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OFFICE OF  
PREVENTION, PESTICIDES  
AND  
TOXIC SUBSTANCES

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**MEMORANDUM**

SUBJECT: Data evaluation records, updated executive summaries, and toxicology information for *Metam Sodium* (PC Code 039003); *Methyl isothiocyanate* (MITC, PC Code 068103); and *Carbon disulfide* (PC Code 600017)

FROM: Anna Lowit, Ph.D., Toxicologist  
Judy Facey, Ph.D., Toxicologist  
Reregistration Branch 2  
Health Effects Division (7509C)

THRU: Alan Nielsen, Branch Senior Scientist  
Reregistration Branch 2  
Health Effects Division (7509C)

TO: Carol Christensen, Risk Assessor  
Reregistration Branch 2  
Health Effects Division (7509C)

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The present memo contains a summary of new studies on genotoxicity, acute toxicity, and developmental toxicity submitted by Taminico on MITC (Table 1) followed by lists of the data evaluation records (DERs) and/or revised executive summaries have been produced for metam sodium, MITC, and carbon disulfide. All DERs and updated executive summaries are attached.

I. Summary of MITC studies recently submitted by Taminico.

Table 1. Summary of toxicology studies recently submitted by Taminico		
MRID No.	Study Type	Summary
45919407	Acute oral toxicity in rat	LD <sub>50</sub> = 103-147 mg/kg Confirms Toxicity Category II in MRID no. 00162331
45919408	Acute dermal toxicity in rat	LD <sub>50</sub> = 1290 mg/kg Inconsistent with MRID nos. 00162330 and 42442501. Toxicity Category will remain I.
45919409	Dermal irritation in rabbit	Confirms results from MRID no. 00162328 "Irritating"
45919410	Acute inhalation toxicity in rat	LC <sub>50</sub> = 0.54 g/m <sup>3</sup> Confirms results of MRID no. 00115178; MRID no. 00162327 is considered an outlier (see below).  Toxicity Category is revised to be II.
45919411	Sensitizing potential in guinea pigs	Positive for sensitization
45919412	Ames test	Negative; confirm results of MRID no. 41221410
45919413	Recombination assays with <i>B. subtilis</i>	Negative; tested up to toxic doses of 5004 µg/plate Confirms negative results of MRID no. 41221410
45919414	<i>In vitro</i> cytogenetics	Negative up to 1 µg/mL with activation and up to 0.5 µg/mL without activation Confirms results of MRID no. 41221412
45919417	Developmental toxicity in rats	Unacceptable/guideline; DER attached.
45919418	Developmental toxicity in rabbits	Unacceptable/guideline; DER attached.

Previous reviews of MITC by OPP's Health Effects Division (HED) have indicated that the acute inhalation  $LC_{50} < 0.0296$  mg/L and was therefore categorized as Acute Toxicity Category I for the inhalation route. However, based on the data provided in MRID 4599410, this has been revised. The  $LC_{50}$  of  $0.54$  g/m<sup>3</sup> will replace the previous value. The following text was extracted from California's Department of Pesticide Regulation human health assessment for MITC (August, 2002). This text summarizes the existing acute inhalation studies and provides an explanation for the current revision.

"Studies of acute inhalation exposure to MITC in animals generate a conflicting picture of the resultant toxicity, particularly in rats. Ullman (1985b), using Wistar rats, showed that all animals died within 30 minutes of nose-only exposure to  $29.6$  mg/m<sup>3</sup> (~10 ppm) MITC. However, there was no description of how this value was obtained, nor was there an indication as to whether it was nominal or analytically derived. Associated clinical signs included restlessness and excitement. In contrast,  $1900$  mg/m<sup>3</sup> (~633 ppm) was the  $LC_{50}$  value generated in the 1-hour whole-body exposure study of Clark and Jackson (1977) using Sprague-Dawley rats. No animals died at  $630$  mg/m<sup>3</sup>, a dose 21-fold higher than the dose causing 100% lethality in the Ullman study. Clinical signs included initial hyperactivity followed by hypoactivity, eye irritation, dyspnea and, at  $2200$  mg/m<sup>3</sup> and above, convulsions. The same group reported a 4-hour  $LC_{50}$  of  $540$  mg/m<sup>3</sup> (~180 ppm) in Sprague-Dawley rats (Jackson *et al.*, 1981), 18-fold higher than the dose required to kill all animals in the Ullman study, but similar (considering the increased exposure time) to the finding of Clark and Jackson (1977). Finally, Nesterova (1969) claimed that no rats died at MITC doses of at least  $79.1$  mg/m<sup>3</sup> (~26.4 ppm). Again, the strain was undefined. Nesterova also showed that 80-100% of mice died at  $75-79$  mg/m<sup>3</sup> (~25-26 ppm) and that no cats died at  $0.5$  mg/m<sup>3</sup> (~0.167 ppm). Unfortunately, because the Nesterova study was bereft of experimental and methodologic detail, its quantitative aspects are considered of little use for regulatory purposes. There was no clear explanation for the disparity in the rat inhalation data. Two subchronic inhalation studies are described in section V.A. [of DPR, August, 2002; See TXR no. 0052321] in which Wistar rats (the strain used in the Ullmann acute inhalation study) were exposed on a daily basis to MITC air concentrations as high as 45 ppm. No deaths were observed in those studies, even at the highest concentrations and even after as long as 13 weeks of daily exposure (Klimisch *et al.*, 1987; Roskamp, 1979). The Ullmann study is therefore viewed as an outlier that, for unexplained reasons, may be anomalous. The studies of Clark and Jackson (1977) and Jackson *et al.* (1981) in Sprague-Dawley rats provide full methodologic and toxicologic accounts, and are consistent with each other and with the later subchronic studies on the Wistar rat. For the present they are deemed the most reliable acute lethality studies."

#### References for the above text

00162331 Ullmann, L. (1985) Acute Oral Toxicity (LD50) Study with Methylsenfoel (MITC) in Rats: RCC Project No. 042647. Unpublished study prepared by Research & Consulting Co., AG. 45 p.

00162327. Ullmann, L. (1985) 4-Hour Acute Vapour Inhalation Toxicity (MITC) in Rats: Project 042660. Prepared by RCC Research and Consulting Co. AG. 7 p.

42365605 Ullmann, L. (1985) Acute Inhalation Toxicity (LD50) Study with Methylisothiocyanate (MITC) in Rats: Supplement No. 1: Lab Project Number: 042660. Unpublished study prepared by Research & Consulting Co., AG. 12 p.

00060304 Clark, G.C.; Jackson, G.C. (1977) Vorlex: Acute Inhalation Toxicity: One Hour LC<sub>50</sub> in Rats. (Unpublished study received Dec 15, 1977 under 2139-55; prepared by Huntingdon Research Centre, England, submitted by Nor-Am Agricultural Products, Inc., Naperville, Ill.; CDL:232496-B)

45919410 Jackson, G.; Clark, G.; Prentice, D.; et al. (1981) Methyl Isothiocyanate: Acute Inhalation Toxicity in Rats--4 Hour Exposure: Lab Project Number: 81/082: 378/801109. Unpublished study prepared by Huntingdon Research Center. 115 p.

The revised acute toxicity table is shown below (Table 2). [Note: The Acute Toxicity table for MITC included in the HIARC Report (TXR n. 0052291) is incorrect.

Table 2: Acute Toxicity of Methyl Isothiocyanate (PC Code 068103)				
Guideline No.	Study Type	MRID #(S)	Results	Toxicity Category
81-1	Acute Oral-Rat	00162331	LD <sub>50</sub> = 82 mg/kg ♂ 55 mg/kg ♀	II
81-2	Acute Dermal-Rat	00162330 42443501	LD <sub>50</sub> = 136-436 mg/kg ♂ 181 mg/kg ♀	I
81-3	Acute Inhalation-Rat	45919410	LC <sub>50</sub> = 0.54 mg/L	II
81-4	Primary Eye Irritation	00162328	corrosion of the cornea and conjunctivae	I
81-5	Primary Skin Irritation	00162329	all animals died within one hour	I
81-6	Dermal Sensitization	459194101	positive for sensitization in guinea pig	

**II. List of DERs and/or Updated Executive Summaries considered for metam sodium, MITC, and carbon disulfide (see attached)**

**A. Metam Sodium:**

162041 Knapp, H. (1983) Subchronic Inhalation Study with Vapam Technical in Rats: T-11006. Unpublished study prepared by Stauffer Chemical Co. 296 p.

40330901 Hellwig, J. (1987) Report on the Study of the Prenatal Toxicity of Metam-Sodium (Aqueous Solution) in Rabbits after Oral Administration (Gavage): Final Report: Registration Document No. (BASF) 87/0255. Unpublished study prepared by BASF Aktiengesellschaft. 258 p.

41577101 Hellwig, J.; Hildebrand, B. (1987) Report on the Study of the Prenatal Toxicity of Metam Sodium in Rats after Oral Administration (Gavage): Lab Project Number: 87/0128. Unpublished study prepared by BASF Aktiengesellschaft. 387 p.

42117301 Whiles, A. (1991) Metam Sodium: 90 Day Drinking Water Study in Mice with a 28 Day Interim Kill: Lab Project Number: CTL/P/3185: PM08 08. Unpublished study prepared by ICI Central Tox Lab. 517 p.

42117302 Allen, S. (1991) Metam Sodium: 90 Day Drinking Water Study in Rats: Lab Project Number: CTL/P/3213: PR0797. Unpublished study prepared by ICI Central Tox Labs, Inc. 414 p.

42600001 Brammer, A. (1992) Metam Sodium: 90-day Oral Dosing Study in Dogs: Lab Project Number: CTL/P/3679. Unpublished study prepared by ICI Central Toxicology Lab. 349 p.

42963101 Hodge, M. (1991) Metam Sodium: Developmental Toxicity Study in the Rabbit: Lab Project Number: CTL/P/4035: RB0623. Unpublished study prepared by Zeneca Central Toxicology Lab. 309 p.

42977802 Lamb, I. (1993) An Acute Neurotoxicity Study of Metam-Sodium in Rats: Final Report: Lab Project Number: WIL-188009: WIL-188010: WIL-99034. Unpublished study prepared by WIL Research Labs, Inc. 1136 p.

42983701 Tinston, D. (1993) Metam Sodium Developmental Toxicity Study in the Rat: Lab Project Number: CTL/P/4052: RR0624. Unpublished study prepared by Zeneca Central Toxicology Lab. 415 p.

43136101 Milburn, G. (1993) Metam Sodium: Multigeneration Study in the Rat: Lab

Project Number: CTL/P/3788: RR0564/F0: RR0564/F1. Unpublished study prepared by Zeneca Central Toxicology Lab. 2211 p.

43233501 Horner, S. (1994) Metam Sodium: Two Year Drinking Study in Mice: Lab Project Number: CTL/P/4095: PM0841. Unpublished study prepared by Zeneca Central Toxicology Lab. 2418 p.

43248801 Allen, S. (1994) Metam Sodium: Subchronic Neurotoxicity Study in Rats: Lab Project Number: CTL/P/4334: PR0959. Unpublished study prepared by Zeneca Central Toxicology Lab. 313 p.

43275801 Brammer, A. (1994) Metam Sodium: 1 Year Oral Toxicity Study in Dogs: Lab Project Number: CTL/P/4196: PD0905. Unpublished study prepared by Zeneca Central Toxicology Lab. 472 p.

43275802 Rattray, N. (1994) Metam Sodium: 2 Year Drinking Study in Rats: Lab Project Number: CTL/P/4139: PR0838. Unpublished study prepared by Zeneca Central Toxicology Lab. 3556 p.

**B. MITC:**

132815 Tsubura, Y.; Watanabe, F.; Shimomura, H.; et al. (1983) One-month Toxicological Study of MITC in Rats by Dermal Application. (Unpublished study received Nov 28, 1983 under 2139-126; prepared by Nara Medical College, Dept. 2 of Pathology, Japan, submitted by Nor-Am Agricultural Products, Inc., Naperville, IL; CDL: 251810-H)

150075 Satoh, R. (1980) Two-year Chronic Oral Toxicity and Oncogenicity Study with Methyl Isothiocyanate in Albino Mice (106 Week Final Report). Unpublished study prepared by Nippon Experimental Medical Research Institute Co. 612 p.

150078 Brown, D. (1984) Methyl Isothiocyanate: A Chronic Oral (Drinking Water) Toxicity and Carcinogenicity Study in the Rat: Report No. 2611-14/1R. Unpublished study prepared by Hazleton Laboratories Europe Ltd. 2596 p.

40974601 Barker, L. (1987) T98 Technical Methylisothiocyanate: 2 Generation Oral (Drinking Water) Reproduction Study in the Rat: Proj. ID. 5280-194/8. Unpublished study prepared by Hazleton UK. 733 p.

41221406 Schobel, Chr.; Schweinfurth, H. (1986) T/20 Methyl Isothiocyanate: Revised Final Report: Methyl Isothiocyanate - Subacute (28-30) Dermal Toxicity Study in the Rat: Project ID PF 15/86. Study prepared by Schering Ag. 221 p. Unpublished.

41221407 Roskamp, G.; Schobel, G.; Bhargava, A.; et. al. (1978) T22 Methyl

Isothiocyanate: ZK 3.318: A 12-13 Week Inhalation Study in the Rat: Project ID 374/77. Unpublished study prepared by Schering AG. 202 p.

44733602 Stump, D. (1998) A Prenatal Developmental Toxicity Study of Methylisothiocyanate (MITC) in Rats: Final Report: Lab Project Number: WIL-316002. Unpublished study prepared by WIL Research Laboratories, Inc. 423 p.

45919417 Hellwig, J. Hildebrand, B.(1987) Report on the study of the prenatal toxicity of MITC in rats after oral administration. BASF Aktiengesellschaft, Department of Toxicology, D-6700 Ludwigshafen/Rhien, Federal Republic of Germany. Report NO. 87/0326, September 2, 1987. Unpublished.

45919418 Becker, H. and Sachsse, K. (1986) Report on the study of the embryotoxicity (including teratogenicity) in the rabbit with MITC. RCC, Research & Consulting Company AG, CH-4452 Itingen, Switzerland. RCC Project No. 056687, September 5, 1986. Unpublished.

### **C. Carbon disulfide**

41628804 Morgan, J. M. (1983). 90-Day vapor inhalation toxicity study of carbon disulfide in Sprague-Dawley rat. Toxicogenics, Inc., Decatur, IL. Laboratory report no: 420-0711B, February 25, 1983. Unpublished.

41628805. Morgan, J. M. (1983). 90-Day vapor inhalation toxicity study of carbon disulfide in Fischer 344 rats. Toxicogenics, Inc., Decatur, IL. Laboratory report no: 420-0711A, February 25, 1983. Unpublished.