mayr GmbH).

During the conduct of the study rats were housed in pairs (2 animals/cage) in type DK III stainless steel wire mesh cages (floor area about 900 cm^2). Cages of test animals were arranged on the racks in a manner that would provide uniform ventilation and light. Deviation from the targeted range of temperature (20 - 24°C) and relative humidity (30-70%) was reported as zero to minimal (deviation values not provided). Animals were maintained on a 12 hour light dark cycle.

Animals were fed Kliba 343 feed rat/mouse/hamster "A" (supplied by Klingentalmuhle AG, CH-4303 Kaiseraugst, Switzerland) ad libitum throughout the study. Tap water was also available ad libitum throughout the study. Every batch of feed used in the study was analyzed for contaminants by the supplier. Drinking water was routinely checked for contaminants by the municipal authorities of Frankenthal and the Department of Water Chemistry and Technical Services of BASF Aktiengesellschaft.

Animals were identified by ear tatoo and picric acid.

2. Study Design

This study was designed to assess the developmental toxicity potential of Metam-sodium (aqueous solution) when administered by gavage to rats on gestation days 6 through 15, inclusive. Due to technical reasons (not specified) the study was carried out in 2 sections.

Section	Start of Study	Start of Treatment	End of Treatment	Sacrifice
I	1/21/86	1/27/86	2/5/86	2/10/86
II	1/28/86	2/3/86	2/12/86	2/17/86

3. Mating

Animals were acclimated for at least 5 days before mating. Four females were mated with one untreated fertile male of the same breed. Microscopic exam for the presence of sperm in the vaginal smear was the basis for a confirmed mating. The day of a confirmed mating was considered day 0 of pregnancy.

4. Group Arrangement:

Test Group	Dose Level (mg/kg)	Number Assigned
Control	0	25
Low Dose	10	25
Mid Dose	40	25
High Dose	120	25

On day 0 of gestation the animals were assigned to treatment groups according to a randomization technique [Nijenhuis, H. and Wilf, H.S. (1978) Algorithmus zur Erzeugung gleich verteilter Permutationen. Combinatorial Algorithms, Academic Press, New York, San Francisco, London, pp. 62-64.].

5. Dosing:

All doses were in a volume of 10 ml/kg of body weight/day. Dosing solutions were prepared freshly each day during the dosing period. The dosing solutions were analyzed for concentration and stability. Dosing was based on gestation day 6 body weight. The protocol states on page 269 that the animals should be treated under a hood. The vehicle control group received doubly distilled water.

6. Observations

Clinical signs, feed and water consumption were monitored daily during the study. In addition, inspections were performed daily for dead or moribund animals. Body weight was recorded on days 0, 1, 3, 6, 8, 10, 13, 15, 17, and 20 of gestation.

Dams were sacrificed on day 20 by cervical dislocation, necropsied, and evaluated by gross pathology. The uterus and ovaries were removed and weighed prior to opening the uterus. The number of corpora lutea, implantations (and distribution), viable, and non-viable (including resorptions) fetuses were recorded.

Each fetus was weighed, sexed, and examined macroscopically for any external abnormalities. Fetal membranes and liquids were examined as well as fetal viability. Individual placental weights were recorded. Approximately 2/3's of each litter were placed in ethanol and 1/3 was placed in Bouin's solution for fixation. Fetuses fixed in ethanol were eviscerated, and their organs were examined macroscopically. They were subsequently prepared for a double skeletal staining technique according to a modified method of Kimmel (1981). Fetuses fixed in Bouin's were examined for any findings in the organs according to the method of Barrow and Taylor (1969).

The author provided the following definitions (p.22):

- Early Resorptions (according to Salewski)
  From uteri from apparently non-pregnant animals and the empty uterus horn in the case of single-horn pregnancy.

- Early Resorption
  Dead embryos visible to the naked eye as yellowish brown spots.

- Intermediate Resorptions
  Dead and resorbed embryos in which no parts of the body could be differentiated macroscopically.

- Late Resorptions
  Dead and resorbed embryos in which individual parts of the body could be differentiated macroscopically.

- Dead Fetuses
  Hypoxic fetuses which did not breathe spontaneously after the uterus had been opened.

This reviewer was unable to locate the author's definition of a runt.

Historical control data were provided to allow comparison with concurrent controls and have been appended (appendix II). One set of historical control data (vitamin A acid) does not indicate the strain of rat used.

7. Statistical Analysis

The Williams Test was used for statistical evaluation of body, uterine, and placental weight. **Feed and water consumption were not statistically evaluated.** Conception rate, mortality, and the percentage of litters with anomalies, variations, or retardations were analyzed by the Fisher Test. Corpora lutea, implantations, percentage of live and dead implantations per pregnant animals, and percentage of live fetuses with anomalies, variations, or retardations per litter were analyzed by the Krauth Test.

8. Compliance

A signed Statement of Confidentiality Claim was provided that was dated May 1, 1990 (p. 2 of report).

A signed Statement of Compliance with EPA GLP's was provided which indicated the study was not conducted in accordance with EPA GLP regulations. The study was conducted in compliance with "OECD Principles of Good Laboratory Practice (Paris 1981)". This statement is dated May 1, 1990 (p. 3 of report).

A signed Flagging Criteria Statement was provided which was dated July 24, 1990. This statement indicates this study meets or exceeds the criteria numbered 5 (p. 3A of report). Criteria 5 indicates when compared with concurrent controls, treated animals show a dose-related increase in malformations (or deaths) on a litter basis in the absence of significant maternal toxicity at the same dose levels (CFR §158.34).

A signed Quality Assurance Statement was provided which was dated March 25, 1987 (p. 7 of report).

C. Results

1. Analyses of the Test Substance

a. **Purity:** Information on the purity of the test substance was not provided. The content of the active ingredient was reported to be 42.2% or 517.3 g/L (report or raw data not provided.)

b. **Stability:** The report indicates that due to analytical problems the results of samples sent to the laboratory on January 29 and February 12, 1986 could not be used (reasons not provided). Therefore, additional samples were sent for analysis on February 24, 1986. The available data appear to indicate that the test substance was stable.

TABLE 1 Results of Test Substance Analyses

Target Concent. (mg/100mL)	Sample No	Date of			Analytical Value (%)		
		Prep.	Receipt	Analysis	I	II	Mean
100	2	1/29/86	1/29/86	1/31/86	0.08	0.08	0.08
400	3	1/29/86	1/29/86	1/30/86	0.38	0.39	0.39
1200	4	1/29/86	1/29/86	1/30/86	1.26	1.26	1.26
100	2	2/24/86	2/24/86	2/24/86	0.09	-	0.09
400	3	2/24/86	2/24/86	2/24/86	0.39	0.40	0.40
1200	4	2/24/86	2/24/86	2/24/86	1.21	1.20	1.21
100	6	2/12/86	2/12/86	2/18/86	0.02	-	0.02
400	7	2/12/86	2/12/86	2/17/86	0.33	0.34	0.34
1200	8	2/12/86	2/12/86	2/17/86	1.18	1.22	1.20
100	2	2/24/86	2/24/86	2/27/86	0.07	-	0.07

Data extracted from report no. 87/0128 pp. 331-338.

2. Analyses of Feed and Water

The text of the report indicates that reduced copper values were occasionally detected in the feed. Page 274 of the report has a hand written notation made next to the copper value which was not translated from german. A high bacterial count was found in several samples of the drinking water [p. 354 the evaluation of the drinking water for samples delivered Jan. 7, 1986 indicates from a bacteriological point of view, there is no concern about using the water as drinking water except for samples no 12, 13, 29, and 41 which exhibit an increased number of colonies (#13 had 488, the others had > 1000 colonies in 1 mL p. 353 has a translation of hand written notes stating: will be rinsed with either RED/ST or OW) ... p. 357 reports the same concern for samples 6, 24e, 49, 54, and 65 that were delivered Feb. 4, 1986 although the counts are lower no corrective measures were indicated.]

3. Maternal Toxicity

a. Mortality
There were no maternal deaths during this study.

b. Clinical Observations
The author did not report any disturbance of the general behavior in the animals. Alopecia and body fur smeared with urine and blood were observed in two low and 4 high dose animals which did not appear to be related to treatment (neither a summary table or raw data were provided).

c. Body Weight
The investigators supplied the following data:

TABLE 2: Mean Maternal Body Weight Gain (grams)[a]

Dose (mg/kg)	0	10	40	120
Days 0-1	0.83	2.92	3.13	3.23
Days 1-3	11.71	10.71	11.08	11.73
Days 3-6	12.63	10.13	12.33	12.41
Days 6-8	5.50	4.33	-0.42**	-4.59**
Days 8-10	10.00	9.71	9.04	6.95**
Days 10-13	18.42	16.46	15.21*	15.32*
Days 13-15	11.04	11.54	11.79	9.05
Days 15-17	21.88	19.83	20.17	20.95
Days 17-20	47.50	44.17	43.25	41.32
Corrected BWG Days 6-15	-25.17	-23.29	-25.75	-35.32
Corrected BWG Days 0-20	69.38	64.46	64.21	54.32**
Uterine Wt.	70.13	65.33	61.38	62.05

Data extracted from report no. 87/0128 pp. 54-55, 96-104 and 129-132.
* Significantly different from control ($p \leq 0.05$)
** Significantly different from control ($p \leq 0.01$)
Corrected BWG Days 6-15 was calculated by this reviewer and was not statistically analyzed.
Corrected body weight gain for dosing period = body weight gain for dosing period (days 6-15) minus gravid uterine weight.
Corrected body weight gain for entire gestation period = body weight gain for entire gestation period (days 0-20) minus gravid uterine weight.

The body weight of the 120 mg/kg group was significantly reduced during treatment (days 6-15) and after treatment (days 16-20). Body weight gain was significantly reduced in the 40 mg/kg group during days 6-8 and days 10-13. The 120 mg/kg group had a significant reduction in body weight gain during days 6-8, 8-10, and 10-13. The corrected body weight gain during days 6-15 was calculated by this reviewer and was not statistically analyzed. However, body weight gain for the 120 mg/kg group was reduced by 40.3% of the control value. The corrected body weight gain for the entire gestation period for the 120 mg/kg group was significantly reduced. These significant reductions are considered to be treatment related.

d. Feed Consumption

The investigators supplied the following data:

TABLE 3: Mean Maternal Feed Consumption ± S.E.M. (g)

Dose (mg/kg)	0	10	40	120
Days 0-1	16.3±1.0	17.5±0.4	17.0±0.3	17.5±0.4
Days 2-3	20.5±0.3	20.8±0.4	20.9±0.2	21.4±0.3
Days 4-6	22.0±0.4	21.5±0.3	21.6±0.2	22.6±0.3
Days 7-8	21.2±0.3	20.2±0.4	17.8±0.3	17.1±0.4
Days 9-10	22.0±0.2	21.3±0.3	19.5±0.3	18.4±0.4
Days 11-13	23.9±0.2	23.2±0.5	21.9±0.3	20.3±0.4
Days 14-15	24.5±0.3	23.7±0.4	23.3±0.3	20.6±0.5
Days 16-17	26.2±0.4	25.3±0.7	25.4±0.2	23.4±0.6
Days 18-20	27.8±0.3	27.2±0.6	28.1±0.3	26.8±0.7
Days 0-20	23.3±0.2	22.8±0.3	22.3±0.2	21.4±0.4

Data extracted from report no. 87/0128 pp. 54-55, 96-104 and 129-132.

Feed consumption data were not statistically analyzed. However, there was a dose related decrease in feed consumption during the treatment period days 7-8, 9-10, 11-13, and 14-15. The reduction is most pronounced in the 40 and 120 mg/kg groups during days 7-8 (16 and 19% respectively, relative to the control). The feed consumption of the dams in the 120 mg/kg group was consistently decreased relative to the control from the beginning of treatment until the end of the study. The overall consumption of feed of this group was decreased relative to the control. These apparent decreases are considered to be treatment related.

e. Water Consumption

TABLE 4: Mean Maternal Water Consumption ± S.E.M. (g/day)

Dose (mg/kg)	0	10	40	120
Days 0-1	19.3±1.0	20.3±0.6	19.8±0.7	20.8±0.5
Days 2-3	25.3±0.5	25.3±0.6	26.2±0.5	26.7±0.5
Days 4-6	25.6±0.4	25.5±0.5	25.5±0.5	26.2±0.6
Days 7-8	23.1±0.5	22.6±0.8	20.8±0.9	21.3±0.9
Days 9-10	24.9±0.5	25.5±0.8	26.8±0.8	28.5±0.6
Days 11-13	29.0±0.4	32.2±1.3	32.9±0.9	35.6±1.0
Days 14-15	31.4±0.5	35.1±1.4	38.0±1.1	35.9±1.4
Days 16-17	36.1±0.7	38.4±1.6	41.2±0.9	40.8±1.2
Days 18-20	39.3±0.6	41.3±1.6	42.4±0.9	42.0±1.1
Days 0-20	29.1±0.4	30.6±1.0	31.4±0.7	31.9±0.7

Data extracted from report no. 87/0128 pp. 50-51.

Water consumption was not analyzed statistically. Prior to treatment there was an increase in the consumption of water in the treatment groups. During the treatment period there was a dose related increase in water consumption. During days 9-10 there was a 2.4, 7.6, and 14.5% increase, relative to control, for the 10, 40, and 120 mg/kg groups, respectively. During days 11-13 there was a 11.0, 13.4, and 22.8% increase, relative to the control, for the 10, 40, and 120 mg/kg groups, respectively. Except for days 7-8, the 120 mg/kg group consumed more water than the control during every interval. Therefore, it would appear that the increase in water consumption is not explicitly related to treatment.

f. Gross Pathological Observations

The text of the report indicates that there were no necropsy findings at all in any group (there were no summary tables or raw data to substantiate this claim).

Cesarean Section Observations

TABLE 5: Cesarean Section Observations[a]

Dose (mg/kg)	0	10	40	120
#Animals Assigned	25	25	25	25
#Animals Mated/Inseminated	25	25	25	25
Pregnancy Rate (%)	96	96	96	88
Maternal Wastage				
#Died	0	0	0	0
#Died/pregnant	0	0	0	0
#Non pregnant	1	1	1	3
#Aborted	0	0	0	0
#Premature Delivery	0	0	0	0
N	24	24	24	22
Total Corpora Lutea	365	375	348	331
Corpora Lutea/Dam	15.21	15.63	14.50	15.05
Total Implantation	330	329	299	307
Implantations/Dam	13.75	13.71	12.46	13.95
Total Live Fetuses	303	282	277	261
Live Fetuses/Dam	12.63	11.75	11.54	11.86
% Live Fetuses/Dam	92.72	82.11*	93.34	85.21*
Total Resorptions	27	47	22	46
Early (Salewski)	0	1	0	0
Early	25	34	19	39
Intermediate	2	12	2	5
Late	0	0	1	2
Resorptions/Dam	1.13	1.96	0.92	2.09
Total Dead Fetuses	0	0	0	0
Dead Fetuses/Dam	0	0	0	0
Preimplantation Loss(%)	10.37	10.20	15.24	7.37
Postimplantation Loss(%)	7.28	17.89*	6.66	14.79*
Mean Fetal Weight (g)	3.72	3.75	3.60	3.42**
Males	3.78	3.82	3.71	3.51**
Females	3.64	3.69	3.50	3.34**
Total No. of Runts	2	0	2	3
Mean Placental Weight (g)	0.44	0.43	0.41*	0.41**
Males	0.44	0.43	0.42	0.41*
Females	0.43	0.42	0.40*	0.39**

a = Data extracted from report no. 87/0128 pp. 34, and 61-63.
* Significantly different from control ($p \leq 0.05$)
** Significantly different from control ($p \leq 0.01$)

The authors did not statistically analyze preimplantation loss because implantation occurred prior to treatment. However, preimplantation loss in the 40 mg/kg group was increased 47% relative to the control.

The percentage of dead implantations/litter (postimplantation loss) was significantly increased at the 10 and 120 mg/kg levels, which was apparently due to the high number of early resorptions. Therefore, the percentage of live fetuses/litter was also significantly reduced.

Although these findings were not observed in the 40 mg/kg group, it is the opinion of this reviewer that they are treatment related because of the following:

1. The mean number of corpora lutea/dam, implantations/dam, resorptions/dam and percentage of postimplantation loss was slightly lower in the 40 mg/kg group (non significant), than in the concurrent control group.

2. The % live fetuses/dam was higher (non significant) in the 40 mg/kg group than in the concurrent control group.

3. There is no increase in postimplantation loss in the 40 mg/kg group. However, preimplantation loss was increased 47% relative to the control. In the 120 mg/kg group postimplantation loss was significantly increased while preimplantation loss was decreased below the control value.

4. The percentage of dead implantations/litter (postimplantation loss) was also increased in a dose related manner in the dose-range finding study in the Wistar rat (25 animals/group).

5. A dose related increase in postimplantation loss and a reduction in the total number of live fetuses/dam was also reported when this test substance was evaluated in rabbits (MRID 403309-01).

6. The values reported in the current study for the 10 and 120 mg/kg group are outside of the range reported in the historical controls.

Based upon the available data, the consistency of these findings leads this reviewer to believe that these observed effects are treatment related.

The authors have provided data which report the number of fetuses per litter and their viability without describing the sex distribution. However, they report that the sex distribution was not affected by treatment. In the manner that raw fetal litter data are presented, one cannot discern the sex of the fetuses or track the assignment of individual fetuses within a litter to either soft-tissue or skeletal analysis since fetal numbers were

not included [i.e. dam no 26, fetus 4 (♂)]. Correlations between anomalies and fetal body weights etc., cannot be made. This is of significance due to the anomalies observed during the cesareans (meningocele) in table 6. The reviewer cannot determine whether these fetuses underwent skeletal or soft-tissue examination.

4. Developmental Toxicity

TABLE 6: External Examinations of Fetuses

Dose (mg/kg)	**0**	**10**	**40**	**120**
#pups(litters) examined	303(24)	282(23)	277(24)	261(22)
#pups(litters) affected	-	-	-	2(1)
Meningocele	-	-	-	2(1)

Data extracted from report no. 87/0128 pp. 64-68.

The only finding which was observed during the macroscopic examination of the fetuses at the time of cesarean was meningocele in 2 fetuses (0.51% of fetuses examined per litter) in 1 litter (4.55% of litters) of the 120 mg/kg group. This was considered to be related to treatment because the finding was observed in the dose-range finding study and it has not been observed in the historical control. Furthermore, this finding was also observed in an evaluation of this test substance in rabbits (MRID 403309-01).

TABLE 7: Visceral Examinations

Dose (mg/kg)	0	10	40	120
EVISCERATION				
#pups(litters) examined	204(24)	189(23)	183(24)	173(22)
Anomalies				
Microphthalmia, Bilat	-	-	-	1(1)
Variations				
Enlarged Renal Pelvis Bilateral	4(3)	11(7)	29(13)	14(9)
Enlarged Renal Pelvis Unilateral	12(6)	17(10)	43(19)	12(8)
Retardations	-	-	-	-
BARROW/TAYLOR				
#pups(litters) examined	99(24)	93(23)	94(24)	88(22)
Anomalies	-	-	-	-
Variations				
Enlarged Renal Pelvis Bilateral	23(13)	14(8)	5(3)	4(4)
Enlarged Renal Pelvis Unilateral	17(14)	17(12)	8(5)	14(11)
Hydroureter, Bilat	3(3)	1(1)	5(3)	-
Hydroureter, Unilat	3(3)	3(3)	-	2(2)
Retardations	-	-	-	-
COMBINED VARIATIONS (Barrow/Taylor plus Evisceration)[a,b]				
#pups(litters) examined	303(24)	282(23)	277(24)	261(22)
Enlarged Renal Pelvis Bilateral	27(14)	25(9)	34(14)	18(12)
Enlarged Renal Pelvis Unilateral	29(16)	34(16)	51(19)	26(13)

Data extracted from report no. 87/0128 pp. 69-79, and 175-225.
[a] = These combined values were generated by this reviewer.
[b] = Some litters may contain both observations.

The percentage of litters and the percentage of fetuses with variations observed at evisceration was significantly increased ($p \leq 0.01$) in the 40 mg/kg group relative to the control. This was apparently due to the number of fetuses with renal variations. No indications of retarded development were observed during eviscerations.

TABLE 8: Skeletal Examinations

Dose (mg/kg)	0	10	40	120
#pups(litters) examined	204(24)	189(23)	183(24)	173(22)
Anomalies				
Sternebrae Ossif. Centers Dislocated, ventral seg. of Ribs Asym Fused w/ Sternum	-	**2(2)**	**12(11)**	**3(3)**
Sternebra Ossif. Centers Dislocated, ventral seg. of Ribs Asym Fused w/ Sternum	1(1)	1(1)	1(1)	1(1)
Thoracic Vert., Absent	-	1(1)	-	-
Thoracic Vert. Body Dumbbell Shaped Notch in Cartil. -				
Caudal	-	-	1(1)	-
Cranial	**9(8)**	**14(10)**	**17(13)**	**9(9)**
Cranial/Caudal	21(12)	23(11)	24(14)	20(15)
Thoracic Vert. Bodies Dumbbell Shaped Notches in Cartil.-				
Cranial	1(1)	2(2)	4(4)	2(1)
Thoracic Vert. Bodies Dumbbell Shaped Notches in Cartil.-				
Cranial/Caudal	**1(1)**	**3(3)**	**2(2)**	**4(4)**
Thoracic Vert. Body Dumbbell Shaped Cart. Bipartited	1(1)	-	2(2)	-
Thoracic Vert. Bodies Dumbbell Shaped Cart. Bipartited	-	1(1)	1(1)	-
Thoracic Vert. Body Bipartited Ossif. Centers not Connected w/ Cartilage	-	-	1(1)	-
Thoracic Vert. Body Bipartited Ossif. Centers Connected w/ Cartil., Notches of Cartil. Cranial/Caudal	-	-	-	2(2)
Lumbar Vert., Absent	-	1(1)	-	-
Lumbar Vert., Bipartite Arch	-	-	-	1(1)
Fetus w/ Multiple Anomalies	1(1)	-	-	-

TABLE 8: Skeletal Examinations - cont'd

Dose (mg/kg)	**0**	**10**	**40**	**120**
#pups(litters) examined	204(24)	189(23)	183(24)	173(22)
Variations				
Accessory Rib, Unilat. Cartil., Missing	-	-	-	1(1)
13 Ribs, & Cartil., Absent	-	1(1)	-	-
13th Rib & Cartil. Absent, Bilat.	-	1(1)	-	-
13th Rib Shortened, Cartil. present, Unilat.	-	1(1)	1(1)	-
13th Rib Shortened, Cartil. Absent, Unilat.	23(13)	21(15)	15(9)	15(9)
13 Ribs Shortened, Cartil. Absent Bilat.	19(8)	27(11)	20(12)	17(7)
13 Ribs Shortened, Only Cartil. Present	-	-	-	1(1)
Rib-Cartil., Bipartited	-	1(1)	-	-
Xiphoid Process Bipartited	9(7)	16(11)	19(11)	8(7)
Sternebra Bipartited, Ossif., Centers Connected w/ Cartil.	5(4)	1(1)	1(1)	-
Sternebra Irregularly Shaped	-	2(2)	-	-
Sternebrae Ossif. Centers Dislocated	12(8)	10(7)	-	-
Sternebrae Bipartited, Ossif. Centers Connected w/ Cartil.	-	-	1(1)	-
Sternebra Ossif. Centers Dislocated	6(6)	4(4)	1(1)	1(1)
Thoracic Vert. Notches in Cartil., Cranial/Caudal or Cartil. Bipartited	1(1)	-	-	-
Thoracic Vert. Notch in Cart. Cranial	1(1)	2(2)	1(1)	1(1)
Thoracic Vert. Body Dumbbell Shaped, Cartil. Unchanged	27(14)	15(11)	28(16)	30(17)
Thoracic Vert. Bodies Dumbbell Shaped, Cartil.	**17(8)**	**22(12)**	**49(19)**	**62(21)**
Thoracic Vert. Notch in Cartil., Cranial	-	1(1)	-	-
Cervical Vert. Notches in Cartil. Cranial/Caudal or Cartil. Bipartited	-	-	1(1)	-
Cervical Vert. Notches in Cartil. Cranial/Caudal or Cartil. Bipartited	1(1)	-	-	-

TABLE 8: Skeletal Examinations - cont'd

Dose (mg/kg)	**0**	**10**	**40**	**120**
#pups(litters) examined	204(24)	189(23)	183(24)	173(22)
Variations				
Sacral Vert. Body Dumbbell Shaped, Cartil. Unchanged	-	-	-	1(1)
Lumbar Vert. Body Dumbbell Shaped, Cartil. Unchanged	-	-	1(1)	3(3)
Lumbar Vert. Bodies Dumbbell Shaped, Cartil. Unchanged	-	-	1(1)	-
Retardations				
Frontal Bone Inc. Ossif.	1(1)	6(2)	2(1)	4(3)
Hyoid Not Ossif. Cartil. Present	2(1)	-	2(1)	5(4)
Hyoid Inc. Ossif. Cartil. Present	**15(12)**	**9(6)**	**13(12)**	**27(11)**
Interparietal Not Ossif. Cartil. Present	-	1(1)	-	2(1)
Interparietal Inc. Ossif. Cartil. Present	**1(1)**	**8(4)**	**20(11)**	**15(10)**
Nasal Inc. Ossif. Cartil. Present	1(1)	1(1)	1(1)	4(3)
Occipital Inc. Ossif. Cartil. Present	1(1)	2(1)	2(1)	6(4)
Parietal Not. Ossif. Cartil. Present	-	1(1)	-	2(1)
Parietal Inc. Ossif. Cartil. Present	1(1)	8(4)	7(3)	4(3)
Xiphoid Process - Center Bipartited	38(18)	25(15)	15(14)	20(11)
Sternebra-Only One Center Ossified Cartil. Present	7(7)	10(8)	4(3)	-
Sternebrae Not Ossif. Cartil. Present	**12(5)**	**7(6)**	**10(8)**	**35(13)**
Sternebra Not Ossif. Cartil. Present	34(16)	44(17)	34(16)	31(16)
Sternebrae Inc. Ossif. Cartil. Present	42(18)	25(15)	57(21)	78(21)
Sternebra Inc. Ossif. Cartil. Present	72(22)	75(23)	75(21)	52(19)

TABLE 8: Skeletal Examinations - cont'd

Dose (mg/kg)	0	10	40	120
#pups(litters) examined	204(24)	189(23)	183(24)	173(22)
Retardations				
Thoracic Vert. Bodies Inc. Ossif. Cartil. Present	-	-	-	1(1)
Thoracic Vert. Body Inc. Ossif. Cartil. Present	-	-	-	1(1)
Sacral Vert. Bodies Inc. Ossif. Cartil. Present	-	-	-	1(1)
Ischium Inc. Ossif. Bilat. Cartil. Present	-	-	-	1(1)
Pubis Inc. Ossif. Bilat. Cartil. Present	-	-	-	3(3)
Metacarpal Inc. Ossif. Bilat. Cartil. Present	**-**	**1(1)**	**6(4)**	**13(8)**
Metacarpal Not Ossif. Unilat. Cartil. Present	-	-	1(1)	-
Metacarpal Inc. Ossif. Unilat. Cartil. Present	**-**	**3(3)**	**7(5)**	**14(11)**
Metatarsal Inc. Ossif. Bilat. Cartil. Present	**2(2)**	**4(2)**	**11(7)**	**20(10)**
Metatarsal Inc. Ossif. Unilat. Cartil. Present	**-**	**1(1)**	**8(5)**	**12(7)**
Generalized Retardation	**-**	**-**	**6(3)**	**7(6)**
Anomalies				
% Litters	70.83	73.91	87.50	77.27
% Fetuses/Litter	18.54	22.53	29.82*	21.83
Variations				
% Litters	95.83	95.65	100	100
% Fetuses/Litter	44.32	50.16	56.84*	67.27**
Retardations				
% Litters	100	100	100	100
% Fetuses/Litter	75.82	77.13	90.64**	91.84**

Data extracted from report no. 87/0128 pp. 81-89, and 226-256.
* Significantly different from control ($p \leq 0.05$).
** Significantly different from control ($p \leq 0.01$).

There were significant increases in the % fetuses/litter with anomalies, variations, and retardations at the 40 mg/kg level, which were dose-related (except for anomalies). There were significant increases in the % fetuses/litter with variations and retardations at the 120 mg/kg level which were dose-related. There were dose-related increases in thoracic vertebrae bodies dumbbell shaped with unchanged cartilage, metacarpals and metatarsals that were incompletely ossified (unilaterally) with cartilage present, and generalized retardation. The table for skeletal retardations (table 41 p. 88) under the heading of pelvic girdle has two observations i.e. PNU and PUU which did not appear in any of the treatment groups.

D. Discussion/Conclusions

1. Maternal Toxicity:

Maternal toxicity was observed at the 40 and 120 mg/kg levels as significantly decreased body weight gain during the dosing period. The corrected maternal body weight gain was significantly reduced at 120 mg/kg. Although not statistically analyzed, mean maternal feed consumption was reduced during the treatment period. The greatest decrease in feed consumption occurred days 7-8 at the beginning of the treatment period in the 40 and 120 mg/kg group (reduced by 16 and 19% of the control, respectively).

2. Developmental Toxicity:

a. Deaths/Resorptions:

The cesarean section data indicate a significant increase in postimplantation loss, and a significant decrease in the % of live fetuses/dam at the 10 and 120 mg/kg levels.

b. Altered Growth:

Fetal weights were significantly reduced for male and female fetuses in the 120 mg/kg group. Examination of the viscera of fetuses that underwent skeletal examination revealed a significant increase in variations at the 40 mg/kg level. This was due to renal variations. Skeletal examinations of fetuses appeared to indicate that there was a delay in the development of the fetuses at the 40 and 120 mg/kg level. This was apparently due to incomplete ossification of sternebrae, vertebrae, skull bones, metatarsals and metacarpals.

c. Developmental Anomalies:

The administration of Metam-sodium at high doses [120 mg/kg (HDT in the main study) and 240 mg/kg (HDT in the range finding study)] resulted in meningocele which was not reported in the historical or concurrent control.

E. Study Deficiencies:

1. The purity of the test substance was not provided.

2. The report indicates that due to analytical problems the results of samples sent to the laboratory could not be used. The report does not explain why these samples could not be used.

3. The raw data from the dose-range finding study was not provided.

4. The raw data for the daily clinical examination of the dams was not provided.

5. The raw data for the necropsy of the dams was not provided.

6. The fetal sex ratio was not provided.

7. The manner in which raw fetal litter data are presented makes it impossible to discern fetal sex or track the assignment of individual fetuses within a litter to either soft-tissue or skeletal analysis since fetal numbers were not included (i.e. dam/litter no 26, fetus 4 ♂). Correlations between anomalies and fetal body weights etc., cannot be made. This is of significance due to the anomalies observed during the cesareans (meningocele) in table 6. The reviewer cannot determine whether these fetuses underwent skeletal or soft-tissue examination.

8. The EPA Subdivision F Pesticide Assessment Guidelines (1984) state that 1/3 to 1/2 of each litter should be prepared and examined for skeletal anomalies, and the remaining part of each litter should be prepared and examined for soft tissue anomalies using appropriate methods. The current study evaluated 2/3's of each litter for skeletal changes and the remaining fetuses were evaluated for soft tissue changes via the Barrow and Taylor technique. Given that the administration of this test substance appears to result in meningocele (in two species - rat and rabbit) it is the opinion of this reviewer that examination of 2/3's of each litter for soft tissue changes as directed in the guidelines would have provided a better assessment of the potential for neural defects.

9. Clarification should be made regarding the bacteria content of the animals drinking water.

10. Information was deficient for the number of animals obtained from the breeder for the purpose of this study, the fate of the animals not placed on the study, as well as the source and total number of males used for mating.

11. This study did not determine a NOEL for developmental toxicity.

F. Core Classification: Supplementary

Maternal NOEL = 10 mg/kg
Maternal LOEL = 40 mg/kg
Developmental Toxicity NOEL = not determined
Developmental Toxicity LOEL = 10 mg/kg

Primary Review by: Stephen C. Dapson, Ph.D. Stephen C. Dapson 8/14/91
Senior Pharmacologist, Review Section 1, Toxicology Branch II/HED

Secondary Review by: Yiannakis M. Ioannou, Ph.D., D.A.B.T. JMI 8/14/91
Section Head, Review Section 1, Toxicology Branch II/HED

DATA EVALUATION RECORD

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

EPA Identification No.s: EPA MRID No. 403309-01
EPA Pesticide Chemical Code: 039003
Toxicology Chemical Code: 780
HED Project No. 1-1988

Test Material: Metam-Sodium (aqueous solution)

Synonyms: Sodium-N-methyl-dithiocarbamate, BAS 005 00 N/Metam-Fluid 510 g/l

Sponsor: BASF CORPORATION CHEMICALS DIVISION, Agricultural Chemicals Group, 100 Cherry Hill Road, Parsippany, NJ 07054

Study Number(s): Project No. 38R0232/8579

Testing Facility: BASF Aktiengesellschaft
D6703 Limburgerhof, Federal Republic of Germany

Title of Report: Report on the Study of the Prenatal Toxicity of Metam-Sodium (aqueous solution) in rabbits after Oral Administration (gavage).

Author(s): Dr.med.vet. J. Hellwig

Report Issued: July 15, 1987

Conclusions: 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 cannot be determined with available data; additional information is required.

Core Classification: **Core-Supplementary Data**
This study does not satisfy the guideline requirements (§ 83-3) for a teratology study in rabbits. Additional data are required; if these data are supplied and found acceptable to the Agency the study may be upgraded.

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

Test Compound: Purity: stated as 42.2% aqueous solution
Density: not provided
Description: liquid
Lot No.: Batch No. ZH 130585/April 1985
Receipt date: not provided
Other provided information: in material and methods
Contaminants: list in CBI appendix: not provided

Vehicle(s): distilled water

Test Animal(s): Species: Himalayan rabbits
Strain: Chbb:HM (outbred strain)
Source: Karl THOMAE
Biberach an der Riss, FRG
Age: 23 to 33 weeks
Body Weight: 2.0 to 2.8 kg
Any information on males used: none provided

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 18, inclusive.

Mating Procedure

Artificial insemination after an acclimatization period of "at least" 7 days. Procedure was not provided.

Animal Husbandry

Animals were kept under standard animal care conditions. Both food and water were analyzed for contaminants. Food was pelleted Kliba maintenance diet type 23-341-4 supplied by KLINGENTALMUHLE AG, CH-4303 Kaiseraugst, Switzerland. The animals received 130 gm of the diet daily with tap water available *ad libitum* (according to the investigators about 500 ml/animal/day).

Group Arrangement:

Test Group	Dose Level (mg/kg)	Number Assigned
Control	double distilled water	15
Low Dose	10	15
Mid Dose	30	15
High Dose	100	15

This was done according to "a randomization plan" which was not provided; although a reference was suggested the pages were not present (page 30 of BASF document was not included in submission, no break in submission pagination).

Dose Administration:

All doses were administered in a volume of 10 ml/kg of body weight/day prepared daily during the dosing period. The dosing solutions were analyzed for concentration and stability. Dosing was based on gestation day 6 body weight.

It was not clear from the data provided if the doses were corrected for the 42.2% or if the actual dose received is therefore 42.2% of the value presented.

According to the investigators "Due to technical reasons, the study was carried out in 3 sections. Each dose group was represented in each section. A treatment interval of 7 days elapsed before the next section." See following figure from the investigators report:

Fig. 3.6.1.: Time schedule

	Beginning of acclimatization period	Beginning of study (day 0 p.i.)	Beginning of treatment (day 6 p.i.)	End of treatment (day 18 p.i.)	Sacrifice (day 29 p.i.)
1st section	March 18, 1986	March 25, 1986	March 31, 1986	April 12, 1986	April 23, 1986
2nd section	March 25, 1986	April 1, 1986	April 7, 1986	April 19, 1986	April 30, 1986
3rd section	April 1, 1986	April 8, 1986	April 14, 1986	April 25, 1986	May 7, 1986

A brief description of the pilot study with some data provided in the protocol was provided by the investigators stating that 15 animals per dose group received 0, 50, 100, and 200 mg/kg body weight. They observed reduced body weight gains in all dosed groups at beginning of dosing with significant decreased body weight gains noted in the 100 and 200 mg/kg dose groups along with a decrease in food consumption. Uterine weights were decreased in the 100 and 200 mg/kg dose groups. There was a dose related decrease in dead implantations reaching statistical significance at the 100 and 200 mg/kg levels; data from protocol presented below. The investigators stated that "Evaluation of the fetuses revealed no findings which could be clearly attributed to the test substance administered"; again no data were provided.

The following was extracted from the attached protocol:

a) Dead implantations

The number of dead implantations shows a dose-dependent increase, and it is striking that at 100 and 200 mg/kg body weight there is a markedly increased number of late abortions.

	Dead implantations					
	total	thereof				
		early resorption	intermediate resorption	late resorption	late abortion	dead fetuses
Controls	10 = 10.10%	8	2	-	-	-
50 mg/kg b.w.	19 = 21.84%	14	4	-	-	1
100 mg/kg b.w.	56 = 57.73%	32	6	2	16	-
200 mg/kg b.w.	76 = 95.00%	19	2	1	54	-

b) Live fetuses

The number of live fetuses shows a dose-dependent decrease, which must be seen in relation to the increasing number of dead implantations.

Controls b.w. 89 ≙ 5.93 per animal
50 mg/kg b.w. 68 ≙ 5.23 per animal
100 mg/kg b.w. 41 ≙ 2.73 per animal
200 mg/kg b.w. 4 ≙ 0.31 per animal

c) Uterus weights

Also the mean uterus weights of the treated animals are below that of the control group.

Controls 321
50 mg/kg b.w. 282
100 mg/kg b.w. 149**
200 mg/kg b.w. 27**

d) Body weights

- Body weights:

Whilst the mean body weights of the treated and untreated rabbits are about the same at day 0 (artificial insemination), the body weight of the animals treated with 200 mg/kg body weight is from day 11 of gestation until the end of the study significantly below the corresponding body weight of the control animals. At the end of the study there is a slight impairment of the mean body weights of the rabbits of the 100 mg/kg b.w. group, too.

	Day 0 p.i.	Day 29 p.i.
Controls	2352	2577
50 mg/kg b.w.	2382	2566
100 mg/kg b.w.	2375	2479*
200 mg/kg b.w.	2367	2324**

- Body weight increase:

Between day 6 and day 9 of gestation, all the animals treated with the test substance lose weight dose-dependently. In the subsequent time, the increase in body weight of these animals was less marked than that of the control group (50 and 100 mg/kg b.w.) or even was negative (200 mg/kg b.w.). The differences, however, are not significant in each case.

Body weight increase
from day 0 - day 29 p.i.

	absolute (g)	%
Controls	225	100
50 mg/kg b.w.	184	82
100 mg/kg b.w.	104	46
200 mg/kg b.w.	- 43	- 19

* = significance $\geq$ 95%
** = significance $\geq$ 99%

Observations

The animals were checked daily for mortality or abnormal condition. Dams were sacrificed on day 29 of gestation. Examinations at sacrifice consisted of: assessment of "gross pathology"; the uterus and ovaries were removed and the gravid uterine weight, number of corpora lutea, number and distribution of implantation sites with clarification of findings were recorded.

The fetuses were examined in the following manner: each fetus was weighed, sexed, examined macroscopically for external findings, viability was determined, the condition of fetal membranes and fluids was determined and individual placental weights recorded. Following external examination, each fetus was sacrificed, the abdomen and thorax were opened to examine internal organs and then the heads after being x-rayed were fixed in Bouin's solution and examined by Wilson's technique. All fetuses were x-rayed for skeletal examination, after which the trunks were placed in ethyl alcohol for possible staining of the fetuses. According to the investigators: "In general, the skeletons were assessed on the basis of the x-rays. However, in cases of unclear findings the skeletons were stained according to KIMMEL, examined under a stereomicroscope, evaluated and assessed."

Historical control data were provided to allow comparison with concurrent controls.

Statistical analysis

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

> Statistical evaluation
>
> The data were evaluated statistically in the Computer Center of BASF Aktiengesellschaft (scientific information processing, responsible: Dipl.Math. G. Helmstädter) or using the computer systems of the Department of Toxicology of BASF Aktiengesellschaft (laboratory data processing, responsible: Dr. H.D. Hoffmann).

Examinations of dams and fetuses

The Williams test (9, 10) was used for statistical evaluation of body weight, uterus weight and weight of placentae*.

The Fisher test (11) was used for statistical evaluation of conception rate, mortality, percentage of litters with anomalous fetuses and of fetuses with variations and/or retardations.

The Krauth test (12) was used for statistical evaluation of corpora lutea, implantations, percentage of live and dead implantations per pregnant animal, and percentage of live fetuses with anomalies and with variations and/or retardations per litter.

In the tables these tests are called ANALYSIS OF TREND, FISHER TEST and KRAUTH TEST. In each case the test was carried out at the levels of 95% and 99% (error of first kind = < 0.05 and = < 0.01, respectively), and dose groups were always compared with the control group.

In general, significant differences indicating an improvement (e.g. fewer resorptions) or differences in brackets (=) were not taken into account in the results section. Due to the small number of non-pregnant animals, possible significant differences were not taken into account.

Compliance

A signed statement of no data confidentiality claims was provided.

A signed statement of compliance with OECD GLP's was provided; however, not for EPA GLP's.

A signed quality assurance statement was provided.

Results

Analysis of the Test Substance

According to the investigators: "The stability of the test substance was proven. The content of active ingredient was 42.2% or 517.3 gm/l." Further, "The stability of the test substance solutions at room temperature over a period of up to one day could be demonstrated." Data were possibly provided in german; therefore the above claims cannot be substantiated, these data must be provided as a translation.

Maternal Toxicity:

Mortality

No animals were reported to have died; however, 1 control dam was sacrificed after premature delivery, and 2 low dose and 1 high dose dams were sacrificed due to gavage error.

Clinical Observations

The investigators only stated that:

> "The 3 doses (10, 30 and 100 mg/kg body weight) administered by gavage did not lead to any disturbances of the general behavior in any of the animals of the study. In a few animals of all groups, including the controls, marginal spontaneous changes such as partial alopecia, sporadically less feces and some blood in the bedding could be detected during the study. Furthermore, doe No. 16556 (15) (control group) had a premature delivery of 7 viable fetuses on day 28 p.i.."

Further, "All clinical findings mentioned are considered to be independent from the test substance administered; however, although they claim raw data were supplied, no data were provided.

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]

Group:	Prior to Dosing Period	Dosing Period	Post Dosing Period	Entire Gestation Period	Dosing plus PostP.	Corrected Body Weight Gains DosingP.[1]	Entire[2]
Control	24	93	167	284	260	-208	-17
LDT	51	120	197	368	318	-217	-53
MDT	32	108	161	300	268	-173	19
HDT	56	64	80	200	144	-123	13

above values calculated by reviewer

[1] = corrected body weight gain for dosing period = body weight gain for dosing period minus gravid uterus weight.

[2] = corrected body weight gain for entire gestation period = body weight gain for entire gestation period minus gravid uterus weight.

a = Data extracted from Project No. 38R0232/8579, Tables 007 through 014.

The above data indicate a treatment related decrease in body weight gain in the high dose dams.

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]

Group:	Prior to Dosing Period	Dosing Period	Post-Dosing Period	Entire Gestation Period
Control	113	107	111	109
LDT	123	111	117	116
MDT	115	108	112	111
HDT	122	100	111	109

[a] = Data extracted from Project No. 38R0232/8579, Tables 002 through 006.

No treatment related effects were noted.

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

Group:	Prior to Dosing Period	Dosing Period	Post-Dosing Period	Entire Gestation Period
Control	.02	.07	.15	.26
LDT	.04	.11	.17	.32
MDT	.03	.10	.14	.27
HDT	.05	.06	.07	.18

above values calculated by reviewer

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

[a] = Data extracted from Project No. 38R0232/8579, Tables 002 through 014.

No evidence of toxicity was noted from the above calculations.

Gross Pathological Observations

The investigators only stated that:

> "With the exception of doe No. 16556 (15) of the control group, which showed an acute or a peracute colitis and fatty degeneration of the liver cells, only spontaneous necropsy findings in single animals occurred without any dose-response relationship, such as dilatatio pelvis (No. 15688 (46) - test group 4) and one uterus horn not fused with the cervix (partial aplasia) (Nos. 16472 (27) - test group 2 and 16328 (51) - test group 4)."

However, although they claim raw data were supplied, no data were provided.

Cesarean Section Observations

Table IV: Cesarean Section Observations[a]

Dose:	Control	LDT	MDT	HDT
#Animals Assigned	15	15	15	15
#Animals Mated/Inseminated	15	15	15	15
#Animals Pregnant	15	15	14	15
Pregnancy Rate (%)	100	100	93.3	100
Maternal Wastage				
#Died	0	0	0	0
#Died/pregnant	0	0	0	0
#Non pregnant	0	0	0	0
#Aborted	0	0	0	1
#Premature Delivery	1	0	0	0
#Sacrificed	1	2	0	1
Total Corpora Lutea	103	101	111	117
Corpora Lutea/dam	7.36	7.77	7.93	7.80
Total Implantations	85	92	84	107
Implantations/Dam	6.07	7.08	6.00	7.13
Total Live Fetuses	81	85	73*	48**
Live Fetuses/Dam	5.79	6.54	5.21	3.20
Total Resorptions	4	7	11*	59**
As Abortions	0	0	0	7
Early	1	6	7	40
Intermediate	2	1	3	10
Late	1	0	1	2
Resorptions/Dam	3.65	8.06	12.36	54.93
Total Dead Fetuses	0	0	0	0
Mean Fetal Weight (gm)	14.00	13.00	14.00	14.00
Preimplantation Loss(%)	17.5	8.9	24.3	8.6
Postimplantation Loss(%)	4.7	7.6	13.1	55.1
Sex Ratio (Male/Female)	43/38	36/49	39/34	22/26

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

[a] = Data extracted from Project No. 38R0232/8579, Tables 001, 022 and 023 and Figure 4.2.2.3.1..

Toxicity was noted in the mid and high dose groups in the form of increased resorptions, a decrease in the number of live fetuses and an increase in post-implantation loss.

2. Developmental Toxicity

Table V: External Examinations[a]

Observations[+]	Control	Low Dose	Mid Dose	High Dose
#pups/litters examined	81/14	85/13	73/14	48/14
Meningocele	0/0[@]	0/0	0/0	1/1
Spina bifida	0/0	0/0	0/0	1/1
Pseudoanklosis	0/0	2/2	1/1	1/1

(+) some observations may be grouped together
(@) fetal/litter incidence
[a] = Data extracted from Project No. 38R0232/8579, Table 027 and 029.

Although the incidences of meningocele and spina bifida were low, it was noted by the investigators that these observations were also seen in the rat teratology study and the historical control data provided with this study does not present incidence of anomalies of this type.

Table VI: Visceral Examinations[a]

Observations[+]	Control	Low Dose	Mid Dose	High Dose
#pups/litters examined	81/14	85/13	73/14	48/14
Truncus arteriosus communis	0/0[@]	0/0	0/0	1/1
Separate origin of the carotids	40/11	37/7	39/8	28/8
Agnesia of the gall bladder	0/0	0/0	1/1	1/1

(+) some observations may be grouped together
(@) fetal/litter incidence
[a] = Data extracted from Project No. 38R0232/8579, Table 033 and 035.

No treatment related effects were noted.

The skeletal examinations were carried out by a method that has not been validated by the EPA and further, according to the investigators, if the radiograph was not clear, a separate technique was used. All fetuses must be examined by a staining technique. A study submitted to the Agency recently that compared x-ray technique with the more prevalent "Dawson's" technique found that they were not comparable.

D. Discussion/Conclusions

a. Maternal Toxicity:

Maternal Toxicity was evidenced in the mid and high dose groups as either reduced body weight gains, reduced food consumption, increased number of dead implantations and reduced numbers of fetuses or increased post-implantation loss.

b. Developmental Toxicity:

i. Deaths/Resorptions:

Increased numbers of dead fetuses and an increase in post-implantation loss was noted in the mid and high dose group.

ii. Altered Growth:

Additional data are required.

iii. Developmental Anomalies:

Additional data are required.

iv. Malformations:

One observation each of meningocele 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.

D. Study Deficiencies:

1. Purity was apparently only 42.2% a.i., must be clarified.
2. Analysis of test compound and concentrations were provided in german only.
3. Artificial insemination procedure was not provided.
4. References to techniques were not provided.
5. Pilot study was not provided, must be supplied.
6. The fetal skeletal examinations were carried out by a method that has not been validated by the EPA and further, according to the investigators, if the radiograph was not clear, a separate technique was used. All fetuses must be examined by a validated staining technique.
7. Clinical observations and gross pathological observations were not supplied as summary tables and/or as raw data, this must be provided.

The above deficiencies must be corrected before the Developmental Toxicity NOEL and LOEL can be determined. The study may be upgraded if the deficiencies are corrected and a Developmental Toxicity NOEL is determined.

E. Core Classification: Core Supplementary Data.

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

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 along with the 2 incidences of neural tube defects similar to what was observed in the rat teratology study; however the Developmental Toxicity NOEL and LOEL cannot be determined with available data; additional information is required.

F. Risk Assessment: None at this time.

Metam-sodium toxicology review

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Pages 41 through 52 are not included in this copy.

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___ Identity of product impurities

___ Description of the product manufacturing process

___ Description of product 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

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Chemical name Metam-Sodium

Study/Lab/Study #/Date	Material	MRID #	Results	CORE Grade/ Doc. No.
83-3(b) Teratology-Rabbit BASF/38R0232/8579/ ?/15/87	Metam-Sodium 42.2&% aqueous solution	403309-01	Maternal Toxicity NOEL = 10 mg/kg/day Maternal Toxicity 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 One observation each of meningocele 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 cannot 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.	Supple- mentary

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Tox Chem No. 780 File Last Updated _____ Current Date 8/15/91

STUDY/LAB/STUDY #/DATE	MATERIAL	EPA MRID NO.	RESULTS: LD50, LC50, PIS, NOEL, LEL	TOX CATEGORY	CORE GRADE/DOC. #
83-3(A) Developmental Toxicity Species: Rat BASF 87/0128; March 1987	Metam-sodium (42.2% a.i.)	415771-01	An aqueous solution of Metam-sodium was administered at 0, 10, 40, and 120 mg/kg 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 postimplantation 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 meningocele. Based upon deficiences this study cannot be upgraded. Maternal NOEL = 10 mg/kg; Maternal LOEL = 40 mg/kg Developmental Tox NOEL = not determined; Developmental Tox LOEL = 10 mg/kg		Supplementary

Metam-Sodium toxicology review

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