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PREVENTION, PESTICIDES AND  
TOXIC SUBSTANCES

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MEMORANDUM

SUBJECT: Quantification of carcinogenic potential for MITC with metam sodium cancer slope factor

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PC Codes: Metam sodium 039003  
MITC 068103

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Members of the metam sodium risk assessment team and the Health Effects Division's Science Policy Council met to discuss issues related to characterizing cancer risk to methylisothiocyanate (MITC). Attendees included: Karl Baetcke, William Burnam, Carol Christensen, Vicki Dellarco, Judy Facey, Bill Hazel, Jeff Herndon, Ray Kent, Anna Lowit, Margaret Stasikowski, and Steven Weiss. This memo describes the discussion and conclusions from that meeting.

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**Background:**

Metam sodium, metam potassium, dazomet, and MITC are fumigants whose toxicology and exposure profiles are interrelated. Specifically, metam sodium, metam potassium, and dazomet are considered carriers of MITC as they convert to MITC quickly under environmental conditions, particularly in soil. MITC is also the major rat metabolite *in vivo* following oral exposure to metam sodium, metam potassium, and dazomet.

The database of toxicology studies for metam sodium and dazomet are complete for risk assessment purposes. The database for MITC, however, is incomplete; many toxicological studies via the oral route with MITC do not meet the guideline requirements, and inhalation toxicity data are limited. At low to mid dose levels, there is remarkable similarity in toxic effects observed at similar molar doses (MITC equivalents) in metam sodium, dazomet, and MITC toxicology studies for rats, mice, and dogs. However, at higher doses, the toxicological profiles differ somewhat among the chemicals. Some of the MITC data gaps are being filled through bridging with the toxicology databases of metam sodium and dazomet. Specifically, chronic and carcinogenicity studies in rats and mice have been considered "unacceptable" primarily due to problems surrounding inadequate characterization of exposure concentrations or doses. The rodent cancer bioassay studies for dazomet and metam sodium are considered acceptable. Exposure to dazomet in oral toxicity testing did not result in increased tumor incidence in mice or rats. Metam sodium is considered a probable human carcinogen based on increased incidence of angiosarcomas in male and female mice, no tumor response was found in rats. The cancer risk to metam sodium is quantified using linear extrapolation based on the total incidence of angiosarcomas in male mice, all sites combined. In 2000, the Hazard Identification and Assessment Review Committee (HIARC) of the Health Effects Division (HED) recommended that the carcinogenic potential of MITC be estimated using the cancer slope factor (Q-1\*) for metam sodium (adjusted by molar conversion to MITC; Doc. No. 014009) given the similarity in oral toxicity profiles. Recently, HED's Division Director, Margaret Stasikowski, requested that the HED Science Policy Council evaluate this recommendation and provide any necessary guidance to the risk assessment team.

**Key Data and Information:****1. MITC carcinogenicity study in rats.**

As mentioned above, the MITC carcinogenicity studies in mice and rats are considered "unacceptable" according to the guideline requirements. The study report for the rat study (MRID no. 00150078) describes a problem with the drinking water dosing solutions in the early weeks of the study. Analytical concentration data provided in the study do not include concentration data prior to week 23. Once the problems were corrected by the laboratory, the dosing solutions were typically changed every two to three days. Detailed analytical concentration data beginning at 23 weeks were provided which showed that after three days an average of 10-20% (range 5-40%) of the MITC would be lost from the solution. Given the early problems with the stability of the dosing solutions, the lack of detailed analytical data prior to week 23, and the variation in concentrations, it is difficult to determine the actual amount of MITC consumed by the rats.

Based on the lack of overt toxicity observed in this study, a maximum tolerated dose was not achieved. However, at the high dose level (approximately 5 mg/kg/day), according to the study report, the dosing solutions had a pungent odor. This odor likely contributed to the reduced drinking water intake observed at this dose level. As the animals may not be able to tolerate higher concentrations of MITC in the drinking water, it is unlikely that an additional oral carcinogenicity study in rats would provide any additional information on the carcinogenic potential of MITC.

**2. Comparison of the metam sodium, MITC, and dazomet carcinogenicity studies in mice .**

In the MITC mouse carcinogenicity study (MRID no. 00150078), drinking water dosing solutions were replaced daily for 106 weeks, thus reducing some of the stability and variability problems encountered in the rat carcinogenicity study (discussed above). The study does not provide data periodically characterizing the actual solutions provided to the animals during the study. Thus, it is difficult to estimate the actual amount consumed. It is, however, reasonable to assume that procedures for making the MITC solutions used during the stability analyses were similar to those used in the in-life portion of the study. Although it may not be possible to accurately calculate the amount of MITC consumed, it is possible derive a reasonable estimate of the intake amount.

Table 1 provides a brief summary of the dose levels and tumor incidence results from the mouse carcinogenicity studies with metam sodium, MITC, and dazomet. It is notable that at doses *similar and greater* to those resulting in statistically significant (pairwise comparison) increase in incidence of angiosarcomas following exposure to metam sodium, there is *no* increase in tumor incidence of any type with MITC and dazomet studies. *These data suggest that for purposes for characterizing carcinogenic potential of MITC the oral data on metam sodium is not appropriate.*

Table 1. Summary of results from mouse oncogenicity studies in metam sodium, MITC, and dazomet

Metam Sodium		MITC		Dazomet	
Dose mg/kg/day (MITC equivalents)	Total incidence of angiosarcomas	Dose mg/kg/day	Results	Dose mg/kg/day (MITC equivalents)	Results
0	7/55 M 4/55 F	0		0	
1.6 (0.896)	12/55 M 2/55 F	0.82	No increase in tumors	3.9 (1.8)	No increase in tumors
6.5 (3.64)	12/55 M 6/55 F	3.30	No increase in tumors	15.8 (7.0)	No increase in tumors
27.7 (15.51)	27/55 M 10/55 F	11.3	No increase in tumors	69.9 (31.5)	No increase in tumors
		25.71	No increase in tumors		

3. Route of exposure.

Inhalation is the primary route of exposure to MITC. However, the majority of the toxicity studies available for MITC are via the oral route. Route to route extrapolation is appropriate only when systemic effects, not port-of-entry effects, are identified. Following 28-days of inhalation exposure to MITC (MRID no. 45314802) focal squamous cell metaplasia in the respiratory epithelium was observed in rats at 100 µg/L. These results are indicative of port-of-entry effects and suggest that the oral carcinogenicity studies may not be predictive of carcinogenic potential following inhalation exposure.

**Conclusion:**

HED's Science Policy Council was asked to evaluate issues related to characterizing cancer risk to MITC. The HED SPC determined that:

- 1) Due to limitations in the rat and mouse oral carcinogenicity studies and notably the lack of chronic testing via the inhalation route, at this time, there is insufficient data to characterize the cancer risk to MITC.
- 2) It is **not** appropriate to quantify MITC cancer potential using the metam sodium cancer slope factor based on:
  - negative cancer studies in rats and mice with dazomet and also lack of tumor response with MITC at doses similar to and greater than those resulting in angiosarcomas with metam sodium.
  - results from a 28-day inhalation study on MITC indicative of port-of-entry effects, suggesting that oral carcinogenicity studies may not be predictive of carcinogenic potential following inhalation exposure.

**References:**

*METHYL ISOTHIOCYANATE* - Report of the Hazard Identification Assessment Review Committee, February 22, 2000 HED Doc. No. 014009

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.

41865101 Kunbroth, B. (1989) Report on the Study of the Oral Toxicity of Dazomet Mice after 78 Week Administration in the Diet: Lab Project Number: 89/0341. Unpublished study prepared by BASF

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.

45314802 Klimisch, H. (1987) Study of the Subchronic Inhalation Toxicity of Methyl Isothiocyanate in Wistar Rats (4-Week Study): Lab Project Number: 87/0244: 4010231/8539. Unpublished study prepared by BASF Aktiengesellschaft. 272 p.

**Attachment:**

Revised toxicology endpoint selection table for use in risk assessment.