J-TF 4/3
p1 only

Tom M. - I just received!
Look at p.1 and 11, especially.
Do we need to tell
registrants anything we
haven't already?
Pls. give this high
priority. by 3/25

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

DEC 24 1991

DEC 24 1991

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

MEMORANDUM

SUBJECT: Developmental and Reproductive Toxicity Peer Review of Metam-Sodium

FROM: Gary J. Burin, Ph.D., D.A.B.T.
Executive Secretary
Developmental/Reproductive Toxicity Peer Review Committee
Science Analysis and Coordination Branch
Health Effects Division (H7509C)

Yiannakis M. Ioannou, Ph.D., D.A.B.T.
Section Head, Review Section I
Toxicology Branch II

TO: Jay Ellenberger, Chief
Accelerated Reregistration Branch
Special Review and Registration Division (H7508C)

The Health Effects Division Peer Review Committee (PRC) for Developmental and Reproductive Toxicity met on October 15, 1991 to discuss and evaluate the weight-of-the-evidence on metam-sodium with particular reference to its potential for developmental toxicity. This was the first evaluation of metam-sodium by the PRC. A second meeting, held on December 12, 1991, considered additional information not available at the first meeting.

The Committee concluded that metam-sodium induces developmental toxicity in 2 species (rat and rabbit) although neither study was considered to be fully adequate due to deficiencies in study design and reporting. Developmental toxicity (post-implantation loss) was observed at nominal dose levels as low as 30 mg/kg bw/day in the rabbit. In the rat, developmental toxicity (in the form of increased variations, retardations and anomalies) is suggested at nominal dose levels as low as 10 mg/kg. Because nominal dose levels do not appear to be adjusted for the actual amount of active ingredient present, all dose levels should be multiplied by 0.42. The NOEL is therefore considered to be 4.2 mg a.i./kg/day in the rabbit and equal to or less than 4.2 mg a.i. /kg/day in the rat. The NOELs for maternal toxicity are 4.2 mg a.i./kg/day in the rat and 12.6 mg a.i./kg/day in the rabbit.

A. Individuals in Attendance:

1. Peer Review Committee: (Signatures indicate concurrence with the peer review unless otherwise stated.)

Penelope A. Fenner-Crisp

William L. Burnam

Karl Baetcke

Marcia Van Gemert

Gary J. Burin 12/27

Bob Sonawane

Thomas F.X. Collins

Jennifer Orme Zavaleta

Laurence D. Chitlik

Roger Gardner

James Rowe

Hugh Pettigrew

2. Reviewers: (Non-committee members responsible for data presentation; signatures indicate technical accuracy of panel report.)

Yiannakis M. Ioannou

Karen Whitby

Stephen Dapson
Peer Review Committee Member

3. Peer Review Members in Absentia: (Committee members who were unable to attend the discussion; signatures indicate concurrence with the overall conclusions of the Committee.)

Jennifer Seed

Reto Engler

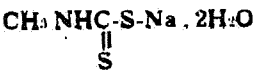
B. Material Reviewed:

The material available for review consisted of DER's, one-liners, and other data summaries prepared by Drs. Dapson, Whitby and Ioannou. A published article from a Soviet journal

(and its translation) were provided to the meeting by V. Miller. In addition, excerpts from the submitted studies were included in the package. The material reviewed is attached to the file copy of this report.

C. Background Information:

Metam Sodium (Sodium-N-methyldithiocarbamate), also known as Vapam, Metham Sodium and SMDC, has the following chemical structure:



Metam Sodium is a fumigant-type pesticide with end-use products formulated as 18% to 42% aqueous solutions. This chemical is registered for a wide variety of different types of use patterns including as an agricultural preplant soil fumigant, wood preservative, slimicide, tree-root killer and aquatic weed control agent. The agricultural soil fumigant uses are available for homeowners as well as commercial growers for preplant soil treatments to control certain weeds, insects, nematodes, bacteria and fungi in the soil. As a slimicide, metam sodium is sprayed inside sewer mains and drain pipes to control slime-forming fungi; the wood preservative uses involve injection of standing utility poles to control wood-destroying insects and to arrest wood rot. There are approximately 35 different metam sodium products registered for a wide variety of uses. Approximately 10 million pounds of the active ingredient were used in 1990, with 40-45% used for agricultural purposes.

D. Studies Pertaining to Developmental Toxicity

1. Rat - BASF Aktiengesellschaft (Testing Facility) Agricultural Research and Development D-6703 Limburgerhof, West Germany Study # 87/0128; Date: 3/1987.

An aqueous solution of metam sodium was administered by gavage to pregnant Wistar rats on days 6-15 of gestation at nominal dose levels of 0, 10, 40 and 120 mg/kg/day. Dams were sacrificed on day 20 of gestation by cervical dislocation, necropsied and evaluated by gross pathology. Fetuses were removed, weighed, sexed and examined macroscopically for external abnormalities. Approximately two-thirds of each litter were placed in ethanol for macroscopic organ examinations and subsequently prepared for a double skeletal staining technique, and one-third were placed in Bouins fixative for organ examination.

No maternal mortality was reported throughout this study.

Corrected body weight gains were statistically significantly decreased in the 120 mg/kg/day dose group on days 6-8, 8-10, 10-13 and 0-20. Similar reductions in body weight gain were reported for the 40 mg/kg/day dose group on days 6-8 and 10-13. There was a dose-related decrease in food consumption during treatment period days 7-8, 9-10, 11-13 and 14-15. This reduction was most pronounced in the 40 and 120 mg/kg/day groups during days 7-8 (16% and 19%, respectively). Other maternal parameters did not appear to be affected by metam sodium. Based on decreases in body weight gain and food consumption, the maternal toxicity LOEL was considered to be 40 mg/kg/day and the NOEL 10 mg/kg/day. These are equal to 16.8 mg a.i./kg/day and 4.2 mg a.i./kg/day, respectively.

As shown in Table 1 (Caesarean Section Observations), a number of parameters were statistically significantly different between the control and the metam sodium treated groups.

TABLE 1

Caesarean 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
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
Resorptions/Dam	1.13	1.96	0.92	2.09
Pre-implantation Loss (%)	10.37	10.20	15.24	7.37
Post-implantation Loss (%)	7.28	17.89*	6.66	14.79*
Mean Fetal Weight (g)	3.72	3.75	3.60	3.42**
Total No. of Runts	2	0	2	3
Mean Placental Weight (g)	0.44	0.43	0.41*	0.41**

* Significantly different from control ($p \leq 0.05$)
** Significantly different from control ($p \leq 0.01$)

Although post-implantation loss was found to be elevated at 10 mg/kg (but not at 40 mg/kg), this observation may not necessarily be related to treatment at that dose level. The individual animal data do not suggest a clear effect because most dams in the control and 10 mg/kg dose levels have either 1 or 2 losses, unlike the high dose group in which several dams have more than 2 losses. In addition, the range-finding study reports 27, 33, 36 and 46 dead implantations at dose levels of 0, 60, 120 and 240 mg/kg, suggesting that the NOEL for post-implantation loss may be 40 mg/kg and that the apparent increase at 10 mg/kg may be an artefact.

External examination of fetuses revealed that two fetuses in one litter had meningocele in the high dose group. This finding was not observed in the historical controls. A higher incidence of meningocele was also reported in the range-finding study in rats where the dose of 240 mg/kg/day resulted in 12 out of 291 fetuses and seven out of 24 litters with meningocele. Visceral examinations of fetuses revealed that the percentage of litters and fetuses with renal alterations such as hydronephropathy was significantly increased in the 40 mg/kg/day group relative to control. Skeletal examinations showed significant increases in the percent of fetuses/litters with variations and retardations in the 40 and 120 mg/kg/day dose groups compared to controls (Table 2). Slight increases for these same effects were observed at 10 mg/kg/day which may be treatment-related.

TABLE 2

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. Asym Fused w\sternum	-	2(2)	12(11)	3(3)
Thoracic vert. Body Dumb-bell Shaped Notch in Cartil. - Cranial	9(8)	14(10)	17(13)	9(9)
Thoracic Vert. Bodies Dumbbell Shaped Notches in Cartil.-Cranial/Caudal	1(1)	3(3)	2(2)	4(4)
Variations				
Thoracic Vert. Bodies Dumb-bell Shaped, Cartil.	17(8)	22(12)	49(19)	62(21)

(continued)

Retardations				
Interparietal Inc. Ossif. Cartil. Present	1(1)	8(4)	20(11)	15(10)
Sternebrae Not Ossif. Cartil. Present	12(5)	7(6)	10(8)	35(13)
Metacarpal Inc. Ossif. Bilat. Cartil. Present	-	1(1)	6(4)	13(8)
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**

* Significantly different from control ($p \leq 0.05$).
** Significantly different from control ($p \leq 0.01$).

This study was classified as Core-Supplementary Data based on several deficiencies which included the evaluation of a smaller percentage of each litter for visceral alterations than required by OPP test guidelines and the apparent lack of a NOEL for developmental toxicity. The nominal dose level which is the LEL (10 mg/kg/day) is equal to 4.2 mg a.i./kg/day.

2. Rat- G.Y. Chegrinets, V.E. Karmazin, V.E. Rybchinskaya, R.P. Petrova, G.I. Leonskaia. "Study of the Influence of Carbathion on Embryogenesis of White Rats", published in Gig. Sanit. (Russian) May (5): 40-1.

An unspecified number of White rats (strain not reported)

were administered either 0, 3-4.5 or 90 mg/kg/day of metam sodium by daily gavage in water solution throughout pregnancy. On the 20th day of pregnancy, rats were sacrificed by decapitation and fetuses were examined for external, visceral and skeletal defects. No changes were reported in the low dose group. An increased rate of post-implantation loss was reported at the high dose level. No external malformations were reported. Effects on skeletal ossification (unspecified) were reported at the high dose level. Maternal toxicity was apparently not assessed.

3. Rabbit - BASF Aktiengesellschaft (Testing Facility) Agricultural Research and Development D-6103 Limburgerhof, West Germany Study # 38R0232/8579; 7/15/1987.

Nominal dose levels of 0, 10, 30 and 100 mg/kg of an aqueous solution of metam sodium were administered by gavage to Himalayan rabbits on gestation days 6 through 18. Dams were sacrificed on day 29 of gestation, necropsied and evaluated by gross pathology. Fetuses were weighed, sexed, and examined macroscopically for external findings; viability, as well as individual placental weights were recorded and the condition of fetal membranes and fluids was determined. Upon sacrifice, the abdomen and thorax of each fetus was opened for examination of internal organs; heads were X-rayed, fixed in Bouin's Solution and examined by Wilson's Technique; all fetuses were X-rayed for skeletal examination and trunks were placed in ethyl alcohol for possible staining.

No maternal mortality was reported in this study. A dam from the control group was sacrificed after premature delivery while one high dose and two low dose dams were sacrificed due to gavage error. Body weight gains were significantly reduced in the high dose tested during the dosing period, post dosing period, entire gestation period and during dosing and post dosing period.

As shown in Table 3 (Caesarean Section Observations), developmental toxicity in the form of increased resorptions, decrease in the number of live fetuses and an increase in post-implantation loss was observed in the mid and high dose groups compared to controls.

Table 3: Cesarean Section Observations

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
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**
Resorptions/Dam (%)	3.65	8.06	12.36	54.93
Mean Fetal Weight (gm)	14.00	13.00	14.00	14.00
Pre-implantation Loss (%)	17.5	8.9	24.3	8.6
Post-implantation Loss (%)	4.7	7.6	13.1	55.1

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

Based on reduced body weight gains, the PRC considered the maternal NOEL to be the nominal dose level of 30 mg/kg/day. This is equal to 12.6 mg a.i./kg/day. The NOEL for developmental toxicity was established as the nominal dose level of 10 mg/kg/day based on increased number of dead implantations, reduced number of fetuses, and increased post-implantation loss in the mid and high dose groups. This is equal to 4.2 mg/kg/day.

External examinations of fetuses revealed that one fetus in one litter had meningocele in the high dose group. Spina bifida was also observed in the high dose group in one fetus. Although the incidence of meningocele and spina bifida was very low, these observations may be treatment related since they were also observed in the rangefinding study and rat developmental toxicity study while concurrent and historical control data did not present evidence for these findings. Visceral examinations did not reveal any treatment related effects. The skeletal examinations were carried out by X-ray, a method that has not been validated.

This study was classified as Core-Supplementary data due primarily to the use of a procedure for skeletal examination that has not been validated.

E. Other Aspects of Toxicity

A. Acute, Subchronic and Chronic Toxicity Data

The acute oral LD_{50} in rats is 226 mg/kg in males and 231 mg/kg in females; the acute dermal LD_{50} in male and female rabbits is 1012 mg/kg. The acute inhalation LC_{50} in rats is greater than 4.7 mg/L. Metam sodium is a mild eye irritant, a moderate to severe dermal irritant and a skin sensitizer. There are no data available on the subchronic and chronic toxicity of metam sodium.

B. Reproduction Studies

There are no data available on the reproductive toxicity of metam sodium.

C. Mutagenicity Studies

Metam sodium was negative for bacterial gene mutation in Salmonella typhimurium strains when tested at levels up to 2500 ug/plate with and without metabolic activation. Metam sodium gave a positive response in an in vitro cytogenetic assay using cultured human lymphocytes with or without metabolic activation. It was, however, negative in an in vitro Chinese hamster bone marrow cytogenetic assay. Metam sodium was also negative in the Unscheduled DNA Synthesis Assay using primary rat hepatocytes.

D. Metabolism/Pharmacokinetic Data

Administration of ^{14}C-metam sodium to male and female rats either as a single oral dose (10 mg/kg) or as a high single oral dose (100 mg/kg) resulted in its rapid absorption through the gastrointestinal tract and distribution to all examined tissues. Metam-sodium was extensively metabolized and excreted. Over 80 percent of the administered radioactivity was excreted within 24 hours in both sexes. Elimination was mainly through the urine and the expired air with lesser amounts in the feces in both sexes either at the low or the high dose tested. Elimination of radioactivity after 24 hours appeared to be very slow resulting in a half-life ranging from 61 to 74 hours. Peak plasma concentrations of metam sodium derived radioactivity were observed within one hour after administration in male and female rats at both dose levels tested. Tissue concentrations were highest in thyroid gland, liver and kidneys seven days after administration. No parent compound was detected in the urine or the expired air. Metabolites identified in the expired air were methyl isothiocyanate (MITC), CO_2, CS_2/COS. In urine, up to five metabolites were isolated but only one of these metabolites was positively identified as N-acetyl-S-(N-methylthiocarbamoyl)-L-cysteine, presumably the conjugation product of MITC and glutathione.

E. Structure Activity Relationships

Metam sodium is readily metabolized mainly to methyl isothiocyanate (MITC) and carbon disulfide. Carbon disulfide is a potent developmental toxicant. MITC has been tested for developmental toxicity in the rat and rabbit. In both species, study deficiencies preclude a definitive assessment of developmental toxicity. However, in the rat developmental toxicity (growth retardation and variations), appeared to occur at 25 mg/kg, a level which also induced maternal toxicity. The tentative NOEL for maternal and developmental toxicity is 5 mg/kg. In the rabbit, developmental toxicity was observed at 5 mg/kg in the form of growth retardation, and an increased incidence of bilateral lens opacity and fused sternebrae in the absence of maternal toxicity. A tentative NOEL can be established at 3 mg/kg.

Metam sodium is structurally related to several compounds belonging to the general class of dithiocarbamates (all derivatives of dithiocarbamic acid). Partial developmental and/or reproductive toxicity data exist for some of these chemicals including Dazomet, Maneb, Zineb, Metiran, Nabam, Ziram, Vancide, Busan-85, and Thiram. From the available data, however, only Nabam, Thiram, Vancide, Busan-85 and Dazomet appear to be of concern for developmental toxicity. Carbon disulfide appears to be a common metabolite for these chemicals. However, of the above chemicals, only Dazomet is known to be metabolized to MITC.

Busan-85: In a rabbit developmental toxicity study with Busan-85, the developmental NOEL was found to be 12.8 mg/kg and LEL was 38 mg/kg based on malalignment of sternebrae, post-implantation loss and decreased fetal body weight. The maternal NOEL and LOEL were 12.8 and 38 mg/kg/day, respectively, based on clinical signs of toxicity and possible increases in maternal death and abortions.

Dazomet: In a rabbit developmental toxicity study with Dazomet, the developmental NOEL was tentatively established at 25 mg/kg and LOEL at 50 mg/kg based on decreased live fetuses/dam, increased total resorptions and resorptions/dam and increased post-implantation loss. The maternal NOEL and LOEL were found to be 12.5 and 25 mg/kg, respectively, based on decreased body weight gain.

Nabam: In a rabbit developmental toxicity study the developmental NOEL was lower than 10 mg/kg (the LDT) and the LEL 10 mg/kg based on hydrocephaly. Maternal NOEL and LEL were 10 and 100 mg/kg, respectively, based on reduced body weight gain.

In a rat developmental toxicity study with Nabam the developmental NOEL was established at 7.5 mg/kg (LDT) and the LEL at 75 mg/kg based on the increased incidence of incompletely ossified cranial bones. The maternal NOEL and LEL were also set at 7.5 and 75 mg/kg based on body weight gain decrement.

Thiram: In a rat developmental toxicity study the developmental NOEL was lower than 12.5 mg/kg (LTD) and the LEL was equal to or lower than 12.5 mg/kg, based on delayed skeletal ossification. Maternal NOEL and LEL were 12.5 and 25 mg/kg, respectively, based on decreased body weight gains and food consumption. Developmental effects observed at the 25 mg/kg and higher dose levels (50 and 100 mg/kg) included hydrocephaly, anophthalmia and microphthalmia).

Vancide: In a rat developmental toxicity study the developmental NOEL was found to be 2 mg/kg and the LEL was 20 mg/kg for possible ossification and fetal weight decreases. The maternal NOEL and LEL were 2 and 20 mg/kg, respectively, based on decreased body weight.

F. Issues and Recommendations

1. The data base for metam sodium in the area of developmental toxicity is considered to be poor. Deficiencies exist in studies conducted in both the rat and rabbit and a reproductive toxicity study is not available for this chemical.

2. The Committee concluded that the developmental toxicity study in rat (submitted by the registrant) indicates a variety of forms of developmental toxicity at a nominal dose level of 120 mg/kg/day (increased variations, retardations and anomalies, post-implantation loss and two instances of meningocele (in a single litter) which appear to be compound related. At the nominal dose level of 40 mg/kg and to a lesser extent at 10 mg/kg (equal to 4.2 mg a.i./kg/day), an increased incidence of skeletal anomalies was observed which appears to be compound-related. The committee concluded that the increase in post-implantation loss at 10 mg/kg/day was probably not compound-related based on examination of individual animal data and the results of the range finding study. However, historical control data for skeletal anomalies are needed prior to making a final determination on the NOEL for developmental toxicity in this study. The NOEL for maternal toxicity in this study is 10 mg/kg (equal to 4.2 mg a.i./kg/day) based on decreased body weight gain.

3. The published developmental toxicity study in the rat (Chegrinets et al., 1990) provides support for an increased incidence of post-implantation loss being associated with compound administration at high dose levels (90 mg/kg/day in this study). However, the information available in the publication was not considered adequate to allow a full evaluation of this study.

4. The developmental toxicity study in the rabbit shows developmental toxicity in the form of increased post-implantation loss at nominal dose levels of 30 mg/kg/day and greater. A single instance of spina bifida and a single instance of meningocele may be compound-related at the 100 mg/kg/day dose level. The NOEL for developmental toxicity in the rabbit is 10 mg/kg/day (equal to 4.2 mg a.i./kg/day). Based upon decreased body weight gain during the dosing period, the NOEL for maternal toxicity is 30 mg/kg/day (equal to 12.6 mg a.i./kg/day).

5. Metam sodium is metabolized to carbon disulfide, a potent developmental toxicant. A second metabolite, MITC, may also induce developmental toxicity at levels of 5-25 mg/kg/day, although the studies for MITC are not considered definitive. Certain other related compounds (Nabam, Ziram and Vancide) have NOELs for developmental toxicity similar to those cited above for metam sodium.