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

OFFICE OF
PREVENTION, PESTICIDES, AND
TOXIC SUBSTANCES

MEMORANDUM

TXR No. 0052776

DATE: August 19, 2004

SUBJECT: Addendum to Memo from May 13, 2004 (TXR No.0052547): Quantification of carcinogenic potential for MITC with metam sodium cancer slope factor and cancer classification of metam sodium

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Members of the metam sodium risk assessment team and the Health Effects Division's Science Policy Council met on August 10, 2004 to discuss issues related to characterizing cancer risk to methylisothiocyanate (MITC) and metam sodium. The purpose of this meeting was to 1) consider public comments received on EPA's preliminary risk assessment of metam sodium (May, 2004) and 2) reevaluate data requirements related to carcinogenicity for MITC. Attendees included: Karl Baetcke, William Burnam, Carol Christensen, Judy Facey, Bill Hazel, Jessica Kidwell, Anna Lowit, Tim McMahon, and P.V. Shah. This memo describes the discussion and conclusions from that meeting.

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1. Quantification of carcinogenic potential for MITC with metam sodium cancer slope factor (Error correction to May 13, 2004 memo, TXR no. 0052547 based on public comments from Metam Sodium Alliance)

The Metam Sodium Alliance noted an error in EPA's May 13, 2004 memo (TXR no. 0052547) entitled "Quantification of carcinogenic potential for MITC with metam sodium cancer slope factor" This comment by the Alliance was specifically regarded EPA's statement that

> "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."

EPA has revised this statement and corrected the error contained in the above sentence. The revised statement is provided here.

> "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 ***female*** rats."

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 female 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.

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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 by that route of administration.

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.

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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	15.6 (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.

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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.

2. Cancer Classification for Metam Sodium

In response to the public comments provided by the Metam Sodium Alliance regarding the preliminary risk assessment of metam sodium (May, 2004), the risk assessment team and members of the HED Science Policy Council (HED-SPC) met on August 10, 2004 to discuss the carcinogenicity classification of metam sodium. In 1995, the HED Carcinogenicity Peer Review Committee (CPRC) classified metam sodium as a *Group B2- probable human carcinogen* based on statistically significant increases in malignant angiosarcomas in both sexes of the CD-1 mouse, supported by a similar tumor type (malignant hemangiosarcomas) in male Wistar rats. The CPRC recommended that for the purpose of risk characterization, a low dose extrapolation model be applied to the animal data for the quantification of human risk (Q_1*) based on the total incidence of angiosarcomas in male mice, all sites combined.

The Metam Sodium Alliance submitted reviews of the scientific data used in the evaluation of the carcinogenic potential of metam sodium (MRID Nos. 44276402, 44276403) as well as new data on *in vitro* cytogenetics in human lymphocytes (MRID No. 44276401). They requested that metam sodium be classified as a Group C - possible human carcinogen rather than as a group B2.

The HED-SPC reviewed the submitted information and concluded that the evidence provided by the Metam Sodium Task Force does not warrant re-evaluation by the Cancer Assessment Review Committee (CARC) to change the current classification of metam sodium at this time. This decision was based on the following:

- Although the 1995 CPRC report stated that the evidence of similar tumors (malignant hemangiosarcomas) in male rats was supportive of the tumors seen in the mouse, HED agrees with the Metam Task Force's position that the rat data contribute little to the weight of evidence.

- HED accepts, subject to verification, the Metam Task Force's conclusion that metam sodium shows no evidence for genotoxic potential. Preliminary review of the new study on *in vitro* cytogenetics in human lymphocytes indicates metam sodium may be negative in this assay. Detailed review of this study is on-going; the results of this study will be incorporated into the hazard characterization of metam sodium in the future.

- HED agrees that the SAR data do not contribute substantially to the weight of evidence for the potential carcinogenicity of metam sodium.

The Metam Sodium Task Force has acknowledged that there was an increase in the incidence of hemangiosarcomas at the top dose in both sexes in the carcinogenciltiy study conducted in mice. The evidence given the most weight by the HED Cancer Assessment Review Committee (CARC) in the original evaluation of the carcinogenic potential of metam sodium was this finding of an increase in hemangiosarcomas in both sexes of mice. The classification of Group B2 with a Q_1^* , based on an increase in malignant tumors in mice, is consistent with the 1986 Guidelines and the 1999 Draft Guidelines for Carcinogen Risk Assessment for a chemical with malignant tumors in both sexes of one species, where the incidence of the tumors at the top dose was outside the historical control range.

Conclusion:

HED concludes that re-evaluation by the CARC is not warranted at this time–the Group B2 cancer classification for metam sodium remains.

3. Reevaluate data requirements related to carcinogenicity for MITC

EPA has recently evaluated MITC ambient air exposure studies performed in California and has concluded based on these data that potential chronic exposure to MITC (6 months or longer) exists. As noted above and also in the May 13, 2004 (TXR No.0052547) memo entitled "Quantification of carcinogenic potential for MITC with metam sodium cancer slope factor," 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. There is concern that this lesion could potentially progress and result in cancer. This nasal lesion has also been noted in tumor-producing nasal irritants, such as formaldehyde and butylaldehyde.
Therefore, based on 1) the data which indicates that chronic exposure to MITC in ambient air is possible and 2) incidence of focal squamous cell metaplasia in the respiratory epithelium following 28-days of exposure to MITC in rats, at this time *EPA is requiring carcinogenicity studies in mice and rats. These studies should be conducted via the inhalation route.*

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