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Office of Environmental Health Hazard Assessment

Joan E. Denton, Ph.D., Director
Headquarters • 301 Capitol Mall, Rm. 205 • Sacramento, California 95814-4327 • www.calepa.cahwnet.gov/oehha
Berkeley Office • Mailing Address: 2151 Berkeley Way, Annex 11, • Berkeley, California 94704

Peter M. Rooney
Secretary for Environmental Protection

Pete Wilson
Governor

MEMORANDUM

TO: Gary T. Patterson, Ph.D., Chief
Medical Toxicology Branch
Department of Pesticide Regulation
1020 N Street
Sacramento, CA 95814-5624

FROM: Anna M. Fan, Ph.D., Chief
Pesticide and Environmental Toxicology Section
2151 Berkeley Way, Annex 11
Berkeley, California 94704

DATE: June 3, 1998

SUBJECT: Comments on the Draft Risk Characterization Document for Methyl Isothiocyanate Prepared by the Department of Pesticide Regulation

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We have reviewed the draft risk characterization for methyl isothiocyanate (MITC) prepared by the Department of Pesticide Regulation (DPR). The document is well written and, for the most part, we agree with the conclusions of the risk assessment as stated in the draft document. A summary of our general technical comments is provided below. Certain portions of the draft document would be enhanced with further clarification or corrections in key sections. For more detail, please refer to the attached staff memorandum.

1) In 1992, the Office of Environmental Health Hazard Assessment (OEHHA) issued a draft risk assessment of the health risk from metam and MITC exposure following the 1991 train accident that spilled 20,000 gallons of the herbicide into the Sacramento river. In some cases, there are differences in interpretation of the results of experimental studies reviewed by DPR and OEHHA. The risk characterization document should identify these differences and provide a discussion and rationale for selecting alternative interpretations than those in the 1992 OEHHA risk assessment which preceded DPR's risk characterization document.

2) Human health risk from the acute or short-term exposure to MITC following agricultural use of metam was based on the eight-hour NOEL of 220 ppb for eye irritation. This NOEL was identified in an acute toxicity study with human volunteers and was used for calculating

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margin of exposures (MOEs) for various groups. In widely accepted practice, when a human study serves as a basis for risk assessment, an uncertainty factor of 10 is applied to the identified NOEL to account for variability among human population (intraspecies variability). However, the human MITC exposure study has limitations, such as numbers and variety of people exposed. Therefore, it might be appropriate to discuss in more detail the uncertainties in documentation of an effect threshold with this type of study. In addition, a discussion of the potential for other effects with prolonged exposure or transient higher levels (such as reactive airways dysfunction syndrome) would be desirable.

3) In the key 90-day inhalation study in Wistar rats, the draft risk characterization document identified a NOEL of 1 ppm based on decreased body weight gain, increased water consumption, and decreased serum total protein. OEHHA (1992) identified 1 ppm as a LOEL based on organ weight changes. The U.S. Environmental Protection Agency in 1995 apparently identified 1 ppm as a NOEL as cited in the draft risk characterization document. This is an important difference of opinion because the seasonal (subchronic) toxicity from MITC exposure in agricultural workers and "residential/bystanders" was estimated from this study. We request that this difference of scientific judgment be reviewed and, if appropriate, that an estimate of risk be provided for a LOEL as well as for a NOEL of 1 ppm.

4) MOEs calculated for different exposure scenarios (acute occupational and residential/bystander, and seasonal occupational) are presented in the draft risk characterization document both as mean values and as a range. MITC exposures within these ranges clearly represent potential human health risks for injury or illness (e.g., upper respiratory irritation). It would be useful if the document could estimate the size of the at-risk population, and estimate the area extent of the potential high-level exposures (although we acknowledge that this might require further investigation, outside the scope of the risk characterization).

5) The risks from chronic exposures to MITC were not assessed. No calculation of absorbed daily dosages for potential chronic exposures to MITC is provided. This information is important for the complete assessment of risks from MITC exposure. We recommend that DPR include an assessment of the chronic risks from inhalation exposure using the best available data from oral toxicity studies. In the future, when more appropriate study data become available, the risk assessment results could be reevaluated.

6) The exposure assessment does not address the main toxicity problem documented in the risk characterization, that is, exposure of eyes to irritating vapors. Correspondingly, the risk characterization does not address population exposures which might result in this adverse health effect. More information on the size of the affected area(s), the number of people exposed, and the duration of these exposures will be required for any discussions of further actions. In addition, a discussion of the uncertainty and variability in exposures and effects might be appropriate. Because the risk characterization estimates that excessive exposures to

MITC vapor can occur, resulting at least in acute irritative effects, more extensive air sampling would help to refine the exposure assessment.

7) Airborne MITC following the agricultural use of metam is likely not the only source of human exposure to this chemical in California. MITC is also the active principle of another soil fumigant, dazomet, which may be used in the same agricultural areas, as well as the industrial biocide, potassium N-methyl dithiocarbamate. The draft risk characterization document is understandably limited to the assessment of the potential risk from exposure to MITC following the agricultural use of metam. For the risk characterization document, we recommend inclusion of a statement that actual human exposure to MITC might be somewhat higher than presented in the document because of other potential sources.

Thank you for providing us the draft document for review. If you have any questions or would like to further discuss our comments, please contact me or Dr. Michael DiBartolomeis at (510)-540-3063.

Attachment

cc: Joan E. Denton, Ph.D., Director
Office of Environmental Health Hazard Assessment
301 Capitol Mall, Room 205
Sacramento, CA 95814-4327

Val Siebal, Chief Deputy Director
Office of Environmental Health Hazard Assessment
301 Capitol Mall, Room 205
Sacramento, CA 95814-4327

George V. Alexeeff, Ph.D., Deputy Director
Office of Environmental Health Hazard Assessment
2151 Berkeley Way, Annex 11
Berkeley, CA 94704

Michael J. DiBartolomeis, Ph.D.
Pesticide and Environmental Toxicology Section
2151 Berkeley Way, Annex 11
Berkeley, CA 94704

Office of Environmental Health Hazard Assessment

Joan E. Denton, Ph.D., Director
Headquarters • 301 Capitol Mall, Rm. 205 • Sacramento, California 95814-4327 • www.calepa.cahwnet.gov/oehha
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Peter M. Rooney
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MEMORANDUM

TO: Anna M. Fan, Ph.D., Chief
Pesticide and Environmental Toxicology Section

VIA: Michael J. DiBartolomeis, Ph.D., Chief RSomar for M.D.
Pesticide and Food Toxicology Unit

FROM: Jolanta Bankowska, Ph.D. JB
Staff Toxicologist

DATE: June 1, 1998

SUBJECT: Review of the Draft Risk Characterization for Methyl Isothiocyanate Prepared by the Department of Pesticide Regulation

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We have reviewed the Department of Pesticide Regulation's (DPR's) draft risk characterization for methyl isothiocyanate (MITC). The document is well written and, for the most part, we agree with the conclusions of the risk assessment as stated in the draft document.

MITC is the main degradation product of metam sodium (metam) released upon its contact with moist soil. Metam is a biocide used to control weeds, soil-borne diseases, and nematodes in soil and wood fungi. The draft risk characterization document addresses potential human exposure from the California agricultural use of metam. The risk assessment was initiated because of the toxic effects reported in animal studies and odor and eye irritation complaints from agricultural workers and the public.

In 1992, the Office of Environmental Health Hazard Assessment (OEHHA, 1992) issued a draft risk assessment of the health risk from metam and MITC exposure following the 1991 train accident that spilled 20,000 gallons of the herbicide into the Sacramento river. Although this 1992 draft OEHHA report was referenced by DPR in its draft risk characterization document, DPR conducted an independent selection, analysis, and interpretation of the available toxicological studies, and its risk appraisal uses different methodology to some extent. In some cases, there are differences in interpretation of the results of experimental studies reviewed by both departments. The risk characterization document should identify these differences and

provide a discussion and rationale for selecting alternative interpretations than those in the 1992 OEHHA risk assessment which preceded DPR's draft risk characterization document. Some examples of these inconsistencies are provided below.

TOXICOLOGICAL PROFILE

The following is a summary of the toxicological information provided in the draft risk characterization document unless noted otherwise.

Acute Toxicity

The acute toxicity of MITC was studied in rats, mice, rabbits, dogs, cats, guinea pigs, monkeys, and human volunteers. Acute effects produced in laboratory animals following inhalation exposure included excitement, eye irritation, and dyspnea. Cats appear to be the most sensitive laboratory species. The NO(A)EL for irritation of the ocular mucosa in a four-hour exposure in this species was identified to be 35 ppb (this is consistent with OEHHA, 1992). In rabbits, MITC was shown to be a severe skin and eye irritant. Studies in guinea pigs demonstrated that MITC is a strong dermal sensitizer. For inhalation toxicity, OEHHA (1992) states on page E-4 that "Because of the inconsistent values reported in several acute inhalation toxicity studies, the U.S. Environmental Protection Agency (U.S. EPA) 1991) requested that the registrant repeat this study in the rat." DPR should inquire as to the status of these requests and provide a brief update in its risk characterization document.

Human volunteers in an experimental study of the toxicity of airborne MITC showed eye irritation as the most sensitive toxicological endpoint. (Note: this human study was not available during the preparation of OEHHA, 1992.) OEHHA staff have reviewed the study protocol and the reported results and generally agree with the interpretation of the results as presented in the draft risk characterization document.

OEHHA (1992) states on page E-11 that "The results of the [dermal and ocular irritation and sensitization studies] described above suggest that MITC is a severe skin and eye irritant in rabbits. While it appears that MITC is a skin sensitizer, it is not possible to rule out that other impurities or degradation products of the pesticides tested may have contributed to the sensitizing effects observed in these studies. In an effort to resolve these issues, U.S. EPA (1991) requested the registrant to repeat both the primary eye irritation study in rabbit (a minimum of six animals should be used), and the dermal irritation study." DPR should inquire as to the status of these requests and provide a brief update in its risk characterization document.

Subchronic Toxicity

There are several subchronic toxicity studies of MITC available for evaluation. Adverse effects from inhalation exposure observed in these studies included: mortality, decreased body weight gain, vascular effects of the lungs, nasal discharge, and bleeding noses and mouths.

In the key 90-day inhalation study in Wistar rats, the draft risk characterization document identified a NOEL of 1 ppm based on decreased body weight gain, increased water consumption, and decreased serum total protein. OEHHA (1992) identified 1 ppm to be a LOEL based on organ weight changes (effects on organ weight were not specified in the report). The U.S. Environmental Protection Agency in 1995 apparently identified 1 ppm as a NOEL as cited in the draft risk characterization document. This is an important difference of scientific judgment because the potential seasonal (subchronic) toxicity from MITC exposure in agricultural workers and "residential/bystanders" was estimated using the results of this study. However, if the effect on organ weights was considered significant and 1 ppm determined to be a LOEL, our interpretation would be that this effect is less severe relative to other toxicological endpoints. Therefore, an additional uncertainty factor of 3 rather than 10 would be sufficient to account for the use of a LOEL instead of a NOEL for organ weight changes in the risk characterization.

MITC administered through feed or by gavage in subchronic toxicity studies resulted in decreased feed consumption and body weight, inactivity, abnormal feces, forestomach acanthosis, hyperkeratosis and submucosal cyst formation, increased liver weight and liver inflammation, altered ovary and adrenal weight, spermatogenic disorder, and blood changes. In one three-week drinking water study in JCL-ICR mice, OEHHA (1992) and the risk characterization document provide different (but probably not important) dose conversions.

Dermal subchronic toxicity studies produced skin ulceration, crust formation, erythema, neutrophil infiltration, enlarged peribronchial lymph nodes, and decreased serum albumin and plasma cholinesterase.

Chronic Toxicity

In the available long-term toxicity studies, MITC was administered via oral gavage or drinking water. There is no long-term experimental toxicity study via inhalation.

The adverse effects produced in these studies included decreased water and food consumption and body weight loss at doses considered LOAELs and vomiting, excessive salivation, liquid feces, changes in liver, kidneys, ovaries and blood at higher levels. In one eight-month oral gavage study in rats, OEHHA (1992) identified a LOAEL of 3 mg/kg-day for

submucosal cysts, hyperkeratosis, and acanthosis. The draft risk characterization document identified this dose level as a NOEL. In the two-year drinking water study in mice, OEHHA (1992) identified a NOAEL of 5 ppm for amyloid degeneration in male mice. The draft risk characterization identified this level as a NOEL, apparently because no historical control incidences of this finding were available. While we agree that historical control data would be necessary to resolve this issue, OEHHA (1992) chose to take the more health-protective approach. It should also be noted that the dose conversions are different between the two departments for the two-year oral studies (OEHHA's non-gender-specific values are slightly higher than DPR's gender-specific values).

There is insufficient evidence of oncogenicity in any of the studies. OEHHA (1992) on page E-20 states that "U.S. EPA requested that the MITC registrant repeat the chronic studies in the rat and dog (U.S. EPA 1991b). An explanation was not provided as to why these studies were deficient." DPR should inquire as to the status of these requests and provide a brief update in its risk characterization document.

Genotoxicity

Among the available tests discussed in the draft risk characterization document, only one performed in Chinese hamster V79 cells indicated a weakly positive response for chromosomal effects. There was no evidence for gene mutation in a mammalian cell assay, and no acceptable microbial cell assays were available. Tests for sister-chromatid exchange and DNA damage were negative.

Reproductive and Developmental Toxicity

One two-generation drinking-water and one three-generation oral gavage study in rats were reviewed in the risk characterization document. No reproductive effects were identified in these studies. Systemic effects observed at the mid- and highest doses tested included decreased water consumption and weight loss.

Three developmental toxicity studies of MITC in rats and rabbits were reviewed. These studies showed decreased fetal body weight and size at doses that also produced maternal adverse effects such as decreased feed consumption and body weight gain. The risk characterization document identified the developmental NOAEL in rabbits to be 5 mg/kg-day (Irving, 1983). OEHHA (1992) identified the NOAEL to be 3 mg/kg-day. (Note: OEHHA, 1992 lists the author as Irvine - we do not have the study to check the spelling.)

OEHHA (1992) states on page E-21 that "U.S. EPA has requested that the registrant repeat the developmental toxicity studies in rat and rabbit (U.S. EPA 1991b), and the two-generation reproductive study in the rat (U.S. EPA 1991a,b)." DPR should inquire as to the status of these requests and provide a brief update in its risk characterization document.

Special Toxicity Studies

The draft risk characterization document described some non-FIFRA-guideline special studies. These studies were designed to evaluate MITC effects on the immune system, cardiovascular system, blood coagulation, hemolysis, and central nervous system. No meaningful conclusions were drawn because only summary information was available for evaluation.

SELECTION OF KEY STUDIES FOR RISK ASSESSMENT

Two critical studies were identified in the draft risk characterization document for assessing human risks from airborne exposures to MITC. The first is the experimental exposure using human volunteers. This study was specifically designed to determine the NOEL for human eye irritation and odor threshold, and not for respiratory irritation. The NO(A)EL for eye irritation was identified to be 220 ppb MITC (eight hours exposure) in air. This value was used for evaluation of potential acute/short-term exposure.

OEHHA (1992) utilized the results of an experimental study in cats (Nesterova). The limitations of using this study were discussed in the 1992 document. The availability of the human exposure study provides important new data to help elucidate the potential human health risks of MITC exposure. Nevertheless, the human study does have its limitations for use in risk assessment. The primary concern is that one acute exposure to high levels of a strong respiratory irritant such as MITC might cause recurring problems following exposure to much lower levels. This was not (for good reason) investigated experimentally in human subjects. Examples of long-lasting effects sometimes seen with direct industrial exposures include chemical bronchitis, followed by prolonged bronchial hyperresponsiveness (so-called "reactive airways dysfunction syndrome" or RADS). Some residents near the town of Dunsmuir complained of symptoms that indicated RADS might have developed in some individuals following the 1991 train derailment. Although not released, OEHHA revised its 1992 document to include a discussion of RADS. See also the publication by Cone *et al.*, (1994) "Persistent Respiratory Health Effects After a Metam Sodium Pesticide Spill," Chest 106:500-508. We would also be available to consult with DPR staff on this issue.

The second critical study was the 90-day rat inhalation study used to assess potential risk from seasonal exposure to MITC (see comments above). In this study, the risk characterization

identified a NOEL of 180 μg/kg-day (absorbed dose equivalent to 1 ppm MITC in air). This NOEL was based on decreased body weight, decreased serum protein, and increased water consumption. This value was used for evaluation of potential seasonal exposures. As noted above, OEHHA (1992) identified 1 ppm as a LOEL. If the effect on organ weights was considered significant and 1 ppm determined to be a LOEL, our interpretation would be that this effect is less severe relative to other toxicological endpoints. Therefore, an additional uncertainty factor of 3 rather than 10 would be sufficient to account for the use of a LOEL instead of a NOEL for organ weight changes in the risk characterization. In other words, the impact of this difference of scientific judgment is that the results of the risk assessment for seasonal exposure might be underestimated by three-fold. We recommend that the risk characterization document discuss this difference of scientific judgment and provide an estimate of risk if 1 ppm were considered a LOEL rather than a NOEL.

RISK CHARACTERIZATION

According to the draft risk characterization document, the groups at the highest health risk include:

1) loaders and applicators exposed to MITC under potential acute or short-term occupational exposure scenarios following ground injection of chemigation of metam (MOE of <1 to 8),

2) adults or children as "bystanders" exposed to MITC under the conditions described above (<1 to 204), and

3) workers under most of the presented occupational activities and adult female and children as residential/bystanders exposed to MITC under seasonal exposure scenarios following ground injection or chemigation of metam (MOE of 1 to 9,000).

GENERAL COMMENTS

Toxicological Summary and Data Gaps

In some cases, there are differences in interpretation of the results of experimental studies reviewed by both departments. The risk characterization document should identify these differences and provide a discussion and rationale for selecting alternative interpretations than those in the 1992 OEHHA risk assessment which preceded DPR's draft risk characterization document.

The "Summary of Toxicology Data" for the active ingredient prepared by the Medical Toxicology Branch, which has in the past been attached to the risk characterization document, was not included for MITC. We found this information very useful in the past. We recommend that the risk characterization document include the summary as a part of the data package for the MITC risk characterization document.

As noted in our comments, we understand that U.S. EPA has requested additional toxicity testing. It is not clear from the draft risk characterization document what the status is of data gaps for MITC. One way to address this is to include a separate section on the adequacy of the currently available toxicity studies and the status of U.S. EPA's requests for more data.

Risk Assessment for Acute Exposures

Human health risk assessment from acute exposures to MITC following agricultural use of metam was based on an eight-hour NOEL of 220 ppb for eye irritation. This NOEL was identified in an acute toxicity study with human volunteers and was used for calculating MOEs for various groups. In widely accepted practice, when a human study serves as a basis for risk assessment, an uncertainty factor of 10 is applied to the identified NOEL to account for variability among human population (intraspecies variability). However, this particular human study is limited because the registrants could not (for good reason) expose human subjects experimentally to higher levels of the irritant gas that might produce prolonged adverse effects such as RADS. Individuals diagnosed with RADS are usually exposed first to a concentration of an irritant gas that causes respiratory irritation. Subsequent exposures to far lower levels of the same or another irritant gas will then trigger respiratory distress symptoms.

Therefore, although useful for assessing short-term acute exposures to MITC for the less severe endpoint eye irritation, the results of this human study cannot be used to evaluate the risks of long-term effects from acute exposures to MITC at levels that cause respiratory irritation. There are reports that MITC causes respiratory irritation in individuals residing near agricultural fields where metam sodium is applied. Ambient air monitoring has confirmed that MITC drifts into residential neighborhoods. Following the 1991 train derailment where residents were clearly exposed to levels of MITC that caused respiratory irritation, RADS was (and is) a concern. Therefore, it might be necessary to increase the uncertainty factor for acute exposures to 30 or 100. For DPR, this would mean that an MOE of 30 or 100 for MITC, rather than 10, might be the health protective level to achieve. Consideration of this approach is warranted by the scientific evidence as well as the reports of respiratory irritation in agricultural communities. At the very least, the risk characterization document should include a discussion on the prolonged effects of exposures to strong respiratory irritants and a discussion of the inherent limitations of the human study.

Risk Assessment for Chronic Exposures

The draft risk characterization document does not provide a calculation of absorbed daily dosages for potential chronic exposures to MITC. This information is important for the complete assessment of risks from MITC exposure.

According to the risk characterization document, chronic inhalation exposures to MITC were not assessed because:

1) No chronic inhalation toxicity studies of MITC were identified.

2) Long-term, oral toxicity studies in experimental animals produced various adverse effects which were different than direct systemic effects produced in the subchronic inhalation study. The unpalatability of drinking water containing MITC, and the irritating effects of MITC following gavage produced numerous effects secondary to decreased food and water consumption, or vomiting and diarrhea.

3) The secondary effects (such as changes in body or organ weight, alterations in blood parameters, fatty change in the liver, and slight alteration in sperm production) may have obscured any direct effects of MITC.

The risk characterization states that the "probable biological irrelevance of exposure by routes other than inhalation to the effects produced by vapor of MITC" applies only to local and not to systemic effects that may be caused by airborne MITC. Systemic effects from MITC, whether by inhalation or other routes, may be the same or similar. For example, changes in body weights and blood parameters were observed in both a 90-day inhalation study in rats and a chronic oral toxicity study in rats. Also, it cannot be excluded that airborne MITC will be inhaled by both occupationally exposed workers and residents/bystanders following ground injection or chemigation of metam under acute, seasonal, and chronic exposure scenarios.

Primary or secondary adverse health effects in oral chronic toxicity studies were produced as a result of exposure to MITC. These effects were measurable and as such could be assessed regardless of underlying mechanism responsible for their production. It is unclear why such effects as changes in body or organ weight, alterations in blood parameters, fatty change in the liver, and slight alteration in sperm production are regarded as secondary and not primary effects of MITC in the risk characterization document. More explanation on this would be helpful.

We appreciate the problems and limitations identified in the draft risk characterization document. Nevertheless, repeated seasonal and sporadic exposures to MITC cannot be overlooked. Although not ideal, one way to conduct such an assessment, in the absence of inhalation toxicity data, is to use the best available data from oral long-term toxicity studies to assess health risks from chronic inhalation exposure. OEHHA has performed such assessments in the past. The results from this assessment would need to be discussed in the context of the methodological uncertainties. We recommend that DPR include an assessment of the chronic risks from inhalation exposure. In the future, when more appropriate study data become available, the risk assessment results could be reevaluated.

Exposure Assessment

The exposure assessment does not address the main toxicity problem documented in the risk characterization, that is exposure to irritating vapors. Correspondingly, the risk characterization does not address population exposures which might result in this adverse health effect. Choosing appropriate mitigation strategies may require more information on the area affected, the number of people exposed, and the duration of these exposures. In addition, a discussion of the variability and uncertainty in exposures and response might be appropriate, rather than mentioning only point estimates. .

Because the risk characterization estimates that excessive exposures to MITC vapor can occur, more extensive air sampling would help to refine the exposure assessment.

Characterization of Exposed Population

MOEs calculated for different scenarios are presented in the draft risk characterization document both as mean values and as a range. It is apparent that many of these values are reflective of potential exposures to MITC that could result in significant human health risk for injury or illness. It would be useful if a description of the exposed population that might be at greater risk, and an estimated proportion of these individuals in California where metam is applied, were included in the document.

Other Sources of MITC Exposure

Airborne MITC following the agricultural use of metam is likely not the only source of human exposure to this chemical in California. MITC is also the active principle of another soil fumigant, dazomet, which may be used in some of the same areas, as well as the industrial biocide, potassium N-methyl dithiocarbamate. The draft risk characterization document is understandably limited to the assessment of the potential risk from exposure to MITC following the agricultural

use of metam. For the risk characterization document, we recommend inclusion of a statement that actual human exposures from exposure to MITC might be higher than presented in the document because of other potential sources of exposure to this chemical in addition to metam.

SPECIFIC COMMENTS

Text. Please cite all references to the 1992 draft report "Evaluation of the Health Risks Associated with the Metam Spill in the Upper Sacramento River" as "OEHHA, 1992." Therefore, in the text of the draft risk characterization document where individual authors of chapters were cited (e.g., Jowa, 1992, Alexeeff, 1992), please substitute with "OEHHA, 1992."

Reference section. Please reference the 1992 draft risk characterization document as "OEHHA (1992). Evaluation of the Health Risks Associated with the Metam Spill in the Upper Sacramento River (External Review Draft). Office of Environmental Health Hazard Assessment, Berkeley, CA."

It would be beneficial for the risk characterization document to include more information about reported human symptoms observed after the metam spill in the upper Sacramento river in 1991. The draft 1992 OEHHA risk assessment or one of the publications that followed are good sources of this information. This information could be discussed, for example, in the "Illness Reports" section of the DPR document on page 5.

Page 11. Third paragraph, "OEHHA, 1992" should be added as the first reference as it was the first report released in which health effects from the Cantara Incident were characterized.

Absorbed daily dose was addressed in the main text of the draft risk characterization document only for potential seasonal exposures to MITC. Absorbed daily dosages for acute exposures were discussed in the appendix prepared by the Worker Health and Safety Branch. We recommend that the discussion of the absorbed daily dosages of MITC from inhalation exposure and their corresponding concentration in the air also be summarized in the main text.

Page 35. The draft risk characterization document states "Metam-sodium was not found to be mutagenic in the bacterial assays, but metam-sodium did cause chromosomal damage in other mutagenicity tests." According to OEHHA (1992), the testing results in mammalian cell assays (CHO) and DNA damage were equivocal. Collectively, the equivocal results in these assays and the chromosomal damage suggest the potential for mutagenicity. A statement in the risk characterization document with this information might be appropriate.

Specific comments on the Exposure Assessment:

Executive Summary, first paragraph: "From 1990 through 1994, there were five annual illness/injury cases classified as definitely, probably, or possibly related to metam-sodium/MITC exposure." This statement might be interpreted as indicating five total cases, instead of five in each category each year, for a total of 79 during the period in question. It should be reworded for clarification, as should the similar sentence in the last paragraph on page 6.

Page 5. MITC is appropriately called "poorly soluble in water" in point #16. This appears to contradict the statement that it has "high water solubility" on page 9, first paragraph. Although the context is quite different (MITC as a bulk material compared to dermal uptake properties), it might be less confusing to call it "moderate water solubility" on page 9, which is just as accurate for the context.

Page 7, Table 2b. Under "Notes:" at the bottom, please add the words, "(excluding the Cantara spill)."

Page 8. "There was no study to substantiate that MITC vapor would adhere to nor would likely have prolonged contact with the skin." Chemical vapors in ambient air necessarily contact the skin, and some fraction is absorbed. No specific study is necessary to document this basic physical fact. The sentence should be removed.

Page 11, fourth line, "the absorption was similar at both doses, but with a somewhat different pattern of absorption." This appears to mean "with a somewhat different pattern of disposition."

Page 12. The point estimate of breathing rate for a female doing light work does not fully represent potential exposures under field conditions. It is not clear why residents and bystanders were assumed to be exposed for the same number of days as metam handlers. Evolution of vapors from treated fields occurs over several days; on the other hand, residents and bystanders will not be traveling around to stand beside multiple fields over a treatment season. The 23-day simplification is not an adequate substitute for real information on the spread and persistence of MITC vapors in an agricultural area where metam is used.

Page 13, "Center-pivot sprinkler injection." The use of this phrase (which refers to the injection of metam into the irrigation line) for a spray irrigation method might be confused with the direct injection of metam solutions into the soil. The use of the phrase "Center-pivot sprinkler irrigation" might be better.

Page 14. Field fortification of tubes for recovery standards. The method of preparing fortified samples should be mentioned. See comment for page 27.

Pages 15, 21, 24, and 25. Inadequate information is given on air concentrations of MITC to allow any kind of an estimate of exposure to irritating levels of MITC. At a minimum, the peak levels and duration of time that air concentrations exceed the irritation threshold should be documented. Estimates of areas over which these excessive concentrations occur and the populations involved also seem to be necessary for the risk characterization.

Page 16. The assumptions used to calculate a dose for an adult male should be stated.

Page 21. In calculating exposures for adult females, more consideration of the variability in breathing rates for different activities might be appropriate.

Page 22. SADD is estimated in the second paragraph from a longer baseline collection than ADD, resulting in a lower input value for the calculation than for ADD. This contradicts the parameter definitions in items 2 and 3 on page 12 which state that SADD is calculated directly from ADD. The inconsistency should be explained, or corrected if appropriate.

Pages 24 and 25. In calculating exposures for children, the potential for a range of exposures depending on variations in physiological parameters and activity levels should be acknowledged.

Page 27. As discussed in the second paragraph, the use of silica gel drying tubes in the sample collection system may have greatly affected results. This greatly undercuts the reliability of and confidence in the reported data. It would be helpful if the discussion of this factor includes reference to how this relates to the field fortification method and whether the very good recoveries noted earlier were obtained with or without the silica gel drying tubes.