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WASHINGTON, D.C. 20460

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JAN 18 1995

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: RfD/Peer Review Report of Metam Sodium [Sodium N-methyldithiocarbamate].

CASRN. 6734-80-1
EPA Chem. Code: 039003
Caswell No. 780

FROM: George Z. Ghali, Ph.D. *G. Ghali*
Manager, RfD/QA Peer Review Committee
Health Effects Division (7509C)

THRU: William Burnam *W Burnam*
Chairman, RfD/QA Peer Review Committee
Health Effects Division (7509C)

TO: Leonard Cole, PM 21
Herbicide-Fungicide Branch
Registration Division (7505C)

The Health Effects Division-RfD/Peer Review Committee met on December 1, 1994 to discuss and evaluate the existing and/or recently-submitted toxicology data in support of Metam Sodium (also known as Vapam, Metham and SMDC) registration and to assess a Reference Dose (RfD) for this chemical.

Material available for review consisted of data evaluation records (DERs) for a combined chronic toxicity/carcinogenicity study in rats (83-5 or 83-1a and -2a), a carcinogenicity study in mice (83-2b), a one-year feeding study in dogs (83-1b), developmental toxicity studies in rats and rabbits (83-3a and -3b), a multi-generation reproductive toxicity study in rats (83-4), subchronic toxicity studies in rats, mice (82-1a) and dogs (82-1b), and a subchronic neurotoxicity study in rats (82-7).

A. Chronic and Subchronic Toxicity:

The Committee considered the chronic toxicity phase of the combined chronic toxicity/carcinogenicity study in rats (83-1a, MRID No. 43275802, 43315501) and the one-year feeding study in dogs (83-1b, MRID No. 43275801) to be acceptable and the data evaluation records for these studies (HED Doc. No. 011192) to be adequate. According to the data evaluation record, the NOEL/LOEL in the chronic toxicity study in dogs were set at 0.1 and 1.0 mg/kg/day, respectively, for females. The Committee questioned the biological



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significance of marginal increase in serum alanine aminotransferase (ALT or SGPT) observed in females of the 1 mg/kg/day group especially in the absence of statistical significance and/or histopathological alteration. Therefore, the Committee recommended revising the NOEL for females from 0.1 mg/kg/day to 1.0 mg/kg/day. It should be noted that, in the subchronic toxicity study in dogs (82-1b, MRID No. 42600001), toxic effects were observed at all dose levels of 1, 5, and 10 mg/kg/day, but were primarily evident at the 5 and 10 mg/kg/day dose levels. These toxic effects included decreased body weight and body weight gain in males and females at 10 mg/kg/day, hematologic alterations (increased cell volume, cell hemoglobin, neutrophils, and monocytes and decreased mean corpuscular hemoglobin concentration) at 5 and 10 mg/kg/day, significant decrease in plasma ALT, AST, ALP and GGT at 5 and 10 mg/kg/day (including significantly increased ALT in females at 1 mg/kg/day), increased amounts of blood, urobilinogen, bilirubin, and protein in urine at 5 and 10 mg/kg/day, and microscopic evidence of hepatitis at 5 and 10 mg/kg/day.

The Committee considered the subchronic toxicity studies in rats, mice (82-1a, MRID No. 42117302; 42117301) and dogs (82-1b, MRID No. 42600001) to be acceptable as supplemental information and the data evaluation records of these studies (HED Doc. No. 010180; 009501; 010028) to be adequate as presented.

Subsequent to the meeting, the subchronic neurotoxicity study in rats (82-7, MRID No. 432248801) was reviewed and was considered acceptable and the data evaluation record for this study (HED Doc No. 011202) was considered adequate. A recommendation was made to include more data tables in the data evaluation record. Marginal toxicity was observed at the high dose, but adequate to define an LOEL for the study (w. Sette, 1/10/1995).

B. Carcinogenicity:

The Committee briefly discussed the carcinogenicity phase of the combined chronic toxicity/carcinogenicity study in rats (83-2a, MRID No. 43275802, 43315501) and the carcinogenicity study in mice (83-2b, MRID No. 43233501). The Committee concluded that the carcinogenicity data warrant further discussion by the Health Effects Division-Carcinogenicity Peer Review Committee (HED-CPRC). The Committee recommended referral of the carcinogenicity issue to the HED-CPRC for weight of the evidence evaluation based on possible increased incidence of hemangiomas/hemangiosarcomas in male rats and increased incidences of angiosarcomas in male and female mice.

C. Reproductive and Developmental Toxicity:

The Committee considered the reproductive toxicity study in rats (83-4, MRID No. 43136101) to be acceptable and the data evaluation record (HED Doc. No. 010928) to be adequate. Decreased

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testes and/or epididymides weight (absolute) were observed for high-dose adults and for F1 and F2 pups. Also, increased male infertility was suspected in F1 treated groups. Even though the histopathological examination does not identify a lesion, these data hint at male reproductive toxicity which becomes more severe in the second generation. However, none of these changes were statistically significant and they were not seen in the chronic toxicity study in rats at comparable dosages.

The Committee considered the developmental toxicity studies in rats (83-3a, MRID No. 42983701) and rabbits (83-3b, MRID No. 42963101) to be acceptable and the data evaluation records for these studies (HED Doc. No. 010693) to be adequate. The Committee generally agreed with the reviewer's evaluation and interpretation of data. However, the Committee thought that the increased variations observed in the 5 mg/kg/day dose group in the rat developmental toxicity study might be "suggestive" of a treatment-related effect.

There were two other developmental toxicity studies available in rats (83-3a, 1987, MRID No. 41577101, 42170101, 92097012) and rabbits (83-3b, 1987, MRID No. 40330901, 92097013). These studies have already been evaluated by the Health Effects Division-Reproductive/Developmental Toxicity Peer Review Committee in their meeting of October 15, and December 12, 1991. Therefore, these studies were not discussed in detail by the RfD/QA Peer Review Committee. At the time of the Reproductive/Developmental Toxicity Peer Review, the only studies available for review were the 1987 developmental toxicity studies in rats and rabbits described above. Although these studies were considered to be deficient, they were adequate to determine that Metam Sodium was associated with developmental toxicity. In the rat, developmental toxicity (manifested as skeletal variations, alterations and anomalies) was suggested at dose levels as low as 4.2 mg/kg/day. Maternal NOEL was set at 4.2 mg/kg/day and developmental NOEL was set at or below 4.2 mg/kg/day. In the rabbit, the developmental toxicity NOEL was set at 4.2 mg/kg/day based on post-implantation loss observed at 12.6 mg/kg/day. The maternal NOEL was set at 12.6 mg/kg/day.

The Committee concluded that the additional reproductive and developmental toxicity studies submitted after the reproductive/developmental toxicity peer review, supported the previous determination by the Reproductive/Developmental Toxicity Peer Review Committee, that Metam Sodium is developmental toxicant in both rats and rabbits. In addition, reduced fertility of F1 males and decreased testes and/or epididymis weights in treated adults and weanling rats were suggestive of potential reproductive toxicity in males. However, this observation was not supported statistically or histopathologically. Furthermore, this effect has not been observed in the long-term study in rats.

In essence, the NOEL/LOEL established in the more recent

developmental toxicity studies, i. e. the 1993 studies, confirm the levels of developmental toxicity that were observed previously in the 1987 studies, although the specific findings were not precisely equivalent. In the old studies, there was a concern regarding meningocele observed in both rats and rabbits; one appeared at the high dose tested in the new rat study (1993) as well, and three incidences of internal hydrocephaly, another neural tube defect occurred at the same dose. The data evaluation record for the 1993 rabbit study does not present low incidence external/visceral findings. But because neural tube defects are not mentioned, one can probably assume they were not observed in the new rabbit study.

The 1987 study in rats, skeletal variations included no mention of the calcaneum or odontoid, and vertebral variations were mostly concentrated in the thoracic vertebrae, rather than the cervical vertebrae which is the location of most of the variations in this study. This may be the result of variations in technician training. The alterations in the cervical vertebrae observed in the rat study are also seen in the new (1993) rabbit study. Skeletal data from the 1987 study was conducted by X-ray techniques; therefore, there are no skeletal findings that can be compared with those observed on this study.

The Committee concluded that: 1) the treatment was associated with reproductive/developmental effects 2) developmental neurotoxicity studies might be required based on the presence (even though at low level) of suspected neural tube defects/brain malformations in rats and rabbits, and 3) the data warrant further discussion by a reproductive/developmental toxicity Ad Hoc group or a subcommittee in order to incorporate the additional data into the peer review report of 1992.

D. Reference Dose (RfD):

The Committee recommended that an RfD be established based on a chronic toxicity study in dogs with a NOEL of 1.0 mg/kg/day, the highest dose level tested. The Committee questioned and discounted the biological significance of marginal increase in serum alanine aminotransferase (ALT or SGPT) observed in one male of the 1 mg/kg/day group, especially in the absence of statistical significance and or histopathological alteration. It should be noted that, in the subchronic toxicity study in dogs, toxic effects were observed at all dose levels of 1, 5, and 10 mg/kg/day, but were primarily evident at the 5 and 10 mg/kg/day dose levels. These toxic effects included decreased body weight and body weight gain in males and females at 10 mg/kg/day, hematologic alterations (increased cell volume, cell hemoglobin, neutrophils, and monocytes; decreased mean corpuscular hemoglobin concentration) at 5 and 10 mg/kg/day, significant decrease in plasma ALT, AST, ALP and GGT at 5 and 10 mg/kg/day (including significantly increased ALT in females at 1 mg/kg/day), increased amounts of blood, urobilinogen, bilirubin, and protein in urine at 5 and 10

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mg/kg/day, and microscopic evidence of hepatitis at 5 and 10 mg/kg/day. An uncertainty factor (UF) of 100 was applied to account for inter-species extrapolation and intra-species variability. On this basis, the RfD was calculated to be 0.01 mg/kg/day.

Because of the closeness of the systemic NOELs for the mouse carcinogenicity study and the dog long-term study, it was suggested to include the mouse study as a co-critical study. The NOEL for systemic toxicity in the mouse study was set at 1.6 mg/kg/day.

It should be noted that this chemical has not been reviewed by the FAO/WHO joint committee on pesticide residue (JMPR).

E. Individuals in Attendance:

Peer Review Committee members and associates present were William Burnam (Chief, SAB, RfD/Peer Review Committee Co-Chairman), Reto Engler (Senior Science Advisor, HED, RfD/Peer Review Committee Co-Chairman), George Ghali (Manager, RfD/Peer Review Committee), Karl Baetcke (Chief, TB I), Marcia Van Gemert (Chief, TB II), Rick Whiting, Henry Spencer, Esther Rinde, Susan Makris, David Anderson and Alberto Protzel. In attendance also were Kerry Dearfield of SAB, HED and Stephen Dapson of TB II, HED as observers.

Scientific reviewer (Committee or non-committee member(s) responsible for data presentation; signature(s) indicate technical accuracy of panel report)

Tim McMahon *[Signature]*

Mike Ioannou *[Signature]*

Respective branch chief (Committee member; Signature indicates concurrence with the peer review unless otherwise stated)

Marcia Van Gemert *[Signature]*

- CC: Richard Schmitt
- Stephanie Irene
- Marcia Van Gemert
- Mike Ioannou
- Tim McMahon
- Debra Edwards
- Albin Kocialski
- Beth Doyle
- Kerry Dearfield
- RfD File
- Caswell File

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F. Material Reviewed:

1. Rattray, N. J. (194). Metam Sodium: Two-year drinking study in rats. MRID No. 43275802, 43315501, HED Doc. No. 011192. Classification: Core-minimum data. This study satisfies data requirement 83-5 or 83-1a and -2a of Subpart F of the Pesticide Assessment Guideline for chronic toxicity/carcinogenicity testing in rats.
2. Horner, S. A. (1994). Metam Sodium: Two-year drinking study in mice. MRID No. 43233501, HED Doc. No. 011139. Classification: Core-minimum data. This study satisfies data requirement 83-2b of Subpart F of the Pesticide Assessment Guideline for carcinogenicity testing in mice.
3. Brammer, A. (1984). Metam Sodium: One-year oral toxicity study in dogs. MRID No. 43275801, HED Doc. No. 011192. Classification: Core-minimum data. This study satisfies data requirement 83-1b of Subpart F of the Pesticide Assessment Guideline for chronic toxicity testing in dogs.
4. Milburn, G. M. (1993). Metam Sodium: multigeneration study in the rat. MRID No. 43136101, HED Doc. No. 010928. Classification: Core-minimum data. This study satisfies data requirement 83-4 of Subpart F of the Pesticide Assessment Guideline for reproductive toxicity testing in rats.
5. Tinston, D. J. (1993). Metam Sodium: Developmental toxicity study in rats. MRID No. 42983701, HED Doc. No. 010693. Classification: Guideline data. This study satisfies data requirement 83-3a of Subpart F of the Pesticide Assessment Guideline for developmental toxicity testing in rats.
6. Hellwig, J. and Hildebrand, B. (1987). Report on the study of parental toxicity of Metam Sodium in rats after oral administration (gavage). MRID No. 41577101, 42170101, 92097012, HED Doc. No. 008520, 009030. Classification: Core-supplementary data. This study does not satisfy data requirement 83-3a of Subpart F of the Pesticide Assessment Guideline for developmental toxicity testing in rats.
7. Hodge, M. C. E. (1993). Metam Sodium: Developmental toxicity study in rabbits. MRID No. 42963101, HED Doc. No. 010693. Classification: Core-minimum data. This study satisfies data requirement 83-3b of Subpart F of the Pesticide Assessment Guideline for developmental toxicity testing in rabbits.
8. Hellwig, J. (1987). Report of the study of the prenatal toxicity of Metam Sodium (aqueous solution) in rabbits after oral administration (gavage). MRID No. 40330901, 92097013, HED Doc. No. 008520, 009030. Classification: Core-supplementary data. This study does not satisfy data

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requirement 83-3a of Subpart F of the Pesticide Assessment Guideline for developmental toxicity testing in rats.

9. Allen, S. L. (1991). Metam Sodium: 90-day drinking water study in rats. MRID No. 42117302, HED Doc. No. 010180. Classification: Core-supplementary data. This study does not satisfy data requirement 82-1a of Subpart F of the Pesticide Assessment Guideline for subchronic toxicity testing in rabbits.
10. Brammer, A. (1992). Metam Sodium: 90-day oral dosing study in dogs. MRID No. 42600001, HED Doc. No. 010028. Classification: Core-supplementary data. This study does not satisfy data requirement 82-1b of Subpart F of the Pesticide Assessment Guideline for subchronic toxicity testing in dogs.
11. Whiles, A. J. (1991). Metam Sodium: 90-day drinking water study in mice with a 28-day interim kill. MRID No. 42117301, HED Doc. No. 009501. Classification: Core-supplementary data. This study was performed as a dose setting for the carcinogenicity study in mice and was considered acceptable for the intended purpose but not to satisfy data requirement 82-1a of Subpart F of the Pesticide Assessment Guideline for subchronic toxicity testing in mice.
12. Allen, S. L. (1994). Metam Sodium: subchronic neurotoxicity study in rats. MRID No. 43248801, HED Doc. No. 011202. Classification: Core-minimum data. This study satisfies data requirement 82-7 of Subpart F of the Pesticide Assessment Guideline for subchronic neurotoxicity testing in rats.

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NOTE

TO: George Ghali, Tim McMahon

FROM: Bill Sette

RE: Comments after the RfD meeting on the 90 day Metam Sodium Neurotoxicity Study.

Enclosed are suggested text for the RfD writeup and a few comments on the study and DER, none very major.

Suggested RfD Report Text

There was a 90 day Neurotoxicity study in rats (MRID No. 43248801) and a DER (HED Doc No. 011202) for that study. The DER was considered adequate and the conclusions of the review sound, with the stipulation that data tables be added to the file for the measures in Tables 9-15 of the study. While the toxicity of this high dose is marginal, based on previous data and other studies, its was a reasonable estimate of a toxic dose.

Comments

I recall that the registrant agreed to perform an NTE assay on this material and the DCI should not be considered to be satisfied until we have that data. (Check on AChE data too).

It would have been more useful to express the NOEL and LOEL in mg/kg rather than mg/l which is less transferable to other settings.

The logic of how a decrease in body weight gain being greater than the decrease in food consumption which corresponded to the decrease in body weight is not apparent to me. It seems clear for this irritating material that its ingestion either through food or water causes decreases in food and water consumption. It is also clearly an irritant. This review rather deftly and intelligently addresses this concern in its suggestion that the toxicity of the effect on body weight gain is not clear.