

US EPA ARCHIVE DOCUMENT

64



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

September 30, 2004

SUBJECT: Metam sodium: HED Human Health Risk Assessment For Phase 1: DP Barcode: DP308417, Metam Sodium PC Code: 039003, MITC PC Code: 068103

FROM: Sherrie Kinard, Residue Chemist/Risk Assessor
Bill Smith, Environmental Scientist/Risk Assessor *B. Smith 9/30/04*
Health Effects Division/Reregistration Branch 2 (7509C)

THRU: Alan Nielsen, Branch Senior Scientist *Alan Nielsen 9/30/04*
Health Effects Division/Reregistration Branch 2 (7509C)

TO: Mark Seaton, Chemical Review Manager
Special Review & Reregistration Division (7508C)

Attached is HED's risk assessment of the fumigant, metam sodium. HED has evaluated the hazard and exposure data and conducted exposure assessments, as needed, to estimate the risk to human health that will result from the registered and proposed uses of metam sodium.

EPA has initiated a systematical evaluation of the risks and benefits of six soil fumigants. The development of a comparative "cluster" risk-benefit assessment of the soil fumigants is presently ongoing. Metam sodium will be included in the comparative assessment which is expected to be released to the public in early 2005.

This risk assessment uses deterministic methods to estimate exposures to bystanders around treated fields. These generally represent an upper-bound estimate of likely exposures. OPP is coordinating with EPA's Office of Air, the California Department of Pesticide Regulation (CDPR), and other stakeholders to develop modeling approaches which determine the entire distribution of potential bystander exposures and thus, more fully characterize the range of risks resulting to bystanders around treated fields. FIFRA Scientific Advisory Panel (SAP) meetings held in August and September reviewed several soil fumigant bystander exposure models which may be used in future metam sodium risk evaluations.

A summary of the findings and an assessment of human-health risk resulting from the proposed uses of metam sodium only are provided in this document.

Changes to this risk assessment since the August 19, 2004 version include:

- Estimates of risk for bystander MITC inhalation exposure from point sources based monitoring data and dispersion modeling were done for acute exposures only. Short- and intermediate-term and chronic estimates were removed from the assessment.

OCT 7 2004

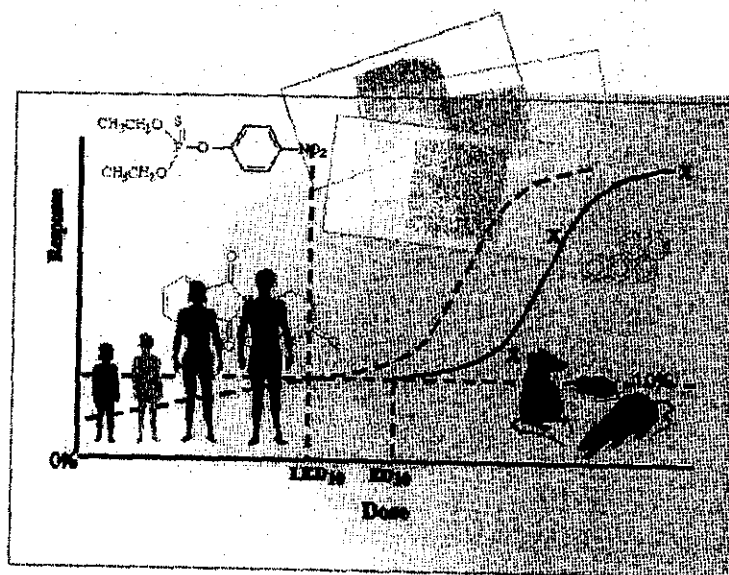
HS

①

- Estimates of risk for bystander MITC inhalation exposure from non-point source based on ambient monitoring data have been updated. Results from monitoring conducted in Lompac in 1998 and 2000 have been added to the assessment.
- Estimates of risk for handler MITC inhalation exposure during sewer treatment based on two Australian studies have been added to the assessment.

HUMAN HEALTH RISK ASSESSMENT

Metam Sodium



U.S. Environmental Protection Agency
Office of Pesticide Programs
Health Effects Division (7509C)
Sherrie Kinard, Residue Chemist/Risk Assessor
Bill Smith, Environmental Scientist/Risk Assessor
Date: September 30, 2004

HUMAN HEALTH RISK ASSESSMENT

Metam Sodium Risk Assessment Team

Risk Assessor:	Sherrie Kinard Bill Smith
Product and Residue Chemistry:	Ken Dockter Sherrie Kinard
Occupational and Residential Exposure:	Steve Weiss
Epidemiology:	Jerome Blondell, MPH, Ph.D.
Toxicology:	Anna Lowit, Ph.D. Judy Facey, Ph.D.
Drinking Water Estimates:	Faruque Khan, Ph.D.

Table of Contents

1.0	Executive Summary	<u>1</u>
2.0	Ingredient Profile	<u>4</u>
2.1	Summary of Registered Uses	<u>4</u>
2.2	Structure and Nomenclature	<u>5</u>
2.3	Physical and Chemical Properties	<u>5</u>
3.0	Metabolism	<u>6</u>
3.1	Description of Primary Crop Metabolism	<u>6</u>
3.2	Description of Livestock Metabolism	<u>6</u>
3.3	Description of Rat Metabolism	<u>6</u>
4.0	Hazard Assessment and Characterization	<u>7</u>
4.1	Hazard Characterization	<u>7</u>
4.1.1	Database Summary	<u>7</u>
4.1.2	Endpoints	<u>8</u>
4.1.3	Dose-response	<u>9</u>
4.1.3.1	Inhalation Exposure	<u>10</u>
a.	Metam Sodium	<u>10</u>
b.	MITC	<u>11</u>
c.	Dazomet	<u>12</u>
a.	Metam Sodium	<u>12</u>
b.	MITC	<u>12</u>
c.	Dazomet	<u>13</u>
a.	Metam Sodium	<u>13</u>
b.	MITC	<u>14</u>
c.	Dazomet	<u>14</u>
4.1.3.2	Dietary Exposure	<u>14</u>
4.1.3.3	Dermal Exposure	<u>14</u>
4.1.3.3.1	Dermal Absorption	<u>14</u>
a.	Metam Sodium	<u>14</u>
b.	MITC	<u>14</u>
c.	Dazomet	<u>15</u>
4.1.3.3.2	Short- Term, Dermal (1-30 days) Exposure	<u>15</u>
a.	Metam Sodium	<u>15</u>
b.	MITC	<u>15</u>
c.	Dazomet	<u>15</u>
4.1.3.3.3	Intermediate- Term, Dermal (1 -6 months) Exposure	<u>16</u>
a.	Metam Sodium	<u>16</u>
b.	MITC	<u>16</u>
c.	Dazomet	<u>16</u>
4.1.3.3.4	Long-Term Dermal (>6 Months) Exposure	<u>16</u>
a.	Metam Sodium	<u>16</u>
b.	MITC	<u>17</u>

5

	c.	Dazomet	<u>17</u>
	4.1.3.4	Classification of Carcinogenic Potential	<u>17</u>
	a.	Metam Sodium	<u>17</u>
	b.	MITC	<u>17</u>
	c.	Dazomet	<u>17</u>
4.2		Uncertainty Factors	<u>18</u>
4.3		Endocrine Disruption	<u>18</u>
4.4		Summary of Toxicological Endpoint Selection	<u>19</u>
5.0		Public Health Data	<u>24</u>
6.0		Non-Occupational Exposure Assessment and Characterization	<u>27</u>
6.1		Residential Bystander Exposure	<u>27</u>
	6.1.1	Bystander Exposure from Known Point Sources	<u>28</u>
	6.1.1.1	Bystander Exposures From Known Point Sources Estimated Using The Monitoring Data Method	<u>31</u>
	6.1.1.1.1	Pre-Plant Agricultural Field Fumigation	<u>31</u>
	6.1.1.1.2	Potting Soil Fumigation	<u>33</u>
	6.1.1.1.3	Sewer Fumigation	<u>33</u>
	6.1.1.2	Bystander Exposures From Known Point Sources Estimated Using The Modeling Method	<u>33</u>
	6.1.1.2.1	Pre-Plant Agricultural Field Fumigation	<u>34</u>
	6.1.2	Ambient Bystander Exposure From Non-Point Sources	<u>36</u>
	6.1.2.1	Exposures From Regionally Targeted Non-Point Source Ambient Air Monitoring	<u>36</u>
6.2		Bystander Risk Characterization	<u>38</u>
6.3		Residue Profile	<u>39</u>
6.4		Water Exposure/Risk Pathway	<u>40</u>
7.0		Aggregate Risk Assessment	<u>40</u>
8.0		Cumulative Risk Assessment and Characterization	<u>40</u>
9.0		Occupational Exposure	<u>41</u>
9.1		Occupational Handler Exposure	<u>41</u>
	9.1.1	Occupational Handler Point Exposure Estimates for Pre-plant Agricultural Field Fumigations	<u>42</u>
	9.1.2	Occupational Handler Point Exposure Estimates for Potting Soil Fumigation ...	<u>43</u>
	9.1.3	Occupational Handler Point Exposure Estimates for Sewer Fumigation	<u>43</u>
9.2		Occupational Reentry Worker Exposures	<u>44</u>
	9.2.1	Pre-plant Agricultural Field Fumigation	<u>44</u>
	9.2.2	Potting Soil Fumigation	<u>45</u>
	9.2.3	Sewer Fumigation	<u>45</u>
10.0		Data Needs and Label Requirements	<u>46</u>
	10.1	Toxicology	<u>46</u>
	10.2	Residue Chemistry	<u>46</u>

6

10.3 Occupational and Residential Exposure 46

Appendix A: Toxicity Profile 48

Appendix B: Methodologies for Inhalation Risk Calculations and Human Equivalent Concentration Arrays
..... 49

Appendix C: Bibliography Of Metam Sodium Exposure Data 52

Appendix D: Summary Datasheets For Single Agricultural Field Fumigation Events 53

Appendix E: Downwind MITC Air Concentrations from Metam Sodium Applications Estimated with
ISCST3 for Pre-Plant Agricultural Uses 54

Appendix F: Occupational Risks Associated With Agricultural Fumigations 55

Appendix G: Downwind MITC Air Concentrations from Metam Sodium Applications Estimated with
ISCST3 for Pre-Plant Agricultural Uses (Used to Calculate Re-entry Risks) 56

1.0 Executive Summary

Metam sodium (sodium N-methyldithiocarbamate) and metam potassium (potassium N-methyldithiocarbamate) are non-selective pre-plant soil fumigants with fungicidal, herbicidal, insecticidal, and nematocidal properties. Metam sodium is one of the most widely used agricultural pesticides in the U.S. with an estimated total of 51 million pounds applied annually. Lesser amounts of metam potassium are used in the U.S. (estimated 1-2 million pounds annually). Unless further qualified or specified, use of the term 'metam sodium' should be assumed to also include 'metam potassium.' EPA has commenced a significant effort to systematically evaluate the risks and benefits of six soil fumigants; metam sodium is included as one of these six. The development of a comparative "cluster" risk-benefit assessment of the soil fumigants is presently on-going and is expected to be released to the public in early 2005.

Metam sodium's volatility in the environment and results of metabolism studies in plants assure that there is no reasonable expectation of finite residues to be incurred in/on any raw agricultural commodity when these products are applied according to label directions. Therefore, this fumigant does not require food tolerances and is not subject to the amendments to the FFDCFA promulgated under the Food Quality Protection Act of 1996; therefore, an aggregate risk assessment is not required.

In an effort to ensure that the best science is used in the assessments, OPP is coordinating with EPA's Office of Air, the California Department of Pesticide Regulation (CDPR), and other stakeholders to further refine modeling approaches used for exposure assessment of MITC from metam sodium applications and other soil fumigants including potential use of probabilistic and/or distributional techniques. EPA has completed FIFRA Scientific Advisory Panel (SAP) meetings in August and September to review three probabilistic soil fumigant bystander exposure models, which include: Fumigant Exposure Modeling System (FEMS), Probabilistic Exposure and Risk model for Fumigants (PERFUM), and the Soil Fumigant Exposure Assessment System (SOFEA). In the coming months after considering the comments of the SAP and a complete evaluation of the utility of these models, they may be used to more fully characterize risks for metam sodium and other soil fumigants.

The scope of this assessment addresses only the major uses of metam sodium being supported by the registrants. These uses include an agricultural fumigant, a root control agent for use in sewers and drains, and a vegetation control agent for shorelines and drained bodies of water. There are also other uses of metam sodium, potassium, and MITC which have been assessed by OPP's Antimicrobial Division and as such are not included in this assessment. Metam sodium and potassium soil fumigant end-use products are registered for all crops. The residue of concern for both metam sodium and metam potassium is MITC.

Following application of metam sodium and potassium, MITC can volatilize into the atmosphere and be transported off-site. This can lead to exposures to MITC in the general public and to workers following application of metam sodium and potassium. [Note: Dazomet is another fumigant which produces MITC upon application. This document does not quantify exposure to dazomet or MITC coming from dazomet applications or use of MITC itself.]

In acute toxicity testing, MITC is Acute Toxicity Category II for the oral and inhalation routes and Category I for the dermal route. MITC also causes skin and eye irritation (Acute Toxicity Category I) and is a sensitizer in guinea pigs. Eye irritation and odor threshold for MITC has been evaluated in humans. Metam sodium is relatively less acutely toxic compared to MITC. Metam sodium is of low toxicity

(Acute Toxicity Category III) in acute toxicity studies by the oral, dermal, and inhalation routes. Metam sodium is not a skin and eye irritant (Category III and IV, respectively) and is positive for skin sensitization in guinea pigs.

Following inhalation exposures to MITC, consistent effects are observed in rats and humans. In rat studies, clinical signs and pathological changes of the respiratory tract consistent with an irritant have been observed. Incident data for MITC are consistent with these findings as exposed individuals have symptoms such as itchy and burning eyes, rash and burning skin, nausea, scratchy throat, salivation, coughing, and shortness of breath. At the present time, the data base of acceptable inhalation toxicology studies is limited to a 28-day study in rat, an eye irritation and odor threshold in human subjects, and an acute lethality study in rat. There are no studies with laboratory animals available which better quantify the dose-response relationship and the continuum of potential *acute, single-day* respiratory effects (i.e., progression to more serious clinical outcomes) from exposure to MITC. There is, however, an eye irritation study in human subjects. This irritation study evaluated both the impact of duration of exposure and dose on human eye irritation. For acute exposures of 1 to 8 hours in duration, a NOAEL was selected from the human eye irritation study based on effects observed at the LOAEL. Typically EPA uses a 10x factor to account for variability within species and another 10x factor to account for interspecies variability. In this case a MOE of 10 defines HED's level of concern (LOC) for acute inhalation risk to MITC because an endpoint was selected for risk assessment from the human eye irritation study. Due to the limitations in the existing inhalation toxicology database for MITC, the degree to which eye irritation predicts more serious outcomes is unclear. However, in the absence of more robust dose-response data from acute exposures, eye irritation can be considered as an appropriate biomarker and surrogate for potential respiratory effects.

For durations other than acute, the 28-day rat inhalation study provides critical effects for estimating short-term (ST), intermediate-term (IT), and long-term (LT) inhalation risk for exposure to MITC. Clinical signs consistent with irritation in both sexes and increased neutrophilic polymorphonuclear granulocytes (indicative of an inflammatory response) in the blood of males were noted at the mid dose in the 28-day study. However, the local effects noted in the nasal passages (metaplasia of the respiratory epithelium and atrophy of the olfactory epithelium) at the highest dose provided the lowest human equivalent concentrations (HECs) and have been selected for developing margins of exposure (MOE). OPP has recently determined that for the soil fumigants, it is appropriate to adopt EPA's reference concentration (RfC) methodology (1994) for purposes of inhalation dosimetry and animal to human extrapolation. The RfC methodology provides equations which account for some of the structural and pharmacokinetic differences regarding the respiratory tract between animals and humans and also physical-chemical properties of chemicals. Using the equations provided in the RfC methodology, systemic and local effects in different regions of the respiratory tract are evaluated separately. As shown for MITC, the HECs for local effects can be more protective than HECs calculated for systemic effects, even if the overall NOAEL identified for the study provides a lower value. The HECs differ between non-occupational and occupational scenarios because the residential HEC is based on 24-hour exposures occurring 7 days per week, whereas the occupational HEC is based on 8-hour exposures occurring 5 days per week. Because EPA's RfC methodology incorporates some pharmacokinetic differences between rats and humans, the interspecies factor is generally 3x. Typically EPA uses a 10x factor to account for intraspecies variability. Therefore, a MOE of 30 defines HED's LOC for ST and IT inhalation risk to MITC. Where there are no chronic toxicity studies available for MITC, HED typically applies a 10x factor to account for the uncertainties when extrapolating from subchronic to chronic duration. Therefore, a MOE of 300 defines

HED's LOC for chronic inhalation risk to MITC.

Metam sodium is currently classified as a probable human carcinogen, based on statistically significant increases in malignant angiosarcoma in both sexes of the mouse. Carcinogenicity studies for MITC *per se* are insufficient to characterize cancer risk, therefore, the carcinogenic potential of MITC cannot be determined at this time. However, due to the potential for chronic exposures and also the observation of metaplasia of the respiratory epithelium following 28-days of inhalation exposure, EPA is requiring inhalation carcinogenicity studies with MITC in rats and mice.

Systemic effects following dermal exposure to metam sodium are not known at this time; the existing dermal study does not take adequate precautions for the volatilization of MITC. Therefore, HED has elected to use oral studies and route to route extrapolation using a dermal absorption factor (2.5%) for risk assessment. The ST dermal endpoint is based on reduced body weight gain and decreased food efficiency in maternal rats seen in a developmental toxicity study with metam sodium. The IT dermal endpoint is an oral NOAEL based on microscopic changes in the liver in females seen in a chronic oral toxicity study in the dog. A NOAEL for inhalation exposure to metam sodium is used to assess ST and IT inhalation exposure. The dose selected is based upon histopathological changes in the nasal passages and changes in clinical chemistry seen at the LOAEL in females following inhalation exposure. Typically EPA uses a 10x factor to account for intraspecies and interspecies variability (combined UF of 100). Therefore, a MOE of 100 defines HED's LOC for ST and IT dermal and inhalation risk to metam sodium.

Releases of fumigants, such as MITC from metam sodium applications, can be categorized into two distinct exposure scenarios. These include residential bystander exposure from two key sources: known or point sources (e.g., at the edge of a treated field), as well as from many or nonpoint sources within a region (e.g., ambient air). Data from field volatility studies were used to estimate known point source exposures. Data from ambient air studies were used to estimate nonpoint source exposures. Ambient-air exposures are most likely to occur to residents living in agricultural areas where there is significant agricultural use during a particular season, such as in the strawberry growing region in California. Data from ambient air studies in California were used to estimate ambient air exposures.

Acute bystander MOEs for MITC inhalation exposure were based on field volatility data from several single application event metam sodium studies. The available field volatility data for metam sodium indicate that most of the acute risks exceed HED's level of concern. These data, however, are limited because they are reflective only of the specific environmental conditions that occurred during the study.

EPA's Industrial Source Complex (ISC) dispersion model was also used to estimate MITC air concentrations near treated fields resulting from metam sodium and potassium application. HED believes that the exposures calculated in this risk assessment are high-end estimates and do not underestimate the risk. Although the Agency has used ISC in the past for regulatory purposes, HED has not previously used the model to estimate air concentrations for pesticides used in agricultural applications. California Department of Pesticide Regulation has been using the ISC model since the early 1990's to estimate bystander exposure to fumigants including methyl bromide. In general, the ISC analyses indicate that acute risks for bystanders exceed HED's level of concern for a minimum of 500 meters from the edge of the treated field under many meteorological conditions and field sizes.

Available ambient data provide results for MITC, but the specific source of MITC cannot be determined

(i.e., from metam sodium, metam potassium, or dazomet). With regard to potential multiple sources of exposures from ambient air, the acute risks to targeted ambient air concentrations for all of the monitoring stations considered do not exceed HED's level of concern.

Acute risks to occupational handlers for the majority of tasks associated with pre-plant field fumigation, applications to ornamentals, food, and feed crops, tobacco plant beds, and turf indicate that risks to exceed HED's level of concern (MOE < 10). Short- and intermediate-term risks to handlers also exceed HED's level of concern (MOE < 30) for most of the tasks assessed. MITC concentrations were also estimated using ISC for the edge of the field at 48 hours after application (minimum time on current labels for worker re-entry). The estimated concentrations for some of the of meteorological conditions assessed exceed the LOC for acute exposure.

Acute risks to occupational handlers for fumigation of sewers indicate that risks exceed HED's level of concern (MOE < 10). Short- and intermediate-term risks to occupational handlers for fumigation of sewers indicate that risks exceed HED's level of concern (MOE < 30).

There are a number of data gaps in both the occupational handler and the occupational and non-occupational (residential bystander) postapplication exposure and risk assessments. Notably, to refine the occupational handler risk assessment, data on actual use patterns including rates, timing, and area treated would better characterize metam sodium and MITC risks. Exposure studies for many equipment types that lack data or that are not well represented in the Agency's PHED (e.g., because of low replicate numbers or data quality) should also be considered based on the data gaps identified in this assessment and based on a review of the quality of the data used in this assessment. Postapplication data gaps include lack of information on the effect of soil seal removal several days after initial application; knowledge of the influence of factors such as wind speed, direction and application rate on the air concentration of MITC after a metam sodium application; effect of an individuals' exposure to multiple metam sodium treated fields; and, the postapplication effect of the use of metam sodium in greenhouses or on lawns.

2.0 Ingredient Profile

2.1 Summary of Registered Uses

Metam sodium and metam potassium are non-selective soil fumigants with fungicidal, herbicidal, insecticidal, and nematicidal properties. The mode of action is inactivation of sulfhydryl groups in amino acids.

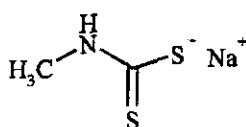
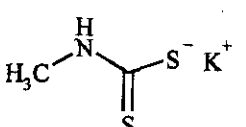
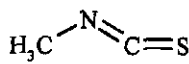
Metam sodium and potassium are active against all living matter in the soil. Metam sodium and potassium end-use products are registered for a variety of crops. Typical applications are made prior to planting to sterilize the soil. Metam sodium may be applied to plant beds as a soil drench treatment, e.g., tobacco plant beds. It may also be applied to field or row crops during pre-plant stages via chemigation, soil broadcast treatment, soil band treatment, soil-incorporated treatment, and soil-injection treatment. Chemigation is the most common method of application. Metam sodium is the third most widely used agricultural pesticide in the U.S. There are a total of 51 active end-use products currently registered. (*Metam Sodium. Residue Chemistry Chapter for the Metam Sodium Reregistration Eligibility Decision (RED) Document. Sherrie Kinard, September 30, 2003.*)

The range of percent of active ingredient in the end-use products is 24-48% for metam sodium and 5-54% for metam potassium for uses on food, fiber and ornamental crops. The maximum application rate is 320 lbs. a.i./A for food and fiber crops; agricultural crops such as tobacco have higher rates. Application equipment that is used to apply metam sodium and metam potassium includes drencher, drip irrigation, gravity irrigation, soil incorporation equipment, soil injector equipment, and sprinkler irrigation. The current entry prohibition period is 48 hours.

Available information from EPA's Biological and Economic Analysis Division (BEAD) using different EPA databases indicates usage for the year 2002 is in the range of 51-55 million pounds per year for metam sodium and 1-2 million pounds per year for metam potassium. (Alsadek, J. *Internal Communication*). Most of the acreage is treated with 190 pounds or less of a.i. per application, the highest use rate is 412 lb a.i./A. Metam sodium's largest markets in terms of total pounds of active ingredient is allocated to potatoes (49%) followed by tomatoes (21%) and cotton (5.5%). The remaining usage is applied over all agricultural sectors but usage in terms of pounds active ingredient used per crop site ranges from less than 1 % to 5%. In terms of percent crop treated, metam sodium's usage is allocated to tomatoes (17%), potatoes (10%) and carrots (5%) (Quantitative Usage Analysis. February 11, 1999).

2.2 Structure and Nomenclature

Table 1 provides the structures and relevant nomenclature for metam sodium, metam potassium, and methyl isothiocyanate (MITC).

Table 1.1. Compound Nomenclature			
Compound	Metam Sodium	Metam Potassium	MITC
Chemical Structure			
Chemical Group	dithiocarbamate	dithiocarbamate	isothiocyanate
Common Name	metam sodium	metam potassium	methyl isothiocyanate
Molecular formula	C ₂ H ₄ NS ₂ Na	C ₂ H ₄ NS ₂ K	C ₂ H ₃ NS
Molecular Weight	129.18	145.289	73.12
CAS No.	137-42-8	137-41-7	556-61-6
PC Code	039003	039002	068103

2.3 Physical and Chemical Properties

A listing of the physical and chemical properties of metam sodium, metam potassium, and MITC included in this assessment is provided in Table 2.

Table 2. Physical and Chemical Properties of Metam Sodium, Metam Potassium, and MITC			
Property	Metam Sodium	Metam Potassium	MITC

12

Mode of Pesticidal Action	not available	not available	Inactivation of sulhydryl groups in amino acids
Appearance	white crystalline solid	yellow to light yellow-green (aqueous formulation (54%) ¹)	colorless crystalline solid
Melting Point	N/A	N/A	35-36° C
Vapor Pressure	4.31 x 10 ⁻⁴ mm of Hg	24 mm of Hg at 25° C (aqueous formulation (54%) ¹)	20 mm of Hg at 25° C
Partition Coefficient	(Log P) <-2.91	N/A	1.05 at 20° C
Solubility in Water	578.29 g/L at 20° C	yes, insoluble in mineral oil	8.94 g/L at 20° C
Toxic Impurities	none ²	none ²	none ²

¹ Data for the aqueous formulations MPs/EPs have been accepted because of the difficulties encountered in producing and maintaining aqueous solutions containing higher concentrations of active ingredient.

² There are no major toxic impurities; however, there are several toxic degradate compounds.

3.0 Metabolism

Metam sodium and metam potassium quickly and predominantly degrade to MITC when placed in soil and water generating 60 to 83% of MITC under prevalent environmental conditions. Environmental fate data suggest that metam sodium photolyzes in surface water with a half-life of 28 minutes and metabolizes aerobically in soil with a half-life of 23 minutes. Metam sodium and metam potassium are also efficiently converted to MITC *in vivo*; therefore, MITC is considered to be the residue of concern for both metam sodium and metam potassium.

3.1 Description of Primary Crop Metabolism

In an acceptable turnip metabolism study, the results show that the ultimate breakdown products consist of natural plant biochemicals. Neither metam sodium, MITC, nor any related thioureas or methylated ureas were detected in the extractable radioactivity or the post-extraction solids. The observed radioactivity was shown to be distributed over a variety of natural products indicating complete incorporation of metam sodium into the carbon pool. These data are supported by the strawberry and tomato studies conducted with another MITC generator, dazomet. Based upon the results of the metabolism studies, residues of metam sodium and MITC are not expected to occur in plants. MITC's volatility in the environment, phytotoxicity to crops, and metabolism in plants assure that there is no reasonable expectation of finite residues to be incurred in/on any raw agricultural commodity when these products are applied according to label directions. Therefore the use of metam sodium/potassium as a soil fumigant is considered to be a non-food use and tolerances are not needed.

3.2 Description of Livestock Metabolism

The requirement for a livestock metabolism study is waived for metam sodium and metam potassium because there are no metam sodium residues of concern detected in plants.

3.3 Description of Rat Metabolism

In a rat metabolism study, dazomet, metam sodium, and MITC were tested at two dose levels. All three were excreted mainly in urine with small amounts excreted in feces. Three different compounds (MITC, carbon dioxide [CO₂], carbon oxide sulfide [COS]/carbon disulfide [CS₂]) were found to be excreted in

the lungs over a 73 hour collection period. There were no differences between males and females in amounts excreted *via* the three excretion routes; however, tissue and plasma levels, and plasma area under the curves (AUCs) were consistently higher in females than in males. It should be noted that these differences were approximately 2-fold or less. All three compounds were rapidly absorbed from the GI tract. High uptake was seen in the liver, kidneys, and lung, with the lowest level in testes, brain and eyes. Metabolic profiles detected in urine, liver, and kidneys were basically similar for the three compounds but there were some differences, mainly quantitative in nature. No inhalation pharmacokinetic studies are available at this time.

4.0 Hazard Assessment and Characterization

4.1 Hazard Characterization

The text and tables below were summarized or extracted from the following documents prepared for EPA's revised risk assessment for metam sodium.

- 3rd Revised Toxicology Disciplinary Chapter for: Metam Sodium (PC Code 039003) and Methyl isothiocyanate (MITC, PC Code 068103) August 19, 2004. TXRNo.: 0050771
- Toxicity endpoint selection and inhalation dosimetry calculations for metam sodium, dazomet, and MITC. August 19, 2004. TXR No: 0051475
- Human eye and nasal irritation resulting from air exposure to MITC. August 19, 2004. TXR No: 0051475
- 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. August 19, 2004 TXR No. 0052776
- METAM SODIUM/METAM POTASSIUM: The HED Chapter of the Reregistration Eligibility Decision Document (RED). PC Codes 039003 and 039002. Case 2390. DP Barcode: D293329. August 19, 2004

4.1.1 Database Summary

Studies available and acceptable (animal, human, general literature)

Although the toxicological database for metam sodium and dazomet are complete for risk assessment purposes, the toxicological database for MITC is not complete. Many toxicological studies via the oral route with MITC do not meet the guideline requirements, primarily due to problems surrounding the volatility of MITC and inadequate characterization of exposure concentrations or doses. Some of the oral data gaps are being filled through bridging with the toxicology databases of metam sodium and dazomet. Relating to the inhalation toxicity with these pesticides, two subchronic inhalation studies in MITC, one subchronic inhalation study in metam sodium, and no inhalation studies in dazomet are available at this time. An eye irritation and odor threshold study in human subjects with MITC is also available.

Metabolism, toxicokinetic, mode of action data

No inhalation pharmacokinetic or metabolism studies are available at this time for MITC, metam sodium, or dazomet. Metam sodium, metam potassium, and dazomet are efficiently converted to MITC *in vivo*. Oral pharmacokinetic and metabolism studies in rats for dazomet, metam sodium, and MITC were submitted. All three were excreted mainly in urine with small amounts excreted in feces. Three different compounds (MITC, carbon dioxide [CO₂], carbon oxide sulfide [COS]/carbon disulfide [CS₂]) were found to be excreted in the lungs over a 73 hour collection period. Tissue and plasma levels at all time periods, and plasma AUCs were consistently higher in females than in males; however these differences were approximately 2-fold or less. Although, the tissue with the highest uptake for all three compounds was the thyroid gland is notable that tissue retention of radioactive material was low in both sexes and at all doses. High uptake were also seen by the liver, kidneys, and lung, with the lowest level in testes, brain and eyes. Metabolic profiles detected in urine, liver, and kidneys were basically similar for the three compounds but there were some differences, mainly quantitative in nature.

The mode of toxic action for MITC is not known at this time; reactivity with biological nucleophiles such as sulfhydryl groups of glutathione or proteins has been proposed (Valentine, et al., 1995).

Sufficiency of studies/data

An acute inhalation neurotoxicity study in MITC with additional measurements to characterize the effects on the complete respiratory tract is required at this time. There are no studies available for evaluating the effects of MITC following inhalation exposure in the young, therefore an inhalation reproductive toxicity study is also required at this time. Because of the potential for chronic exposures and the finding of focal squamous cell metaplasia in the respiratory epithelium following 28-days of inhalation exposure to MITC in rats, at this time, EPA is requiring carcinogenicity studies in mice and rats via the inhalation route.

4.1.2 Endpoints

Following air exposures to MITC, consistent effects are observed in rats and humans. For example, clinical signs and pathological changes of the respiratory tract consistent with an irritant have been observed in laboratory studies in rat. Humans exposed to MITC complain of symptoms such as itchy and burning eyes, rash and burning skin, nausea, scratchy throat, salivation, coughing, and shortness of breath. Histological changes consistent with a highly irritating compound in the nasal passages and lungs were observed in the 28-day study with MITC and also the 90-day study with metam sodium. In the 90-day inhalation study with MITC, negative histopathological findings are questionable because of several reasons including lack of nasal pathology and poor analytical data.

There is remarkable similarity in the oral doses causing similar toxic effects for metam sodium, dazomet, and MITC, particularly at low to moderate doses. Specifically, reduced body weight gain and food consumption in addition to changes in hematological parameters were observed at low doses in oral toxicity studies with rats, mice, rabbits, and dogs. Effects on the liver have been noted in dogs at doses with similar molar levels. Reduced motor activity has been noted at all dose levels in oral acute neurotoxicity testing in studies with metam sodium and dazomet. In oral developmental toxicity studies with MITC, dazomet, and metam sodium, effects such as fetal weight decrements, reduced ossification of various skeletal structures, and increased incidence of resorptions have been noted at similar molar dose levels. There is no quantitative susceptibility observed in the oral developmental and reproductive toxicity studies with metam sodium, MITC, or dazomet. All of the developmental NOAELs are equal to or larger than the NOAELs for maternal toxicity. There is, however, qualitative susceptibility in two rabbit

developmental studies with dazomet and two rat developmental toxicity studies with metam sodium. In these studies, increased incidence of resorptions were noted at a dose that resulted in maternal body weight gain decreases. At higher doses levels of metam sodium, the neurotoxic effects from the *in vivo* production of CS₂ begin to manifest. Specifically, incidence of meningocele has been noted following oral administration of metam sodium in two developmental studies in rat and one developmental study in rabbits. There were no neuropathological changes noted in the oral acute and subchronic neurotoxicity studies with metam sodium and dazomet, however, the doses used in the metam sodium subchronic toxicity study may not be sufficiently high to detect these effects. There is some evidence that MITC may cause immunotoxicity at high oral and dermal doses (Pruett et al., 1992, Padgett, et al., 1992; Kiel et al., 1996).

There is no evidence of endocrine disruption in the database of toxicology studies. The systemic effects following dermal exposure to metam sodium at this time are not known; the existing dermal study does not take adequate precautions for the volatilization of MITC.

4.1.3 Dose-response

Based on the currently registered use pattern of metam sodium, dietary exposure is not expected. Acute and chronic reference doses are not necessary at this time.

Historically, for typical agricultural pesticide chemicals, the Health Effects Division (HED) has not developed quantitative risk assessments based on eye or respiratory irritation. For occupational pesticide workers, EPA assumes that the personal protective equipment (PPE) worn by workers adequately protects against irritation-type effects which could result from exposure to pesticide chemicals. The level of PPE required for workers is based on the results of quantitative risk assessments, acute dermal and inhalation toxicity testing in animals along with eye and skin irritation and skin sensitization studies. For the general population, EPA assumes that respiratory and eye irritation effects are not of concern, in general, since most agricultural pesticides are not volatile and are unlikely to move offsite after application is complete. However, the general public can be exposed to fumigants in air following application because of their volatility. Specifically, fumigants can off-gas into ambient air and can be transported off-site by wind to non-agricultural areas. For example, the California Pesticide Illness Surveillance Program (CPISP) reports that from 1990 to 1998, 278 of 390 reported cases regarding metam sodium/MITC involved non-occupational exposure from drift. The types of symptoms reported by the CPISP are consistent with exposure to an irritant and include: eye effects-- watery, burning, and itchy eyes, blurred vision; skin effects - rash, burns, redness, swelling; systemic effects- nausea, chest pain, scratchy throat, diarrhea, weakness, dizziness, headache, malaise, salivation, vomiting; and respiratory effects- cough, shortness of breath. Hazard effects induced by MITC and metam sodium have been evaluated by HED's Hazard Identification and Assessment Review Committee (HIARC) several times between 2000-2004, most recently on March 16, 2004 (TXR no 0052467). On May 24, 2004, HED's Science Policy Council (HED-SPC) met to discuss issues related to the merit of utilizing eye and/or respiratory irritation for estimating acute inhalation risk and at that meeting recommended that the eye irritation study with MITC be selected as the acute inhalation endpoint. The toxicological endpoints discussed below reflect the combined conclusions of the HIARC and HED-SPC in addition to relevant calculations using EPA's reference concentration methodology.

Based on air monitoring studies, MITC exposures can be acute (less than 24 hours), short-term (1-30

days), intermediate-term (1 month-6 months), and/or long-term (> 6 months) in duration. Occupational exposure to metam sodium and dazomet can occur from the dermal and inhalation pathways. These fumigants do not require food tolerances, are considered to be a 'non-food use.' Thus, acute and chronic reference doses are not needed for metam sodium, dazomet, or MITC.

4.1.3.1 Inhalation Exposure

As discussed in the revised risk assessment for metam sodium (Aug, 2004), following communication with EPA's Office of Air and Office of Research and Development (ORD), OPP has determined that it is appropriate to utilize the methods and dosimetry equations described in EPA's reference concentration (RfC) guidance (1994) for calculating human equivalent concentrations (HECs) and for use in margin of exposure (MOE) calculations. Compared to the methods previously used by OPP, the dosimetry equations in the RfC guidance more appropriately address different properties of gases and particles, different properties of reactive and non-reactive compounds, and explicitly consider some differences in the structure of the respiratory tract between laboratory animals and humans. As shown below, OPP has used the dosimetry equations from the RfC guidance to develop HECs for effects observed in the MITC 28-day rat study. These HECs have been used to estimate short-, intermediate-, and long-term inhalation risk to that chemical. As discussed in detail below, it is noteworthy that the dosimetry equations from the RfC guidance have not been used to develop HECs from the MITC human eye irritation study or the 90-day metam sodium inhalation study.

At present time, EPA and CDPR use different dosimetry equations for calculating inhalation risk. The CDPR procedure is based on data obtained from a 1979 article published in the *International Archives of Occupational and Environmental Health* by Zielhuis and van der Kreek and the Technical Support Document for Exposure Assessment and Stochastic Analysis drafted by the Office of Environmental Health Hazard Assessment (OEHHA) of CalEPA in 1996.¹ The two approaches differ in their use of species-specific parameters to derive HECs. Therefore, differences noted in the short-, intermediate-, and long-term risk assessments of each organization are due, in part, to their use of different methodologies and use of different uncertainty factors (UFs). Both OPP and CDPR have selected the human eye irritation study for purposes of estimating acute inhalation risk. OPP and CDPR have selected port of entry effects from the 28-day inhalation study in rats for purposes of estimating short-, intermediate-, and long-term risk. The NOAELs/LOAELs for this study, however, differ between OPP and CDPR. A detailed comparison of the OPP and CDPR reviews for this study is provided in the 3rd revised toxicology disciplinary chapter for metam sodium and MITC. Comparison of endpoints for dermal risk assessment is also provided in the 3rd revised toxicology disciplinary chapter for metam sodium and MITC. As OPP understands the importance to harmonize, to the extent possible with other regulatory agencies, this risk assessment will present HECs derived using both methodologies. OPP plans to continue its effort to communicate and harmonize with other regulatory organizations. Additional information on the methodologies used in this risk assessment and HEC arrays are available in Appendix B.

Acute Inhalation Exposure

¹ Technical Support Document for Exposure Assessment and Stochastic Analysis. OEHHA (1996) Zielhuis, RL and van der Kreek, FW (1979). "The use of a safety factor in setting health based permissible levels for occupational exposure." *Int. Arch. Occ. Env. Health* 42:191-201

a. **Metam Sodium**

There are no studies which provide appropriate endpoints for estimating acute inhalation risk to metam sodium. Therefore, acute inhalation risk to metam sodium has not been estimated.

b. **MITC**

As suggested by results of the human eye irritation with MITC and oral acute neurotoxicity studies with metam sodium and dazomet, single inhalation exposures may potentially result in adverse effects. At the present time, the data base of acceptable inhalation toxicology studies for MITC is limited to a 28-day study in rat (MRID no. 45314802), eye irritation and odor threshold in human subjects (MRID no. 44400401), and acute lethality in rat (MRID no 45919410). There are no studies with laboratory animals available which specifically evaluate the dose-response relationship and the continuum of potential *acute, single-day* respiratory effects (i.e., progression to more serious clinical outcomes) from exposure to MITC. However, the MITC eye irritation and odor threshold study (MRID 44400401) evaluated the dose-response relationship for eye irritation at exposure durations ranging from 4 minutes to 8 hours. The eye irritation study provides an appropriate endpoint for acute risk assessment for MITC.

The types of symptoms reported by the California Pesticide Illness Surveillance Program (CPISP) following human exposures to MITC are consistent with exposure to an irritant and include: eye effects-- watery, burning, and itchy eyes, blurred vision; skin effects - rash, burns, redness, swelling; systemic effects- nausea, chest pain, scratchy throat, diarrhea, weakness, dizziness, headache, malaise, salivation, vomiting; and respiratory effects- cough, shortness of breath. With respect to respiratory impairment, arguably, eye irritation is less severe compared to other possible effects associated with inhalation exposure to MITC, particularly given the expected reversible nature of the eye irritation effects at lower concentrations. Nonetheless, eye (as well as nose and throat) irritation is uncomfortable and could potentially interfere with everyday tasks or activities. Due to the limitations in the existing *inhalation* toxicology database for MITC, the degree to which eye irritation predicts more serious outcomes is unclear. However, in the absence of more robust dose-response data from acute exposures, eye irritation can be considered as a *biomarker* and *surrogate for potential respiratory effects*. It is also notable that EPA's RfC methodology document (1994) includes eye, nasal, and throat irritation in the list of adverse effects-- albeit at the lower end of the hierarchal list which ranks effects from most to less severe.

- For a one-minute exposure, the NOAEL for eye irritation is 3.3 ppm due to a lack of response in any parameter tested.
- For exposures 4-14 minutes, the NOAEL for eye irritation is 0.6 ppm based on responses on the Likert subjective scale at 1.9 ppm.
- For exposures of 1-8 hours, based on the statistically significant subjective (Likert scale) responses at 0.8 ppm MITC at 1-4 hours and the statistically significant eyeblink responses at 2 and 3 hours, 0.22 ppm was designated as the NOAEL for this study.

Dose and Endpoint for Risk Assessment: As this study used female and male human subjects, animal to human extrapolation is not necessary. No equations have been used to mathematically adjust the NOAELs provided by the eye irritation study. Typically EPA considers an UF of **10x for intraspecies**

extrapolation. This study did not evaluate any persons younger than 18 or older than 67. Children and older people are potentially more sensitive than healthy adults, like those who participated in the study. Therefore, at this time there is not sufficient justification for reducing the 10x factor for intraspecies extrapolation. Consequently, a 10X UF defines HED's level of concern (10x intraspecies variation) in accordance with guidance provided in the RfC methodology (see section 4.2 below) and current HED policy.

c. Dazomet

There are no studies which provide appropriate endpoints for estimating acute inhalation risk to dazomet. Therefore, acute inhalation risk to dazomet has not been estimated.

Short and Intermediate Inhalation Exposure

a. Metam Sodium

The 90-day inhalation toxicity study with metam sodium (MRID no. 00162041) provides the endpoints for short- and intermediate-term exposures. Inhalation exposure to metam sodium, most often as an aerosol, is expected only for occupational activities. In this study, 18 Sprague-Dawley rats/sex/dose group were exposed to aerosolized metam sodium (37% a.i.) in whole-body chambers for 6 hr/day, 5 days/week. The cumulative mean chamber metam sodium concentrations were 0, 6.5, 45 and 160 mg/m³ (measured values based on the *sodium ion* level corrected for sodium ion levels measured from the control). Reviewers at the California Department of Pesticide Regulation calculated the doses to be 0, 1.11, 7.71, and 27.43 mg/kg/day. Mean MITC measured concentrations were 0, 0.78, 2.2, and 5.7 mg/m³ (0, 0.12, 0.38, 0.98 mg/kg/day) (measured by infrared adsorption).

Dose and Endpoint for Risk Assessment: The LOAEL in females is 45 mg/m³ (7.71 mg/kg/day) of metam sodium (based on Na levels; 2.2 mg/m³ [0.38 mg/kg/day] measured MITC), based on histopathological changes in the nasal passages (ie, mucigenic hyperplasia) and changes in clinical chemistry. The LOAEL in males is 160 mg/m³ (27.43 mg/kg/day) of metam sodium (based on Na levels; 5.7 mg/m³ [0.98 mg/kg/day] measured MITC) based on histopathological changes in the lungs and nasal passages.

The NOAEL for females is 6.5 mg/m³ (1.11 mg/kg/day) of metam sodium (based on Na levels; 0.7 mg/m³ [0.12 mg/kg/day] measured MITC). The NOAEL for males is 45 mg/m³ (7.71 mg/kg/day) of metam sodium (based on Na levels; 2.2 mg/m³ [0.38 mg/kg/day] measured MITC).

The inhalation dosimetry equations in the RfC methodology have *not* been used in the calculation of occupational inhalation risk to metam sodium. Because of the nature of the available exposure data for metam sodium and the need to use PHED in occupational risk calculations, OPP has not revised the toxicity endpoint for use in MOE calculation. In the coming months, as the fumigant cluster risk assessment develops and is further refined, OPP may determine that is appropriate to calculate HECs for metam sodium based on the 90-day rat inhalation study. This study is of the appropriate duration for these risk assessments. Default 10x factors for intraspecies and interspecies extrapolation are appropriate for establishing HED's LOC for short- and intermediate-term inhalation risk to MITC. Thus, a combined UF of 100X defines HED's level of concern.

b. MITC

In a 28 day inhalation toxicity study (MRID 45314802), Methyl Isothiocyanate [96.9 % a.i.] was administered to 5/sex/dose of SPF Wistar/Chubb:THOM rats by whole body exposure at analytical concentrations of 0, 5.0, 20, or 100 mg/m³ equivalent to 0, 5.0, 20, or 100 ug/L (measured concentrations 0, 5.1, 19.9 or 100 ug/L) and (equivalent to concentrations of 0, 1.7, 6.8, and 34 ppm) for 6 hours per day, 5 days/week for a total of 28 days.

Dose and Endpoint for Risk Assessment: The RfC methodology recommends the development of array tables which evaluate inhalation dosimetry and animal to human extrapolation for systemic effects in addition to local effects in the extrathoracic, tracheobronchial, and pulmonary regions of the respiratory tract. EPA has developed array tables for the effects from the 28-day MITC inhalation study using the NOAELs and LOAELs shown below. The array tables can be found in "Toxicity endpoint selection and inhalation dosimetry calculations for metam sodium, dazomet, and MITC (August 19, 2004. TXR No: 0051475)".

- The systemic LOAEL is 19.9 mg/m³(6.8 ppm), based on clinical signs consistent with irritation in both sexes and increased neutrophilic polymorphonuclear granulocytes in the blood of males. The systemic NOAEL is 5 mg/m³(1.7 ppm).
- The LOAEL for effects in the extrathoracic (ET) region is 100 mg/m³(34ppm), based on observation of pathological changes of the nasal cavity (metaplasia of respiratory epithelium and atrophy of the olfactory epithelium). The ET NOAEL is 19.9 mg/m³(6.8 ppm).
- The LOAEL for effects in the tracheabronchial (TB) region is 100 mg/m³(34ppm), based on observation of pathological changes (tracheal epithelial proliferation and single cell necrosis, bronchopneumonia and bronchial and bronchiolar epithelial proliferation). The TB NOAEL is 19.9 mg/m³(6.8 ppm).

As shown below, the pathological effects noted in the nasal cavity (i.e. extrathoracic region; metaplasia of respiratory epithelium and atrophy of the olfactory epithelium) are the most sensitive for this study and have been used to estimate short-, intermediate-, and long-term inhalation risk to MITC. Because EPA's RfC methodology accounts for some of the pharmacokinetic differences between animals and humans, the interspecies factor is typically reduced to 3x. [This 3x accounts for pharmacodynamic differences between animals and humans]. A 10x factor for intraspecies extrapolation accounts for within species variability. Thus, HED's LOC for short- and intermediate-term inhalation risk to MITC is an MOE of 30. The HECs differ between non-occupational and occupational scenarios because the residential HEC is based on 24-hour exposures occurring 7 days per week, whereas the occupational HEC is based on 8-hour exposures occurring 5 days per week.

c. Dazomet

There are no inhalation studies with dazomet available at this time. Inhalation exposure to dazomet is expected only for occupational activities. See HECs calculated for MITC.

Chronic Inhalation Exposure**a. Metam Sodium**

Long-term occupational exposure to metam sodium is not expected.

b. MITC

Ambient air monitoring data indicates that chronic exposure is possible. At present time, there are no chronic inhalation studies with MITC. Thus, the 28-day inhalation study in rats provides the most appropriate endpoints for estimating long-term risk to MITC. There is uncertainty regarding effects from chronic exposures and the degree to which the pathological changes in the respiratory tract, notably metaplasia of respiratory epithelium, could occur at lower exposure concentrations following longer exposure concentrations. EPA's RfC methodology accounts for some of the pharmacokinetic differences between animals and humans, the interspecies factor is typically reduced to 3x. [This 3x accounts for pharmacodynamic differences between animals and humans]. A 10x factor for intraspecies extrapolation accounts for within species variability. EPA historically applies a 10x factor to account for the uncertainties in extrapolating from subchronic to chronic duration. Thus, HED's LOC for long-term inhalation risk to MITC is an MOE of 300.

c. Dazomet

Long-term occupational exposure to dazomet is not expected.

4.1.3.2 Dietary Exposure

Metam sodium's volatility in the environment and results of metabolism studies in plants assure that there is no reasonable expectation of finite residues to be incurred in/on any raw agricultural commodity when these products are applied according to label directions. Therefore, this fumigant does not require food tolerances; therefore, a dietary risk assessment is not required.

4.1.3.3 Dermal Exposure**4.1.3.3.1 Dermal Absorption****a. Metam Sodium**

Dermal Absorption Factor: 2.5%

¹⁴C-Metam sodium was applied to male rats in aqueous formulations at the nominal dose levels of 0.1, 1 and 10 mg/rat to an area of 11.6 cm² on the back. The application site was protected by a glass saddle which contained an activated charcoal filter to adsorb any volatile radioactivity which evaporated from the skin surface. Within each group, four animals were killed following a 1, 2, 10, and 24 hours exposure and excreta collected over the study period. For 4 additional animals in each treatment group, the treatment area was washed 10 h after administration and excretion monitored over a total of 72 hours. Mean percent absorbed dose at 10 hours was 2.5% (2.355%, 3.683%, 1.514%, respectively).

b. MITC

No dermal absorption studies are available. The HIARC did not select a dermal absorption factor for MITC. Dermal endpoints were not selected; dermal risk assessments for MITC are not required.

c. Dazomet

Dermal Absorption Factor: 4.5%

No dermal absorption studies are available. A percent dermal absorption can be estimated by comparing the results of the oral and dermal toxicity studies. Ideally, LOAEL for the similar effects and in the same species via oral and dermal route may be used in estimating dermal absorption. However, the NOAEL in rabbit 21-day dermal toxicity was greater than 1000 mg/kg/day (HDT). A dermal absorption value for dazomet is estimated to be 4.5% (developmental and maternal LOAEL of 45 mg/kg/day in rabbits divided by NOAEL of 1000 mg/kg/day dermal study times 100).

4.1.3.3.2 Short-Term, Dermal (1-30 days) Exposure

a. Metam Sodium

The metam sodium developmental toxicity study in rats (MRID nos 41577101, 42170101, and 92097012) provides the endpoint for the short-term dermal risk assessment. In this developmental toxicity study, metam sodium (42.2%) was administered at dose levels of 0, 4.22, 16.88, and 50.64 mg/kg/day (0, 2.36, 9.45 and 28.36 mg/kg/day MITC equivalent) by gavage to pregnant Wistar rats from days 6 through 15 of gestation.

Dose and Endpoint for Risk Assessment: The developmental LOAEL is 16.88 mg/kg bw/day (9.45 mg/kg/day MITC equiv.), based on the increased incidence of skeletal observations and the increase in total resorptions and resorptions/dam. The developmental NOAEL is 4.22 mg/kg /day. Since an oral NOAEL was selected, the 2.5 % dermal absorption factor should be used for route-to-route extrapolation. Default 10x factors for intraspecies and interspecies extrapolation are appropriate for establishing HED's LOC for short-term dermal risk to metam sodium. Thus, a combined UF of 100X defines HED's level of concern.

b. MITC

A short-term dermal endpoint for MITC was not selected. No dermal hazard via typical dermal contact with MITC is expected. Unprotected skin could be exposed to MITC vapor; however this exposure can not, at this time, be quantified.

c. Dazomet

The acute neurotoxicity study with dazomet (MRID no 43465302) provides the endpoint for the short-term dermal risk assessment. This study, Wistar Chbb: THOM (SPF) rats (10/sex/group) were orally gavaged once with dazomet in 0.5% aqueous carboxymethylcellulose at doses of 0 (vehicle only), 50, 150 and 450 mg/kg body weight (a.i. equivalents: 50, 130, and 450 mg/kg) for males and 0, 15, 50, and 150 mg/kg

body weight (a.i. equivalents: 13, 50, and 130 mg/kg) for females.

Dose and Endpoint for Risk Assessment: The LOAELs with dazomet for neurobehavioral effects were established at 50 mg/kg in males (FOB findings and reduced number of rearings) and 15 mg/kg in females (decreased motor activity). Since an oral LOAEL was selected, the 4.5 % dermal absorption factor should be used for route-to-route extrapolation. Default 10x factors for intraspecies and interspecies extrapolation are appropriate for short-term dermal risk to dazomet. A NOAEL was not achieved; an additional 10x uncertainty factor is typically applied for the use of a LOAEL (UF₁). Thus, a combined UF of 1000X defines HED's level of concern for short-term dermal risk to dazomet.

4.1.3.3.3 Intermediate- Term, Dermal (1 -6 months) Exposure

a. Metam Sodium

The chronic toxicity in the dog (MRID no 43275801) provides the endpoint for the intermediate-term dermal risk assessment. Metam sodium (43.148% w/w, Batch Reference: BAS/005/00N 90-2) was administered to 4 beagle dogs/sex/dose in gelatin capsules at doses of 0, 0.05, 0.1, and 1.0 mg/kg/day (0, 0.028, 0.056 and 0.56 mg/kg/day MITC equivalent) for 52 weeks.

Dose and Endpoint for Risk Assessment: The LOAEL is > 1mg/kg/day in males and equal to 1 mg/kg/day for females, based on increased ALT and microscopic changes in the liver. The NOAEL is = 1 mg/kg/day for males and 0.1 mg/kg/day for females. This dose/endpoint is appropriate for the intermediate-term exposure duration since increases in ALT were seen over the course over the study until termination. Since an oral NOAEL was selected, the 2.5 % dermal absorption factor should be used for route-to-route extrapolation. Default 10x factors for intraspecies and interspecies extrapolation are appropriate for establishing HED's LOC for intermediate-term dermal risk to metam sodium. Thus, a combined UF of 100X defines HED's level of concern.

b. MITC

An intermediate-term dermal endpoint for MITC was not selected. No dermal hazard via typical dermal contact with MITC is expected. Unprotected skin could be exposed to MITC vapor; however this exposure can not, at this time, be quantified.

c. Dazomet

The subchronic toxicity in the rat (MRID no 41865502) provides the endpoint for the intermediate-term dermal risk assessment. In this study, dazomet(>97% a.i.) was administered to 10 Wistar Chub-THOM (SPF) rats/sex/dose in the diet for 90 days, at dose levels of 0, 20, 60, 180, or 360 ppm. The achieved doses of dazomet were 1.5, 4.5, 13.7, and 28.0 mg/kg/day in males and 1.7, 5.3, 15.4, and 32 mg/kg/day in females.

Dose and Endpoint for Risk Assessment: The systemic NOAEL is 1.5 mg/kg/day in male rats. The systemic LOAEL is 4.5 mg/kg/day for male rats based on increased liver weight, liver:body weight ratio and pronounced foci of fatty degeneration in the liver. Since an oral NOAEL was selected, the 4.5 % dermal absorption factor should be used for route-to-route extrapolation. Default 10x factors for intraspecies and interspecies extrapolation are appropriate for establishing HED's LOC for intermediate-

term dermal risk to dazomet. Thus, a combined UF of 100X defines HED's level of concern.

4.1.3.3.4 Long-Term Dermal (>6 Months) Exposure

a. Metam Sodium

Long-Term exposure via the dermal route is not expected.

b. MITC

A long-term dermal endpoint for MITC was not selected. No dermal hazard via typical dermal contact with MITC is expected. Unprotected skin could be exposed to MITC vapor; however this exposure can not, at this time, be quantified.

c. Dazomet

A long-term dermal endpoint for dazomet was not selected. Long-Term exposure via the dermal route is not expected considering the use pattern and its stability in the environment.

4.1.3.4 Classification of Carcinogenic Potential

a. Metam Sodium

The Health Effects Division Carcinogenicity Peer Review committee (CPRC) met on March 01, 1995 to discuss and evaluate the weight -of-the-evidence on metam sodium with particular reference to its carcinogenic potential. The CPRC concluded that metam sodium should be classified as a Group B2 - probable human carcinogen, based on statistically significant increases in malignant angiosarcomas in both sexes of the CD-1 mouse in male. 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, at all sites combined. The most potent unit risk (Q_1^*) is 1.98×10^{-1} in human equivalents converted from animals to humans by use of the 3/4's scaling factor (HED Doc. No. 012954).

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 and to consider public comments received on EPA's preliminary risk assessment of metam sodium (May, 2004) regarding a reclassification of metam sodium's cancer risk. HED considered the public comments and documents provided by the Metam Sodium Alliance and concluded that re-evaluation by the CARC is not warranted at this time—the Group B2 cancer classification for metam sodium remains (TXR 0052776).

b. MITC

There are insufficient data to characterize the cancer risk of MITC, due to the limitations in the rat and mouse MITC oral carcinogenicity studies, and also the lack of chronic testing via the inhalation route.

c. Dazomet

At the March 10, 1993 and on May 26, 1993, meeting the HED Cancer Peer Review Committee (CPRC) classified dazomet as a "Group D- not classifiable as to human carcinogenicity" based on the lack of tumors in male B6C3F1 mice, equivocal evidence for hepatocellular tumors in females, and carcinogenicity and chronic feeding studies in Wistar rats which appeared to be negative for carcinogenicity.

4.2 Uncertainty Factors

Based on the currently registered use pattern of metam sodium, dietary exposure is not expected. Acute and chronic reference doses are not necessary at this time; the 10x factor provided by the Food Quality Protection Act of 1996 does not apply.

For metam sodium, dazomet, and MITC, the uncertainty factors differ based on duration and route of exposure.

- For acute inhalation exposures to MITC, because a study using human subjects is being used, an interspecies factor is not necessary. A default 10X was assigned for intraspecies variability.
- For short, intermediate, and long-term inhalations exposures to MITC, the RfC methodology was used to estimate HECs from the 28-day inhalation rat study. The RfC methodology takes into consideration some of the PK differences between ras and humans; thus the UF for interspecies extrapolation may be reduced to 3X while the UF for intraspecies variation is retained at 10X. The combined UF for short- and intermediate-term risk assessment is 30X. An additional 10X factor to account for extrapolation from subchronic to chronic exposure is assigned for long-term exposure; the combined UF for long-term risk assessment for MITC is 300X.
- For dermal occupational exposures to metam sodium, default 10x factors for intraspecies and interspecies extrapolation are appropriate. The combined UF for short- and intermediate-term dermal exposures is 100X.
- For short-term dermal occupational exposures to dazomet, default 10x factors for intraspecies and interspecies extrapolation are appropriate. A 10x factor is applied for a LOAEL to NOAEL extrapolation. The combined UF for short- and intermediate-term dermal exposures is 1000X.
- For intermediate-term dermal occupational exposures to dazomet, default 10x factors for intraspecies and interspecies extrapolation are appropriate. The combined UF for short- and intermediate-term dermal exposures is 100X.
- For inhalation occupational exposures to metam sodium, the RfC methodology was not used to calculate HECs. Default 10x factors for intraspecies and interspecies extrapolation are appropriate. The combined UF for short- and intermediate-term inhalation exposures to

metam sodium is 100X.

- Based on the currently registered uses (as of August 19, 2004) of metam sodium, metam potassium, dazomet, and/or MITC, dietary exposure is not expected. Acute and chronic reference doses are not necessary at this time; the 10x factor provided by the Food Quality Protection Act of 1996 does not apply.

4.3 Endocrine Disruption

Following recommendations of its Endocrine Disruptor and Testing Advisory Committee (EDSTAC), EPA determined that there was a scientific basis for including, as part of the endocrine disruption screening program, the androgen and thyroid hormone systems, in addition to the estrogen hormone system. EPA also adopted EDSTAC's recommendation that the Program include evaluations of potential effects in wildlife. For pesticide chemicals, EPA will use FIFRA and, to the extent that effects in wildlife may help determine whether a substance may have an effect in humans, FFDCA authority to require the wildlife evaluations. As the science develops and resources allow, screening of additional hormone systems may be added to the Endocrine Disruptor Screening Program (EDSP).

It is notable that based on the available toxicology studies in metam sodium and MITC, there is no indication of endocrine disruption.

4.4 Summary of Toxicological Endpoint Selection

Exposure Scenario	Dose Used in Risk Assessment	Uncertainty Factors and Level of Concern for Risk Assessment	Study and Toxicological Effects
Acute Dietary <u>general population</u> including infants and children	Acute dietary endpoints were not selected since the use-pattern does not indicate potential for dietary exposure.		
Chronic Dietary <u>all populations</u>	Chronic dietary endpoints were not selected since the use-pattern does not indicate potential for dietary exposure.		
Dermal Short-Term (1 - 30 days) Occupational	Maternal NOAEL ^{a,d} = 4.22 mg/kg/day Dermal absorption factor = 2.5%	Occupational = LOC ^e for MOE = 1000	Developmental toxicity in rat (MRID 41577101) LOAEL ^f = 16.88 mg/kg/day based on reduced body weight gain and decreased food efficiency in maternal rats
Dermal Intermediate-Term (1 - 6 Months) Occupational	Oral NOAEL ^a = 0.1 mg/kg/day Dermal absorption factor = 2.5%	Occupational = LOC for MOE = 100	Chronic toxicity in dog (MRID 43275801) LOAEL = 1 mg/kg/day based on increased ALT and microscopic changes in the liver in females.

Table 3: Summary of Toxicological Dose and Endpoints for Use in Melam Sodium Oral and Dermal Human Health Risk Assessments			
Exposure Scenario	Dose Used in Risk Assessment	Uncertainty Factors and Level of Concern for Risk Assessment	Study and Toxicological Effects
Dermal Long-Term (> 6 Months) Occupational	Oral NOAEL ^a = 0.1 mg/kg/day Dermal absorption factor = 2.5%	Occupational = LOC for MOE = 100	Chronic toxicity in dog (MRID 43275801) LOAEL = 1 mg/kg/day based on based on increased ALT and microscopic changes in the liver in females.
Cancer	Classification: Probable human carcinogen (B2) Q1* = 1.98x10 ⁻¹ in human equivalents converted from animals		

a Since an oral NOAEL was selected, a dermal absorption factor of 2.5% should be used in route-to-route extrapolation.; b Margin of Exposure (MOE) = 100 [10x for interspecies extrapolation and 10x for intraspecies variations.]; c LOC = level of concern; d NOAEL = no observed adverse effect level; e LOAEL = lowest observed adverse effect level.

Table 4: Summary of Toxicological Dose and Endpoints for Use in MITC Oral and Dermal Human Health Risk Assessments			
Exposure Scenario	Dose Used in Risk Assessment	Uncertainty Factors and Level of Concern for Risk Assessment	Study and Toxicological Effects
Acute Dietary <u>General population</u> including infants and children	Dietary exposure is not expected for MITC at present time.		
Chronic Dietary (All populations)	Dietary exposure is not expected for MITC at present time.		
Dermal All durations	No dermal hazard via typical dermal contact with MITC is expected. Unprotected skin could be exposed to MITC vapor; however this exposure can not, at this time, be quantified.		
Cancer	Classification: Insufficient data to characterize cancer risk		

a Margin of Exposure (MOE) or Uncertainty Factors (UF) = 100 [10x for interspecies extrapolation, 10x for intraspecies variations.]; b LOC = level of concern; c NOAEL = no observed adverse effect level; d LOAEL = lowest observed adverse effect level.

Table 5: Summary of Toxicological Dose and Endpoints for Use in Dermal, Oral and Dermal Human Health Risk Assessments			
Exposure Scenario	Dose-Response Relationship	Frequency of Exposure to Risk Assessment	Study and Associated Effects
Acute Dietary (General population including infants and children)	Acute dietary endpoints were not selected since the use-pattern does not indicate potential for dietary exposure.		
Chronic Dietary (All populations)	Chronic dietary endpoints were not selected since the use-pattern does not indicate potential for dietary exposure.		
Dermal Short-Term (1 - 30 days) Occupational	Oral LOAEL ^a = 15 mg/kg/day	Occupational LOC for MOE = 1000 ^d	Acute neurotoxicity study (MRID 43465302) LOAEL ^f = 15 mg/kg in females (6.75 mg/kg MITC equivalents; decreased motor activity) based on neurobehavioral effects FOB findings and reduced number of rearings.
Dermal Intermediate-Term (1 - 6 months) Occupational	Oral NOAEL ^{a,c} = 1.5	Occupational LOC for MOE = 100 ^e	Subchronic toxicity- feeding rats (MRID 41865502) LOAEL = 4.5 mg/kg/day based on increased liver weight, liver:body weight ratio and pronounced foci of fatty degeneration in the liver
Dermal Long-Term (> 6 Months) Occupational	Long-Term exposure via the dermal route is not expected considering the use pattern and its stability in the environment.		
Cancer	Classification: Not classifiable as human carcinogen.		

a Use 4.5% dermal absorption to convert oral dose to dermal equivalent; c Level of Concern = LOC; d Margin of Exposure (MOE) = 1000 [10x for interspecies extrapolation, 10x for intraspecies variations, 10x NOAEL to LOAEL factor]; e NOAEL = no observed adverse effect level; f LOAEL = lowest observed adverse effect level; g 100 [10x for interspecies extrapolation, 10x for intraspecies variations.]

Table 6: Summary of Toxicological Dose and Endpoints for Use in Mefen Sodium Human Health Inhalation Risk Assessment						
Risk Assessment	Study	NOAEL/LOAEL	Endpoint	HEC	OPP	DPR
Acute	Occupational	No appropriate studies are available.				Same
Short- and Intermediate-Term Inhalation (1 day to 6 months)	Occupational	90-day inhalation study (MRID00162041)	NOAEL= 6.5 mg/m ³ (1.11 mg/kg/day) LOAEL =45 mg/m ³ (7.71 mg/kg/day) in females	histopathological changes in the nasal passages (ie, mucigenic hyperplasia) and changes in clinical chemistry.	HEC: 6.5 mg/m ³ (1.11 mg/kg/day) UF = 300	None selected; Note: OPP and DPR agree on NOAELs and LOAELs
Cancer		Classification: Probable human carcinogen (B2) Q1* =1.98x10 ⁻¹ in human equivalents converted from animals				Q1* =1.85x10 ⁻¹ in human equivalents converted from animals

a Uncertainty Factors = UF [10x for interspecies extrapolation, 10x for intraspecies variations, 10 x for subchronic to chronic.]; b NOAEL = no observed adverse effect level; c HEC = Human equivalent concentration; d HC = Human concentration.; e HECs differ between non-occupational and occupational scenarios because the residential HEC is based on 24-hour exposures occurring 7 days per week, whereas the occupational HEC is based on 8-hour exposures occurring 5 days per week; f LOAEL = low observed adverse effect level.

Table 7. Summary of Toxicological Data and Endpoints for Use in Human Health Inhalation Risk Assessment						
Exposure Scenario	Study	NOAEL/LOAEL	Endpoint	HEC	OPP	
Acute	Non-occupational and Occupational	Eye irritation study (MRID 44400401)	One minute NOAEL ^b = 3.3 ppm 4-14 minutes NOAEL = 0.6 ppm 1-8 hours NOAEL = 0.22 ppm	Subjective responses to the Likert scale and eyeblink responses	One minute HC = 3.3 ppm UF = 10 4-14 minutes HC = 0.6 ppm UF = 10 1-8 hours HC = 0.22 ppm UF = 10	Same
Short- and Intermediate-Term Inhalation (1 day to 6 months)	Non-occupational	28-day inhalation study in rat (MRID 43514802)	NOAEL = 6.8 ppm LOAEL ^f = 34 ppm	Metaplasia of respiratory epithelium and atrophy of the olfactory epithelium	0.16 ppm UF = 30	0.30 ppm UF = 300
	Occupational	Same as non-occupational			0.68 ppm UF = 30 ^e	0.30 ppm UF = 300
Long-Term Inhalation (>6 months)	Non-occupational	28-day inhalation study in rat (MRID 43514802)	NOAEL = 6.8 ppm LOAEL ^f = 34 ppm	Metaplasia of respiratory epithelium and atrophy of the olfactory epithelium	HEC: 0.16 ppm UF = 300	0.30 ppm UF = 3000
	Occupational	Same as non-occupational			HEC: 0.68 ppm UF = 300 ^e	0.30 ppm UF = 3000
Cancer	Classification: Insufficient data to characterize cancer risk					

a Uncertainty Factors = UF [10x for interspecies extrapolation, 10x for intraspecies variations, 10 x for subchronic to chronic.]; b NOAEL = no observed adverse effect level; c HEC = Human equivalent concentration; d HC = Human concentration.; e HECs differ between non-occupational and occupational scenarios because the residential HEC is based on 24-hour exposures occurring 7 days per week, whereas the occupational HEC is based on 8-hour exposures occurring 5 days per week; f LOAEL = low observed adverse effect level; g Differences between OPP and CDPR reflect different methodologies, Ufs, and NOAELs.

5.0 Public Health Data

The effects of drift are usually minor to moderate leading primarily to irritant effects to eyes, throat, and skin, headache, nausea and shortness of breath. A serious threat to bystander health reported in the literature is the development and exacerbation of asthma seen in adults exposed to the fumes from an accidental spill in the Sacramento River in California. This incident is described in detail, below. The potential for metam sodium to drift and cause health effects at distances above one-quarter mile and many hours after application is well documented. Direct contact of metam sodium to skin surfaces is well documented to cause irritative dermatitis. The potential for health effects to large numbers of persons in communities and schools adjacent to metam sodium applications, either by a sprinkler system or poorly sealed soil fumigation is also well documented.

There are a number of different datasets with which HED compiled a human exposure incident report for metam sodium and its toxic degradate MITC. The OPP Incident Data System includes reports of incidents submitted to OPP since 1992. These reports are from various sources, including registrants, other federal and state health and environmental agencies, and private individuals, and are anecdotal unless otherwise noted. The many incidents reported in OPP IDS include incidents related to the sewer use of metam sodium, a 1997 incident involving the use of metam sodium in a greenhouse, and incidents related to the agricultural use of metam sodium. The review by Blondell and Hawkin includes a summary of all metam sodium-related incidents reported to OPP IDS through 2002.

Another OPP source of incident information is Poison Control Center (PCC) data from 1993-1998 that are obtained from about 65-70 centers at hospitals and universities. Dermal symptoms were most commonly reported among Poison Control Center cases, including skin irritation or pain. Other symptoms included erythema, rash, severe burn, eye irritation, nausea, and difficulty breathing.

Detailed descriptions of 902 cases submitted to the California Pesticide Illness Surveillance Program from 1982 to 1994 were also reviewed by Blondell and Hawkin. In 889 of these cases, metam sodium was used alone or was judged to be responsible for the health effects reported. Excluding the 435 cases resulting from the derailment into the Sacramento River of a six-car train carrying metam sodium in 1991, metam sodium still ranked in the top 40 pesticides responsible for systemic poisoning in California from 1982 to 1994. According to these data, changes in wind direction and temperature inversions can readily contribute to significant illness. Metam sodium accounted for nine percent of the nearly 1,000 drift-related (*i.e.*, bystander) cases reported in California from 1994 through 1997 and 22% of the incidents involving clusters of 10 or more people during the same time period.

The state of California summarized 2002 pesticide incident data at www.cdpr.ca.gov/doc/whs/2002pisp/. Between 2001 and 2002, the number of potential cases of pesticide illness in California more than doubled, 979 cases in 2001 and 1,859 cases in 2002. The state attributes this increase to two factors: increased surveillance, and a significant number of reported cases from two metam sodium incidents involving drift from agricultural fields, one involving vineyard workers in Bakersfield on June 6, 2002, and one involving residents of Arvin

on July 8 2002. Both of these incidents are described in greater detail later in this section.

Another source of incident data reviewed by Blondell and Hawkin is the National Institute of Occupational Safety and Health (NIOSH) Sentinel Event Notification System for Occupational Risks (SENSOR). In addition to metam sodium incidents from California, NIOSH compiled data on metam sodium incidents from Arizona (2 incidents) and Oregon (3 incidents) for the period from 1998 to 2002. Under special arrangement with NIOSH, Washington State prepared a summary of 11 metam sodium incidents reported between 1994 and 2001. Washington State identified the following factors as contributing to metam sodium incidents and health effects: non-compliance with personal protective equipment (PPE) requirements, a lack of worker and supervisor understanding of product hazards, inadequately protective labeling for chemigation applications, and the common occurrence of temperature inversions in Washington state during potato chemigation applications. Details about all of these incidents are provided in the Blondell and Hawkins review.

HED also conducted an extensive literature review to find additional information on metam sodium incidents. Calvert, et al. (2004) published "Acute Occupational Pesticide-Related Illness in the US, 1998-1999: Surveillance Findings From the SENSOR-Pesticides Program" which evaluated acute pesticide related illness as reported by seven member SENSOR-pesticide program states using a common case definition for pesticide illness. The report calculated acute pesticide-related illness incidence rates across multiple states. This is the first report of pesticide related illness incidence across more than one state. The states included in the report are: California, Texas, Oregon, New York, Florida, Louisiana, and Arizona. The numerator for the incidence calculation was the total number of illness cases and the denominator was obtained from the full time equivalent (FTE) estimates derived from the Current Population Survey conducted between 1998 and 1999. The incidence rates was 1.17 pesticide-related illnesses per 100,000 FTEs. The study also ranked the pesticides for which the largest number of acute occupational pesticide-related illnesses were reported. Metam sodium was ranked number 9 of the top 16 pesticide active ingredients thought to be responsible for the largest number of acute occupational pesticide related illnesses. Thirty-eight incidents attributed to metam sodium were reported across the seven SENSOR-pesticide states (Calvert et al., 2004).

A great deal of information is available concerning metam sodium incidents in California, from sources including California Department of Pesticide Regulation reports and other scientific articles. In 1991, there was a major spill of metam sodium into the Sacramento River near the Cantara Loop rail curve in the state of California. Hundreds of people in the surrounding area were treated for the effects of exposure. Most individuals reported throat and eye irritation, dizziness, vomiting, shortness of breath, nausea, and headache. Other individuals reported chest tightness, cough, abdominal pain, diarrhea, skin rash, rapid breathing, tremulousness, and paraesthesia. Spill researchers estimated exposure concentrations were likely in the range of 1400-1600 ppb. Three to four months after the spill, researchers found that exposed individuals had significantly higher blood pressure; increased neurological, memory and concentration problems; anxiety; depression; sleep disorders; headaches; visual and olfactory problems; and, dermatological gastrointestinal and cardiac symptoms than those who were not exposed (Bowler et al., as reported by Blondell and Hawkins, 2003). Other researchers investigating the effects of the metam sodium spill concluded that "the time course for symptom reports, large numbers of

symptom reports, consistency of symptoms with known toxicologic endpoints, and comparability of symptom reports with exposure predictions favor the interpretation that MITC caused the health problems" (Kreutzer et al. as reported by Blondell and Hawkins, 2003). It is also noted that MITC is one of a small group of compounds with an irritation threshold that is lower than its odor threshold.

Other researchers reported that after this spill, adults who lived and worked near the spill cite experienced persistent respiratory disorders including irritant-induced asthma. Data collected from the medical records, history, physical examination, spirometry, and methacholine challenge testing and revealed 20 cases of persistent irritant induced asthma and 10 cases of persistent exacerbation of asthma. The 20 cases with new onset of asthma due to exposure to metam sodium included 17 cases that met the criteria for RADS (reactive airway dysfunction syndrome). For these cases, symptoms persisted from 3 to 14 months. Of the 10 patients with persistent aggravation of existing asthma, all patients still had the problems even 3-15 months after the spill as compared to baseline prior to exposure to metam sodium. The study authors concluded that both exposure concentration and duration of exposure were factors in the development of long-term respiratory health effects. The same study authors note that the Bhopal, India release of methyl isocyanate (MIC), a photolysis degradate of MITC, has resulted in acute irritative effects followed by other long-term respiratory effects. These effects included increased cough and phlegm, difficulty breathing, and evidence of reduced lung function. MIC represents 4-7% of the MITC in the air (Blondell and Hawkins, 2003).

In the last five years, a number of major incidents have occurred in California involving drift exposure to worker or residential bystanders following agricultural applications of metam sodium or metam potassium. More detailed analyses of some of these incidents are available in reports and published studies including CDHS-OHB (2001; Cuyama incident), Goh and Barry (2002; Arvin incident), and O'Malley et al. (2004; Earlimart incident).

In addition, OPP received preliminary information on two 2003 incidents involving agricultural applications and bystander exposure. In Bakersfield, California, 15 people (including children) experienced symptoms following a shank injection application of metam sodium in a field across the street from their homes. Three sought medical care. Symptoms included difficulty breathing, sore throats, headaches, stinging and watery eyes, runny nose, flu-like symptoms. In Coachella Valley in Riverside county, at least nine residents reported symptoms to Hazmat responders following a sprinkler irrigation application of metam potassium more than 1300 feet from two mobile home parks. Three of the Hazmat responders also experienced symptoms. Symptoms included eye irritation and coughing.

Review of Metam Sodium Incident Reports. D293158, Blondell and Hawkins September 24, 2003

6.0 Non-Occupational Exposure Assessment and Characterization

Metam sodium and metam potassium produce the degradate methyl isothiocyanate (MITC). HED has assumed that the exposure and risk to MITC from metam potassium use are similar to that estimated in the assessment for MITC from metam sodium use. It should be noted that this assessment is based only on the risk associated with metam sodium and its metabolite MITC; however, application of metam sodium may also result in exposure to other breakdown products that are volatile and have known toxicity including methyl isocyanate (MIC), hydrogen sulfide, and carbon disulfide. HED believes that risks for exposure to the breakdown products will be no worse than those estimated for MITC exposures.

This section describes the potential exposure scenarios associated with the use of metam sodium as an agricultural fumigant. These include residential bystander exposure from two key sources: known or point sources (e.g., at the edge of a treated field), as well as from many or nonpoint sources within a region (e.g., ambient air). There are no residential uses of metam sodium by homeowners so this aspect of the risk assessment focuses on those types of exposures that may occur from commercial uses of metam sodium.

6.1 Residential Bystander Exposure

Residential bystander exposure may occur because of emissions from treated fields or sewers. These emissions can travel to non-target areas which could lead to negative impacts on human health and are referred to as bystander or off-target risks. The bystander exposure and risk assessment for metam sodium and potassium is completely detailed in the document "REVISED Metam Sodium: Occupational and Residential Exposure (ORE) Assessment for the Reregistration Eligibility Decision Document" (D293328. Steven Weiss, August 19, 2004).

Exposures from known uses or point sources have been estimated based on controlled field volatility studies from preplant field applications of metam sodium. An example of this type of exposure would be for individuals living next to a treated agricultural field. Exposures from these sources have been calculated in two distinct ways involving direct use of the monitoring data and through a modeling approach based on a standard Agency model, the monitoring data, and varied other inputs such as weather conditions. The model which has been used is a Gaussian plume model (Industrial Source Complex Short-Term Model; ISCST3) developed by the Office of Air and Radiation which allows better characterization of MITC air concentrations that result from the application of metam sodium at different distances from the emission source that is not possible with direct use of the data.

For exposures from non-point sources or ambient air, air concentrations of MITC are estimated from monitoring data collected to represent ambient conditions at a regional level. In this analysis, bystanders may be exposed to MITC air emissions resulting from (metam sodium, metam potassium, or dazomet) applications to multiple fields in a geographic area, particularly if they live in or frequent agricultural areas where there is significant use. The data used for the ambient assessment is data targeted towards areas and seasons of high metam sodium use developed by the California Air Resources Board (CARB) and a separate study performed by Sieber (1999).

Usually HED assesses risks resulting from short-term exposures to nonoccupational populations, however, MITC air concentration levels vary over the study durations and are not linear in dissipation. As a result, the primary concern for exposure to MITC are peak events that occur during off-gassing after a typical application. Acute exposures typically occur for several hours in duration. HED believes that the acute exposure period is reflective of the length of time that peaks of MITC occur after a metam sodium application. For this risk assessment, HED believes that with the data currently available, assessing risks from acute MITC exposures is protective for short-term exposure.

6.1.1 Bystander Exposure from Known Point Sources

MITC is the major by-product of metam sodium and accounts for most of the fumigant activity. The MITC inhalation exposure database (from metam sodium applications) consists of twelve field volatility studies that measure off-site MITC air concentrations associated with metam sodium applications. The studies provide data from 14 different application sites and for three different application methods (6 sprinkler, 6 shank injection, and 2 drip).

Two methods were used for estimating air concentration of fumigants from point sources such as a treated field: direct use of air monitoring data from controlled volatility studies (e.g., in treated fields or from treated structures) referred to as the *Monitoring Data Method* and the use of ISCST3 referred to as the *Modeling Method*. These are described separately below.

Monitoring Data Method: In the monitoring data method, air concentrations are estimated using actual air monitoring data from controlled volatility studies. In these studies, the fumigant is applied to a field, building, or other areas, and air samplers positioned in and around the treated area continuously sample the air by pulling the air through a filter (e.g., charcoal) which captures the chemical for later analysis. Sampling times can vary but generally range from about 4 hours, so that the samples represent the average air concentrations for the sampling intervals used. Usually shorter times are used at the beginning because fumigants generally quickly make it into the atmosphere.

There are several uncertainties associated with the use of direct sampling methods which limit its utility. First, the air concentrations represent only those for the conditions under which the study was carried out. Air concentrations around treated fields, buildings, or other areas are influenced by a number of factors including how a chemical is applied, application rate, techniques to control emissions (e.g., tarps), and weather conditions. Varying weather conditions, for example, can significantly change the air concentrations at specific sites around a treated area; and since there is such a large range of potential weather conditions which could exist, it is not possible for these studies to represent the entire range of potential exposures which could result from different weather situations. Second, the air concentrations are measured by fixed samplers positioned at various directions around the treated area, both downwind and upwind, as well as at points in between. Air concentrations downwind will be relatively high since the fumigant plume will be pushed by the wind in that direction, while concentrations upwind will be low or close to zero since the plume is pushed by the wind in the opposite direction. Therefore, there can be a very large difference between upwind and downwind air concentrations. For areas where there is a predominant wind direction, averaging of the air concentrations from these

various samplers should not be done since persons around treated areas will generally be in one location relative to the wind and not exposed to an average of these concentrations. Third, samplers are positioned at specific distances from the treated area, and represent air concentrations only at those distances. Since air concentrations vary greatly by distance, the air concentrations estimated from direct measures represent a very narrow range of the possible levels to which people could be exposed.

Modeling Method: The modeling method uses the Agency model, Industrial Source Complex Short Term (ISCST3) together with information about emissions from a treated field, building or structure (i.e., known as flux) to model the range of concentrations which might be found under different conditions of application rate, weather, source size and shape (e.g., field size in acres), and distance from the treated field, building or structure. Before a modeling analysis can be done, one of the most important parameters for ISCST3, the flux rate, which is the quantity of pesticide which is emitted from the treated fields, buildings or structures per unit area per unit time, must be determined. As an example, for field applications it is usually expressed in units of micrograms per square meter per second ($\mu\text{g}/\text{m}^2/\text{sec}$). In essence, flux represents how quickly the pesticide moves or volatilizes into the surrounding atmosphere. Numerous factors can influence flux rates such as application rate, depth of soil injection, type of application (e.g., drip vs. soil injection vs. granule application), techniques used to control emissions (e.g., tarps), temperature, wind and weather conditions, soil type, and others. Flux is also difficult to determine. Three general methods are used to calculate flux which are discussed briefly below. The first two of these measure flux from sampling directly in treated fields, and the third is indirect in that it calculates flux using samples from downwind locations. For metam sodium, the flux estimates were completed using the back calculation method.

Method 1, Flux Chamber: The first direct method for estimating flux uses field fumigant emission data measured in a flux chamber. A flux chamber is basically a box which encloses a small defined area of a treated field, from which air samples are obtained representing defined durations (e.g., air is pulled through a charcoal trap collecting emitted pesticide over a continuous length of time such as 4 hours). Since the surface area is defined by the area of the chamber, and the quantity of pesticide emitted per unit time is defined by the air concentration, this method directly measures flux. A possible issue with flux chambers is that the conditions within the chamber (e.g., temperature, wind, air stability) are not generally identical to those outside the chamber in the treated field; since flux rates can be significantly affected by these factors, flux rates measured in these chambers may not always represent actual flux rates in the field. Flux chambers are not often used for estimating flux rates.

Method 2, Aerodynamic Method: The second direct method used is the aerodynamic flux method. In this method, air samplers are set up in the treated field at various heights on a mast (e.g., 15, 30, 90, and 150 cm from the ground). Using measured air concentrations at these various heights, a vertical gradient of concentrations can be estimated for different time points, which can be integrated across all heights to estimate the flux rate at each time point after application. Some studies are available using this method to determine flux rates.

Method 3, Back-Calculation: The method most often used to determine flux rates is an indirect method known as the back-calculation method. This method uses measured air concentrations taken in a typical field fumigation study in which air samplers are located at various positions around the field. The measured air concentrations, together with information about weather conditions which occurred when the samples were obtained, are used as inputs into the Industrial Source Complex Short Term model (ISCST3). The model assumes that these air concentrations result from a Gaussian plume, the plume being distributed around the treated field as a result of the wind and weather conditions measured. The model then calculates the flux rate which would be required to emit the plume in that manner and to obtain the air concentrations measured.

Determination of the flux rate for all situations to be considered in an assessment is necessary before ISCST3 can be run. After these are defined, other key inputs must be defined such as the size and shape of a treated field, wind direction, wind speed, and atmospheric stability. ISCST3 calculates downwind air concentrations using hourly meteorological conditions, that include wind speed and atmospheric stability. The lower the wind speed and the more stable the environment, the higher the air concentrations are going to be close to a treated field. Conversely, if wind speed increases or the atmosphere is less stable, then air concentrations are lower in proximity to the treated field. Atmospheric stability is essentially a measure of how turbulent the atmosphere is at any given time. Stability is affected by solar radiation, wind speed, cloud cover, and temperature, among other factors. If the atmosphere is unstable, then more off-field movement of airborne residues is possible because they are pushed up into the atmosphere and moved away from the field, thereby lowering the air concentration in proximity to the field. To simplify modeling the transport of soil fumigant vapors from a treated field, a single wind direction, wind speed, and stability category are used for a given 24-hour period. The Agency has not determined if a particular set of meteorological conditions should be used for regulatory purposes, so risk assessment generally present exposures and risks representing a variety of different conditions.

Modeling with ISCST3 produced high-end estimates of air concentration and resulting risks for a number of reasons. First, only the downwind direction is considered. Most people will not be directly downwind from a treated field. Secondly, the model runs are based on constant wind speed, wind direction, and atmospheric stability for a 1-hour period (based on 4-hour flux rates). This will rarely occur resulting in overestimates of air concentrations and risks. The Agency believes that using ISCST3 to predict exposures over more extended periods is inappropriate because constant meteorological conditions over such periods will not occur. Therefore, use of the model for extended periods would yield highly conservative, physically unlikely results. However, the model is useful for examining acute exposures because it allows air concentrations reflecting different conditions based on changing factors such as application rates, field sizes, downwind distances, wind and weather conditions, and other factors, which cannot be done using the monitoring data method described above. Therefore, results using the ISCST3 model should be considered to be potential exposures to the most highly exposed, upper percentile of the population, but are not representative of exposures to most of the population around a treated field.

Future Use Of Distributional Assessments for Bystander Exposures: The methods described

above are deterministic methods which provide high-end point estimates of risk. OPP is coordinating with EPA's Office of Air, the California Department of Pesticide Regulation (CDPR), and other stakeholders to develop modeling approaches which determine the entire distribution of potential bystander exposures, and thus more fully characterize the range of risks resulting to bystanders around treated fields. ISC is an integral part of these new models which include: Fumigant Exposure Modeling System (FEMS), Probabilistic Exposure and Risk model for Fumigants (PERFUM), and the Soil Fumigant Exposure Assessment System (SOFEA). FEMs, PERFUM, and SOFEA were presented to the FIFRA Scientific Advisory Panel (SAP) in August and September 2004. These new models may be used to more fully characterize risks for MITC from metam sodium applications once they have been more thoroughly evaluated.

6.1.1.1 Bystander Exposures From Known Point Sources Estimated Using The Monitoring Data Method

6.1.1.1.1 Pre-Plant Agricultural Field Fumigation

HED used air concentration data from the six most representative field volatility studies to estimate the acute exposure and risk to the residential bystander. Studies that do not reflect current use practices (i.e., application via sprinkler irrigation without a water seal) or field volatility studies in which there are some data quality or consistency issues (i.e., application via shank injection without a water seal) were not included. The six studies provided data from six different application sites, three types of application equipment (shank injection, sprinkler irrigation, and drip irrigation), and four sealing options (standard water seal, intermittent water seal, tarped, and untarped). Risks were estimated using the study data for six distinct application/sealing/method combinations:

- Sprinkler Applications with standard water sealing
- Sprinkler Applications with intermittent water sealing
- Shank Injection Applications with standard water sealing
- Shank Injection Applications with intermittent water sealing
- Drip Applications with a tarp
- Drip Applications with no sealing

It should be noted that Smelt et al. (1989) investigated the accelerated decomposition rates of MITC in previously metam sodium treated soil and suggested that repeated application of metam sodium induced microbial adaptation, resulting in enhanced biotransformation of MITC. Dungan and Yates (2003) reported that the microorganisms responsible for enhanced degradation of MITC specifically target the isothiocyanate functional group. Several studies (Dungan and Yates, 2003; Warton and Metthiessen, 2000; Boesten et al., 1991) attributed that pesticidal efficacy of metam sodium was compromised due to the enhanced biodegradation. Since all of the field volatility studies were reportedly conducted on fields that were previously treated with metam sodium, the risks based on the emission rates and off-site MITC concentrations may underestimate the risk from application of metam sodium to fields that have never been treated.

Acute Exposures: The key route of exposure for MITC is inhalation, and currently HED has limited data indicating MITC air concentration levels in the hours and days following an

application. These data were collected at 4-hour intervals for four days. Acute risks were estimated as Margins of Exposures (MOEs) and were calculated by comparing each individual sample point to the toxicological human equivalent concentration (HEC) selected for acute exposures. The air concentration levels at a given data collection point often fluctuate over an extended period of time, depending on temperature, wind speed and direction, and other meteorological and environmental variables. As a result, HED believes that the acute MOEs may not reflect metam sodium peak 1-hour concentrations that could occur during the "acute exposure period" and, therefore, may under-represent actual acute exposures and risks to bystanders. It should also be noted that these estimates are all based on outdoor samples and do not reflect acute indoor air concentrations.

For acute exposures, Table 8 indicates:

- the number of MOEs calculated at a given distance ('n' is the total number of the samples at a given distance),
- the range of MOEs (minimum and maximum) at a given distance, and
- the number of sample stations at a given distance with concentrations that result in MOEs less than 10. (An MOE of 10 or more does not exceed HED's level of concern for acute exposures.)

Bystander Risk Summary: In almost every study, there was at least one time period (and sometimes a substantial fraction of time periods) where the acute risk exceeds HED's level of concern.

Table 3: Bystander MOE Calculated from Study Point Estimates for Pesticide Application at 2 to 1,000 Meters from the Edge of the Treated Field

Application Method	Water Seal	County (Year)	Site	Soil Type	Distance (m)			MOE	
					2	100	1000		
Sprinkler	Standard Water Seal	Kern County (1999)	457037-01: Site 1	Sandy Loam Soil	150	72	37	1	13200*
					300	72	27	1	13200*
					700	72	12	2	13200*
					1000	48	2	5	13200*
	Intermittent Water Seal	Kern County (2001)	457037-02	Silt Loam Soil	137	96	20	3	4299
					274	192	10	4	4514
					411	24	0	17	4281
					549	24	0	17	4281
Shank Injection	Standard Water Seal	Kern County (1999)	457037-01: Site 2	Sandy Loam Soil	150	72	24	1	13200*
					300	72	17	1	13200*
					700	72	17	1	13200*
					1000	48	2	5	13200*
	Intermittent Water Seal	Lost Hill (2001)	457037-04	Clay Loam	150	116	9	2	1973
					300	187	6	3	1993
					500	24	0	12	1617
					700	48	0	17	1637
Drip	none	Orange County (1997)	457037-08: Site 1	Soil type not specified	3	20	0	15	375
					6.1	10	1	7	60
					15.2	10	1	7	63
					45.7	10	0	12	93
	Tarp	Orange County (1997)	457037-08: Site 2	Soil type not specified	3	18	1	8	440
					6.1	12	1	6	13200*
					15.2	12	1	9	13200*
					45.7	12	1	8	252

The samples times ranged from 152 to 334 minutes and averaged 241 minutes.

* Air concentrations used to estimate MOEs were based on 1/2 the LOQ value.

6.1.1.1.2 Potting Soil Fumigation

HED currently has no exposure data to assess MITC bystander exposures following applications of metam sodium to potting soil.

6.1.1.1.3 Sewer Fumigation

HED currently has no exposure data to assess MITC bystander exposures following applications of metam sodium to sewers. HED believes that exposures to residential bystanders may occur if there are cracks in the sewer structure that would permit MITC to escape the sewer confinement.

6.1.1.2 Bystander Exposures From Known Point Sources Estimated Using The Modeling Method

40

The previous sections describe risks using actual site monitoring data. However, these data represent only the conditions in which the studies were actually conducted. Therefore, in order to estimate the range of air concentrations under various conditions (e.g., distance from emission source and atmospheric conditions), these data are first used as inputs into the ISC model to back calculate flux rates. These flux rates are then incorporated back into the model, varying other parameters (weather, field size, application rates), to extrapolate to conditions under which empirical data may not be available.

In these analyses, the monitoring data described in 6.1.1.1 were first used to estimate flux rates which are key inputs into the model. Flux rates, as described above, are measures of how fast MITC moves into the atmosphere from a metam sodium treated area. Once flux rates were determined they were then incorporated back into ISCST3.

Other parameters also have to be defined to run ISCST3 (e.g., wind speed, atmospheric stability, and field size). These were varied along with flux inputs in order to better characterize how exposures could differ due to changes in these parameters. Descriptions of how these factors were varied are provided in the tables below and associated appendices. Meteorological inputs including wind speed and atmospheric stability were varied in this analysis but each change in these variables required separate ISCST3 runs since in each they are held constant over the duration of the model run (i.e., 1 hour based on a 4 hour flux rate). Wind direction was not varied and as such, estimated concentrations at different distances downwind (i.e., known as receptor points) represent values at constant low wind speed for 1 hour in a single direction with unchanging atmospheric stability and flux rates.

HED believes that the modeling inputs which are used lead to conservative estimates of exposure because flux rates are held constant over time when it is clear that they change over the course of a day. The use of a constant downwind direction 100 percent of the time over a 1-hour period is also conservative since prevailing winds over such durations are highly unlikely. The atmospheric stability and wind speed values used represent a range of conditions from fairly calm and stable (i.e., at lower wind speeds) to a more turbulent situation at higher windspeeds. The slower windspeeds used are believed to be in lower percentiles for this variable (i.e., 10th %tile or less).

6.1.1.2.1 Pre-Plant Agricultural Field Fumigation

For pre-plant agricultural field fumigation scenarios, factors that were varied included field size; emission ratios (ERs; fraction of the applied material emitted per unit of time); wind speed; and atmospheric stability. Table 9 demonstrates that for the majority of cases considered, risks exceed HED's level of concern (MOEs <10) for distances less than 500 meters downwind of the treated field. In the few cases where risks were below HED's level of concern (MOEs > 10) at distances less than 500 meters, treated fields were small, emissions were comparatively lower, and the atmosphere was relatively unstable. Complete results for various field sizes, application methods, and distances downwind are presented Appendix E.

Table 9. Acute Bystander MOE¹ Calculated from the ISC Model by Distance Downwind from Pesticide Agricultural Field Turfgrass

Irrigation System	Seal	Distance (ft)	Wind Speed (mph)	Distance (ft)										
				25	50	100	150	200	250	300	350	400	450	
Sprinkler Irrigation, Standard Seal	2	1	25	<1	<1	<1	<1	1	1	1	1	1	1	1
			100	<1	1	1	1	1	2	2	2	2	4	
			500	2	6	8	10	12	14	17	18	21	47	
		40	25	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	1
			100	<1	<1	<1	<1	<1	<1	1	1	1	1	1
			500	<1	1	1	1	1	1	1	2	2	3	
Sprinkler Irrigation, Intermittent Seal	1	1	25	1	1	2	2	2	3	3	3	4	5	
			100	1	3	4	5	6	6	8	8	9	16	
			500	7	24	31	39	47	55	60	66	83	165	
		40	25	<1	<1	1	1	1	1	1	1	1	2	2
			100	<1	1	1	1	2	2	2	2	3	4	
			500	1	2	3	3	4	5	5	6	7	12	
Shank Injection, Standard Seal	2	1	25	<1	1	1	1	2	2	2	2	3	4	
			100	1	2	3	3	4	5	6	6	7	12	
			500	5	18	23	28	35	39	47	51	55	132	
		40	25	<1	<1	<1	1	1	1	1	1	1	1	2
			100	<1	1	1	1	1	1	2	2	2	3	3
			500	1	2	2	2	3	3	4	4	5	9	
Shank Injection, Intermittent Seal	1	1	25	1	2	3	4	4	5	6	7	8	11	
			100	2	6	7	9	11	13	15	17	18	31	
			500	13	47	60	73	94	110	132	132	165	330	
		40	25	<1	1	1	2	2	2	3	3	3	4	4
			100	1	2	2	3	3	4	4	5	5	8	
			500	2	4	5	6	8	9	10	12	13	23	
Drip Irrigation, Tarped Field	<1	1	25	2	5	6	8	9	11	12	14	15	22	
			100	5	12	15	19	23	26	30	35	39	66	
			500	28	94	132	165	220	220	220	330	330	660	
		40	25	1	2	3	3	4	4	5	6	6	9	
			100	1	3	4	5	6	7	9	9	11	16	
			500	3	8	11	13	16	18	21	24	26	47	
Drip Irrigation, Untarped Field	<1	1	25	3	7	9	11	14	16	19	21	24	33	
			100	8	18	23	29	35	39	47	51	60	94	
			500	41	165	220	220	330	330	330	330	660	660	
		40	25	1	3	4	5	6	7	8	9	10	14	
			100	2	5	6	8	10	11	13	14	16	24	
			500	5	12	16	19	24	28	33	37	41	73	

¹ Acute bystander MOEs were calculated using an HEC of 0.22 ppm, where an MOE of 10 or more does not exceed HED's level of concern.

6.1.2 Ambient Bystander Exposure From Non-Point Sources

Exposures from ambient air that occur from non-point sources of MITC were estimated from monitoring data collected to represent conditions at a regional level. The California Air Resources Board (CARB) generated most of the data considered in this analysis. CARB is a widely recognized institution for these types of programs and it is part of the California Environmental Protection Agency. CARB conducts air monitoring studies for various types of chemicals throughout California. The available ambient studies for MITC conducted by CARB can be described as targeted monitoring that is typically completed upon request to provide information related to specialized issues such as fumigant exposures in areas of high use during the season of use. Additional data were considered that were generated in townships after specific application events (e.g. Bakersfield/Kern County 1997 and 1998, Lompoc 2000). [Note: The MITC ambient air monitoring studies included in this assessment do not distinguish the source of MITC as coming from applications of metam sodium, metam potassium, or dazomet.]

For ease and clarity, the Agency has opted by convention to describe the available ambient bystander data used in this assessment as follows:

(1) "CARB Data": includes all targeted monitoring data generated by both CARB and private research focused on areas of high MITC use in the season of use.

6.1.2.1 Exposures From Regionally Targeted Non-Point Source Ambient Air Monitoring

In 2000 and 2001, the California Department of Pesticide Regulation requested that the California Air Resources Board conduct a series of studies to quantify ambient levels of MITC (<http://www.cdpr.ca.gov/docs/empm/pubs/tac/requests.htm>).

"Because most of California's pesticide applications normally occur in agricultural areas and are seasonal in nature, ARB conducts the monitoring studies to collect data during the worst-case situation - in the areas of high use during the season of peak use - instead of collecting samples throughout the State. This "worst-case" information can then be used to determine the ambient exposures of those people living near places where pesticides are used."

For the targeted ambient air analysis, HED evaluated different durations of exposure including single day acute exposures, short- and intermediate-term exposures, and chronic exposures. Since samples were collected 3 to 5 times per week from each station, and the contribution of specific applications could not be determined, the statistics were calculated by station and not on a regional basis. Risks from acute exposures were calculated using the maximum 24 hour TWA values measured at each station and comparing them to the acute HEC.

Risks from short-/intermediate-term exposures (i.e., same HEC and uncertainty factors apply to both durations) were calculated using the 24-hour study mean for samples taken over the course of the use season and comparing them to the short-/intermediate-term HEC. Concentrations over the course of a season monitored in these studies did not vary extensively. This supposition is supported physically because these studies spanned high use seasons in high use areas and use would not be expected to dramatically change at these locations during use seasons.

Chronic exposure estimates were also calculated using the targeted non-point source ambient data. These calculations should be considered as rangefinder estimates of exposure as none of the available ambient studies adequately reflect long-term monitoring of MITC in these areas. Specifically, short- and intermediate-term estimates were amortized to reflect a potential for exposure of 180 days out of each calendar year in order to calculate chronic estimates of exposure. This was determined based on the approximate use patterns for metam sodium over a year in high use areas. This approach does introduce the potential for significant uncertainty into the estimates, however, the Agency views the potential for chronic exposures in high use regions as significant and has addressed this scenario in order to be health protective. Because there are many uncertainties associated with the approach used in this assessment it is difficult to determine how these estimates either over- or under-predict actual chronic exposures for those living in high use areas. There are several factors that should be considered:

- Monitoring was specifically targeted toward areas of high use, this limits the populations for which these types chronic exposure estimates could be applied (i.e., for those living in such regions);
- More refined amortization approaches on a regional basis could be possible with use data, especially in California, but in most regions such data are not available; and
- Targeted monitoring was conducted during selected seasons of high use, but because the data are limited, the impacts of changing conditions (e.g., from different pest pressures, use patterns, or extended seasons) cannot be quantified, especially for different regions of the country with different climates, which could lead to potentially missing higher end exposures under some conditions.

The results for acute exposures (single day exposures), for the all of the monitoring stations considered, do not exceed HED's level of concern (MOEs < 10). For results for the short- and intermediate-term exposures (24-hour study mean exposures), the only locations that exceeded HED's level of concern (MOEs < 30) were indoor and outdoor samples collected in the summer of 1997 in Bakersfield. The results for the chronic exposures (24-hour study mean exposures), the only locations that exceeded HED's level of concern (MOEs < 30) were indoor and outdoor samples collected in the summer of 1997 and winter of 1998 in Bakersfield.

TABLE 10. Results of 24-Hour Ambient Monitoring in High Use Areas									
Year	Description of Monitoring	Location	No. of Samples	HEC			MOE		
				HEC	MOE	HEC	MOE	HEC	MOE
Bakersfield/Kern County, summer (1997) ¹	12 hour samples (am and pm for 5 days) during known applications in May, Jun, July and August	Lamont - Houses	43 ¹	0.0097	0.0059	23	28	54	
		Lamont - Environment	14 ¹	0.0050	0.0025	44	65	126	
		Weedpatch - Environment	12 ¹	0.0094	0.0047	23	35	67	
		Shafter - Houses	45 ¹	0.013	0.0066	17	25	48	
		Shafter - Environment	15 ¹	0.015	0.0077	15	21	41	
Bakersfield/Kern County, winter (1998) ¹	12 hour samples (am and pm for 4 to 5 days) during known applications in Jan and March	Lamont - Houses	16 ¹	0.0019	0.0012	116	136	263	
		Weedpatch - Environment	8 ¹	0.0017	0.0016	130	102	198	
		Arvin - Houses	15 ¹	0.0014	0.00070	158	233	452	
		Arvin - Environment	6 ¹	0.00030	0.00010	733	1623	3152	
Lompac (1998) ²	12 hour samples collected in am and pm (8/31 and 9/9 to 9/13)	Central	60 ²	0.00019	Insufficient data to calculate average	1138	Insufficient data to calculate		
		Northeast		0.000064		3474			
		Northwest		0.000064		3474			
		Southwest		0.000087		2538			
		West		0.00034		653			
Lompac (2000) ³	8 and 16 hour samples collected for days after 6 applications in Jan, Feb, Oct, and Nov (72hr sampling period beginning start of application. 8hr for day and 16hrs for night)	Central	173 ³	0.00011	0.000016	1953	10362	20117	
		Northeast		0.00010	0.000027	2207	5939	11531	
		Northwest		0.00038	0.000061	577	2661	5167	
		Southwest		0.00015	0.000010	1493	16233	31517	
		West		0.00040	0.000039	552	4162	8081	
Kern (2001) ⁴	24 hour samples collected on 33 sample days during 8 week period that coincided with fumigation use prior to carrot planting (Samples were collected 4 days per week on a random basis)	ARB	198 ⁴	0.00057	0.00019	388	840	1630	
		ARV		0.0015	0.00037	150	439	852	
		CRS		0.00010	0.00007	2200	2319	4502	
		MET		0.0014	0.00014	153	1133	2199	
		MVS		0.0074	0.00010	30	158	307	
		VSD		0.0032	0.00061	69	268	520	
Monterey/Santa Cruz (2001) ⁵	24 hour samples. 32 sample days at 6 sites during 8 week period that coincided with fumigation use prior to strawberry planting (Samples were collected 4 days per week on a random basis)	6 sites (CHUT, LJET, MEST, PMST, SALT, SEST)	192 ⁵	0.00014	0.000070	1535	2319	4502	

¹ Bakersfield/Kern County (1997/98), CDPR's HS-1806. (results taken from <http://www.cdpr.ca.gov/docs/whs/pdf/hs1806.pdf>)

² Lompoc (1998), 50 samples were non-detects (results taken directly from <http://www.cdpr.ca.gov/docs/dprdocs/lompoc/lexpdata.pdf>)

³ Lompac 2000), Forty-three% of samples were non-detects, 19% Trace, 39% quantified (results taken directly from Table 11 in http://www.cdpr.ca.gov/docs/dprdocs/lompoc/vol2_fumigants/volume2_march2003.pdf)

⁴ Kern (2001), Eighty-eight Samples > LOQ of 0.42, LOQ > 68 samples > LOD, 41 samples < LOD, 2 samples invalid. LOQ = 0.42 ug/m3. 1/2 of LOQ used for DET or <MDL (results extracted from <http://www.cdpr.ca.gov/docs/emppm/pubs/tac/tacpdfs/chlormitc03.pdf>)

⁵ Monterey/Santa Cruz (2001), One sample at SEST site > EQL, 2 samples at SEST site had detectable results, 186 samples < MDL, 3 samples invalid. LOQ = 0.42 ug/m3. 1/2 of LOQ used for DET or <MDL (results taken from http://www.cdpr.ca.gov/docs/emppm/pubs/tac/tacpdfs/chlor_metsod04.pdf)

⁶ Acute bystander MOEs were estimated using an HEC of 0.22, where an MOE of 10 or more does not exceed HED's level of concern.

⁷ Short- and intermediate-term bystander MOEs were estimated using an HEC of 0.16, where an MOE of 30 or more does not exceed HED's level of concern.

⁸ Chronic bystander MOEs are were estimated using an HEC of 0.16, where an MOE of 300 or more does not exceed HED's level of concern.

6.2 Bystander Risk Characterization

There are several issues that should be considered in the interpretation of the above assessments

for off-target releases of MITC from metam sodium applications. The first is that essentially all of the data used for this analysis have been generated in California; however, metam sodium is used in many regions of the country. Therefore, the results based on California data and agricultural practices were used to represent the rest of the country due to a lack of adequate information for any other region. It is unclear what potential impacts this extrapolation might have on the risk assessment. For example, available data seem to indicate that factors such as soil type and other environmental conditions might affect the rate at which MITC is emitted from metam sodium treated fields or other sources. Meteorological conditions such as differences in humidity, levels of solar radiation, and atmospheric stability also impact ambient concentrations.

Another factor that should be considered in the interpretation of these results is the data quality associated with the inputs and other factors used in the calculations. For most of the data, HED believes that the data and other information used are of reasonable quality for risk assessment purposes. A significant number of studies were generated by CARB and CDPR. These are generally believed to be of high quality. It is clear from the characterization of the data provided by CARB that some data represent highly targeted monitoring in a region during the season of use. These should be considered conservative in nature. Other factors used in the ISC model calculations, such as flux rates, have been verified by HED in an independent analysis of the available data. Meteorological conditions, field sizes and other factors were intentionally varied to provide a range of risk estimates which could potentially occur under conditions of metam sodium use for consideration by risk managers. It is believed that the ranges of the values selected represent what could reasonably occur in agriculture.

HED notes that the California Department of Pesticide Regulation (DPR) has performed risk assessments for both MITC and metam sodium. While there are many similarities between the two assessments, there are also some distinctions, particularly concerning the hazard characterization of MITC. The non-cancer endpoints used by California DPR are lower than HED (3X-66X lower than HED). These differences arise primarily from two issues: 1) utilization of the human acute eye irritation study for quantitative risk assessment, and 2) interpretation of the effects observed in the 28-day inhalation rat study for purposes of quantitative risk assessment. A fundamental difference underlying these issues concerns the interpretation of toxic effects primarily related to irritation. Another dissimilarity is the respective regulatory entities definition of exposure durations for hazard and exposure assessment, i.e., California DPR's use of 1- to 8-hour acute exposure durations. OPP has begun a dialogue with California DPR regarding the harmonization of the hazard and exposure characterization of metam sodium and MITC.

6.3 Residue Profile

There is no reasonable expectation of finite residues to be incurred in/on food and feed crops when metam sodium and potassium are used as preplant soil fumigants, so these uses are considered to be non-food uses, and tolerances are not needed. (Refer to Section 3.1.)

Along with the uses on all crops, there are also existing antimicrobial uses for metam sodium, metam potassium, and MITC. Metam sodium can be used in paper pulp to control bacteria and fungal slime in the pulp slurries and to inhibit the growth of bacteria in papermaking equipment. Similarly, there is a current use of metam potassium in sugarcane processing to inhibit the

growth of bacteria on the processing equipment, and MITC is registered for use as a wood preservative (e.g., telephone poles). For paper pulp and sugarcane uses, there are numerous processing steps (e.g., boilers, evaporators, vacuum pans, recrystallization, additional dryers, bulk storage, etc.) that occur after the addition of metam sodium and potassium involving high temperatures; that combined with the volatility of the residue of concern (MITC), HED believes that there is no reasonable expectation of finite residues to be incurred in/on sugar, sugarcane products, or food packaged in treated paper products. These uses, along with the MITC telephone pole use, have been assessed by OPP's Antimicrobial Division (Metam Potassium: Dietary Risk Assessment of Antimicrobial Uses for the Reregistration Eligibility Decision Document, T. McMahon and C. Walls, July 13, 2004).

6.4 Water Exposure/Risk Pathway

Environmental fate data suggest that there is a low potential for the parent compound metam sodium or metam potassium to be present in drinking water due to the rapid degradation of metam sodium/potassium to MITC in the environment. However, MITC is very soluble in water and its low adsorption in soil suggests that leaching to ground water and/or transport to surface water may be a potential problem under flooded conditions. Therefore, a qualitative drinking water assessment was performed.

Under most field conditions, the potential for significant ground water contamination of MITC is unlikely due to its volatilization and fast degradation in soil. Based on available non-targeted monitoring data, MITC was not detected in the ground water samples within the USA. MITC can also potentially move to surface water through runoff under an intense rainfall and/or if continuous irrigation occurs right after metam sodium application. However, the Henry's Law Constant of $1.79 \times 10^{-4} \text{ atm}\cdot\text{m}^3/\text{mol}$ for MITC suggests that it will be volatilized quickly from surface water. Based on environmental fate data, the residual contents in soils, and monitoring data, Agency does not expect MITC to adversely impact the drinking water sources such as surface water and ground water.

7.0 Aggregate Risk Assessment

The physical/chemical characteristics, the environmental fate data, and results of metabolism studies in plants assure that there is no reasonable expectation of finite residues to be incurred in/on food and drinking water when these products are applied according to label directions. Therefore, this fumigant does not require food tolerances and is not subject to the amendments to the FFDC Act promulgated under the Food Quality Protection Act of 1996; therefore, an aggregate risk assessment is not required.

8.0 Cumulative Risk Assessment and Characterization

In September, 2001, OPP presented a draft paper entitled "The Grouping of a Series of Dithiocarbamate Pesticides Based on a Common Mechanism of Toxicity" to the FIFRA Scientific Advisory Panel (SAP). Although metam sodium is a mono-methyl compound, this pesticide was included in the evaluation. Overall, the panel concluded that at present time, there is not sufficient evidence to group the dithiocarbamate pesticides based on a common mechanism of action for purposes of cumulative risk assessment.

For information regarding EPA's efforts to determine which chemicals have a common mechanism of toxicity and to evaluate the cumulative effects of such chemicals, see the policy statements released by EPA's Office of Pesticide Programs concerning common mechanism determinations and procedures for cumulating effects from substances found to have a common mechanism on EPA's website at <http://www.epa.gov/pesticides/cumulative/>.

9.0 Occupational Exposure

This section of the risk assessment focuses on potential exposures and risk to occupational handlers, to occupational reentry workers who could be exposed when entering metam sodium-treated areas to perform crop-production tasks, and to occupational bystanders who could be exposed when performing crop-production tasks near (but not inside) metam sodium-treated areas. Based on available metam sodium air concentration data, HED has concerns about occupational handlers performing the application tasks in the field as well as workers performing tasks inside and near – but outside of – metam sodium-treated areas. Air concentration levels from metam sodium-specific handler exposure monitoring studies were used to estimate occupational handler risks. It should be noted that much of the handler exposure monitoring data used in the occupational exposure estimates reflects the use of some engineering controls such as tarps, tractor cabs, deep injection, or other devices. The duration of exposure had little impact on the overall results of this assessment. Exposure estimates obtained through modeling were used to estimate occupational bystander risks. At this time, HED has no data to assess potential exposures and risks to occupational reentry workers.

It is important to consider that in this assessment worker exposure monitoring data have been used directly for risk assessment purposes. In a typical pesticide handler assessment, the Agency uses normalized estimates of exposures based on similar equipment and with similar levels of protective equipment or clothing. Additionally, in typical post-application worker assessments, exposures are scaled based on how residues decay over time. These approaches have not been used in the occupational assessments presented below due to methodological issues. For example, it is not clear how changes in various parameters or conditions (e.g., temperature, emission reduction methods such as tarps or application methods) may impact exposures. It is also not clear how time after application can be used for scaling exposures from one day to the next because worker exposures may be inherently related to the conditions of the field under which monitoring has occurred. Current requirements for entry of post-application workers into previously treated fields are dictated by the Worker Protection Standard as described in PR 93-7. For metam sodium, such workers are excluded for 48 hours after treatment. Refinement of time-based entry requirements is pending related to the investigation of factors that may impact exposures over time and development of an appropriate methodology for such analyses.

9.1 Occupational Handler Exposure

For metam sodium, handler exposure estimates were based on surrogate data from: (1) the Pesticide Handlers Exposure Database (PHED); (2) Outdoor Residential Exposure Task Force (ORETF); and (3) California DPR's review of a sodium tetrathiocarbonate handler study. For MITC, handler exposure estimates were based on four chemical-specific handler studies that examined MITC exposures to handlers involved in metam sodium applications. For a detailed description of that available studies and data gaps, see the August 19, 2004 ORE RED Chapter

(Steven Weiss, D293328).

9.1.1 Occupational Handler Point Exposure Estimates for Pre-plant Agricultural Field Fumigations

Metam Sodium

Risks exceed HED's level for the majority of agricultural scenarios, including applications to ornamentals, food, and feed crops, tobacco plant beds, and turf even at maximum risk mitigation for most cancer and non-cancer assessments for exposures to metam sodium. Tables 5, 6, 7, and 8 of the Aug 19, 2004 ORE Chapter for the RED summarize the estimated exposures and risks. Usage data from a USDA Survey regarding area treated per day, typical application rates, and exposure days per year will be used to refine the metam sodium handler risk estimates in the ORE Chapter.

MITC

Acute Exposures: Durations of the handler air samples ranged from 1 to 254 minutes depending on the task. Acute risks (MOEs) were calculated by comparing the maximum air concentration level of MITC at an individual sample point to the toxicological human equivalent concentration (HEC) selected for acute exposures.

Short- and Intermediate-term Exposures: To calculate the short- and intermediate-term risks to handlers, the geometric mean air concentration level of MITC was calculated across all sites for each different handler task and method of application. This geometric mean air concentration level was then compared to the HEC selected for short- and intermediate-term exposures to calculate the short- and intermediate-term risks (MOEs).

Handler Risk Summary: A summary of the MOEs estimated for handler exposures to MITC is included in Table 11. Acute risks to handlers exceed HED's level of concern (MOE < 10) for most of the tasks assessed. Short-term risks to handlers also exceed HED's level of concern (MOE < 30) for most of the tasks assessed.

The estimated MOEs do not reflect the reduction of inhalation exposure resulting from the use of respirators or additional mitigation controls that were not used in the studies. HED typically shows MOEs for handlers wearing respirators (when feasible) with a protection factor (PF) of 10. It is assumed that a respirator with a PF of 10 will reduce concentrations of MITC in the breathing zone by 90%.

Table 11: MITC Handler MOE Calculated from Same Point Estimates for Pre-Plant Agricultural Field Fumigation								
Exposure Scenario	EPA Pesticide Agency	Acute MOE			ST/IT MOE			
		Min	Max	Mean	Min	Max	Mean	ST/IT
Loader								
Transferring Water Soluble Liquids from Tank Delivery Truck to Shank Injection Equipment	429684-02*	10	3	17	1157	212	2	10
Transferring Water Soluble Liquids from Tank Delivery Truck to Rotary Tiller Equipment	429584-01	10	3	11	1751	314	1	7
Transferring Water Soluble Liquids from Tank Delivery Truck to Pick-up Truck and subsequent transfer to Chemigation Nurse Tank	429684-02*	10	43	78	2739	440	<1	5
	429584-01	5	8	12	125	342	14	6
Transferring Water Soluble Liquids from Tank Delivery Truck to Pick-up Truck and subsequent transfer to Drip Irrigation Nurse Tank	429684-02*	10	43	78	2739	440	<1	5
	429584-01	5	8	12	125	342	14	6
Applicator								
Applying Water Soluble Liquids via Shank Injection Equipment-Personal Sampler Pumps (enclosed cab with charcoal filter)	429684-02*	2	1	78	284	222	2	2
Applying Water Soluble Liquids via Shank Injection Equipment-Personal Sampler Pumps (enclosed cab with cellulose filter)	429684-02*	4	1	74	1791	148/6	<1	1
Applying Water Soluble Liquids via Shank Injection Equipment-Personal Sampler Pumps (open cab)	429684-02*	4	1	77	3851	719	<1	3
Applying Water Soluble Liquids via Shank Injection Equipment-In-cab Sampler Pumps (enclosed cab with charcoal filter)	451239-02/457037-03	9	1	176	664	454	1	4
Applying Water Soluble Liquids via Rotary Tiller Equipment-Personal Sampler Pumps(enclosed cab with charcoal filter)	42958401	5	63	72	2493	596	<1	3
Applying Water Soluble Liquids via Rotary Tiller Equipment (enclosed cab with cellulose filter)	42958401	5	56	63	1218	567	1	4
Loader/Applicator								
Transferring Water Soluble Liquids from Tank Delivery Truck to Shank Injection Equipment (closed system) and then applying them via Shank Injection Equipment (enclosed cab with charcoal filter)	451239-02	9	81	174	1220	566	1	4
Chemigation Monitor								
Monitoring Water Soluble Liquid Chemigation Applications	451239-02/429584-01	10	121	241	349	102	2	20
	429684-02*	10	0.85	254	2806	891	<1	2
Irrigator								
Irrigating Following Shank Injection Application	451239-02/457037-03	11	107	202	329	171	2	12

¹Acute MOEs are based on the maximum concentration
²ST/IT MOEs are based on the geometric mean concentration
 *429684-02 may not be reflective of current cultural practices

9.1.2 Occupational Handler Point Exposure Estimates for Potting Soil Fumigation

HED currently has no exposure data to assess MITC handler exposures during the application of metam sodium to potting soil.

9.1.3 Occupational Handler Point Exposure Estimates for Sewer Fumigation

50

HED has concerns for handler's MITC exposures during the applications of metam sodium to sewers. At this time there has been no data submitted to the Agency regarding MITC air concentration levels during applications to sewers. However, an internet search conducted by HED did reveal two exposure studies performed in Australia that measured MITC during the application of Vaporooter. A formal request was made by SRRD to the Australian Pesticides and Veterinary Medicines Authority (APVMA) to obtain a copy of these studies. Table 12 summarizes the acute and ST MOEs estimated from exposure tables posted on APVMA's website. <http://www.apvma.gov.au/chemrev/methamsodium2attach.shtml>.

Sheers R (1994) Melbourne Water - Sanafoam Vaporooter Trial, 7 November 1994	Operator breathing zone exposure	0.27	1	1
	At point of application	22	<1	na
	Two manholes downstream (approx. 300 m)	0.017	36	na
	At point of application - 24 hours post-application	0.023	26	na
Sheers R (1995) Melbourne Water - Sanafoam Vaporooter Trial, 13-14 February 1995, ICI Australia Operations Pty Ltd.	Operator breathing zone exposure	< 0.017	13	10
	Operator breathing zone exposure	< 0.027	8	7
	Operator breathing zone exposure	0.057	4	3
	At point of application - 30 mins post application	2.6	<1	na
	At point of application - 90 mins post application	1.3	<1	na
	At point of application - 180 mins post application	6.8	<1	na
	At point of application - 270 mins post application	4.4	<1	na
	At point of application - 360 mins post application	0.87	1	na
At point of application - 24 hours post-application	< 0.010	60	na	

Acute MOEs for breathing zones samples based on NOAEL of 0.22 ppm. For other samples (less than 15 mins) acute MOEs based on 0.60 ppm). ST MOE were not estimated for static measure measurements.

9.2 Occupational Reentry Worker Exposures

9.2.1 Pre-plant Agricultural Field Fumigation

HED examined workers reentering treated areas 48 hours after treatment. Using the flux rates from the appropriate studies at 48 hours, HED estimated the maximum concentration occurring at the edge of the treated field using ISC and the wind speed/stability categories used in the previous analysis. Table 13 shows the acute MOEs for maximum concentrations occurring in treated fields 48 hours after treatment.

Table 13: Estimated Acute MOEs based on Maximum ISC-Calculated Air Concentration (µg/m³) after 8 hours

Application Method	Days per Week	100 ft		200 ft		300 ft		400 ft		500 ft	
		Day	Night	Day	Night	Day	Night	Day	Night	Day	Night
Sprinkler Irrigation, Standard Seal	1	2	4	5	6	8	9	10	12	13	18
	5	2	3	4	5	6	7	8	9	11	15
	10	1	3	4	5	6	7	8	9	10	13
	20	1	3	4	4	5	6	7	8	9	12
	40	1	3	3	4	5	6	7	7	8	12
Sprinkler Irrigation, Intermittent Seal	1	7	14	18	22	28	31	37	41	47	60
	5	6	12	15	18	22	25	30	33	37	51
	10	5	10	13	17	21	24	28	30	35	47
	20	5	10	12	15	19	21	25	28	31	44
	40	4	9	12	14	17	20	24	25	29	41
Shank Injection, Standard Seal	1	<1	<1	1	1	1	1	1	1	1	2
	5	<1	<1	<1	1	1	1	1	1	1	1
	10	<1	<1	<1	<1	1	1	1	1	1	1
	20	<1	<1	<1	<1	1	1	1	1	1	1
	40	<1	<1	<1	<1	<1	1	1	1	1	1
Shank Injection, Intermittent Seal	1	6	11	14	17	21	24	29	31	37	47
	5	4	9	12	14	17	20	23	25	29	39
	10	4	8	11	13	16	18	21	24	26	37
	20	4	8	10	12	15	17	19	22	24	35
	40	3	7	9	11	14	16	18	20	23	31
Drip Irrigation, Tarped Field	1	5	11	14	17	21	24	28	30	35	47
	5	4	9	11	13	17	19	22	24	28	39
	10	4	8	10	12	15	17	21	23	25	35
	20	3	7	9	12	14	16	19	21	24	33
	40	3	7	9	11	13	15	17	19	22	30
Drip Irrigation, Untarped Field	1	6	12	16	19	24	28	31	35	39	55
	5	5	10	13	15	19	22	25	29	31	44
	10	4	9	12	14	17	20	24	25	29	41
	20	4	8	11	13	16	18	21	24	26	37
	40	4	8	10	12	15	17	20	22	25	35

9.2.2 Potting Soil Fumigation

HED currently has no exposure data to assess MITC occupational reentry worker exposures following applications to potting soil.

9.2.3 Sewer Fumigation

HED currently has no exposure data to assess MITC occupational reentry worker exposures following applications to sewers.

52

10.0 Data Needs and Label Requirements

10.1 Toxicology

The MITC database is incomplete for pesticidal uses of MITC *per se*, and additional data requirements may be imposed. The following studies on MITC have been identified as data gaps:

1. Acute neurotoxicity study in rat via inhalation with pathological evaluation of the complete respiratory tract.
2. Two generation reproduction study in rat via inhalation with pathological evaluation of the complete respiratory tract. This study should also include a subchronic neurotoxicity component with functional battery and motor activity measurements using the F0 animals. If the F1 animals exhibit developmental neurotoxicity then the F2 generation should be evaluated for the standard developmental neurotoxicity parameters.
3. In vivo cytogenetic assay
4. Repeat of the unscheduled DNA synthesis assay
5. Carcinogenicity study in rats via the inhalation route
6. Carcinogenicity study in mice via the inhalation route

There are no outstanding metam sodium (metam potassium) toxicological data requirements.

10.2 Residue Chemistry

There are a number of product chemistry data requirements listed in the Product Chemistry Chapter for both metam sodium and metam potassium manufacturing products, see chart below. There are no residue chemistry requirements for either metam sodium or metam potassium.

Formulation	EPA Reg. No.	Registrant	OPPTS Guideline Requirements
Metam sodium (039003)			
42.5% FI	1448-107	Buckman Laboratories, Inc.	830.7050-UV/visible absorption
44% FI	5481-469	Anvac Chemical Corporation	830.6313 (Stability), 7050 (UV/visible absorption), and 7840 (water solubility)
42% FI	5481-416		
42% EP	45728-16	Taminco, Inc.	None
42.2% FI	61842-4	Tessenderlo Kerley, Inc.	830.1670 (formation of impurities), 1700 (preliminary analysis), and 6313 (stability)
Metam potassium (039002)			

Form	Product	Supplier	OPPTS Guideline Reference
54% FI	1448-74	Buckman Laboratories, Inc.	830.1700(preliminary analysis), 6302 (color), 6303 (physical state), 6304 (odor), 6313 (stability), 7000 (pH), 7050 (UV/visible absorption), 7200/7220 (melting point/boiling point), 7300 (density), 7370 (dissociation constant in water), 7550 (partition coefficient), 7840 (water solubility), and 7950 (vapor pressure)
54% FI	5481-484	Amvac Chemical Corporation	830.6313 (stability), 7050 (UV/visible absorption), 7220 (boiling point), 7370 (dissociation constant), 7550 (partition coefficient), 7840 (water solubility), and 7950(vapor pressure)
MITC (068103)			
97% EP	69850-1	MLPC International	830.1620 (description of product/process) and 7050 (UV/visible absorption)

10.3 Occupational and Residential Exposure

The assessment of occupational and residential risks associated with the use of dazomet is complex. Additional data are required. These data include both occupational monitoring of various workers in different industry sectors and data to better assess exposures in the general population. The types of data, guideline citations, and examples of the scenarios which need to be addressed are presented below. Final determination of the scenarios should be made in consultation with the Agency.

OPPTS Guideline 835.8100 - Field volatility from soil

- MITC:**
- Volatility studies to determine flux for ISCST3 modeling purposes in major use regions of country for significant application methods (e.g., Florida or Washington).
 - Volatility studies for some application methods (rotary tiller and handheld/stationary equipment).
 - Volatility studies for some sealing methods (e.g. rolling and dragging to compact soil).

OPPTS Guideline 875.1100 - Dermal exposure for applicators (outdoors)

- Metam Sodium:**
- Pre-Plant Field - (e.g., mixer/loader, tractor drivers, water sealers, aerators)
 - Greenhouse (potting soil) - (e.g., mixer/loader, fumigators, media handlers, aerators)
 - Sewers - (e.g., mixer/loader, fumigators)

OPPTS Guideline 875.1300 - Inhalation exposure for applicators (outdoors)

- Metam Sodium:**
- Pre-Plant Field - (e.g., mixer/loader, tractor drivers, water sealers, aerators)
- MITC:**
- Pre-Plant Field - (e.g., applying via flood and furrow irrigation, tractor drivers, water sealers, aerators, tarpers)

OPPTS Guideline 875.1400 - Inhalation exposure for applicators (indoors)

Metam Sodium: Greenhouse (potting soil) - (e.g., mixer/loader, fumigators, media handlers, aerators)
Sewers - (e.g., mixer/loader, fumigators)

MITC: Greenhouse (potting soil) - (e.g., fumigators, media handlers, aerators)
Sewers - (e.g., fumigators)

OPPTS Guideline 875.2500 - Inhalation exposure for postapplication workers

MITC: Pre-Plant Field - (e.g., planters)

Requirements For Special Studies

Meteorological Data For Probabilistic Modeling Purposes
Product Use Information By Major Use Region, Frequency, Application Parameters (e.g., rate, acres treated, data, application equipment and emission control technologies used).

Appendix A: Toxicity Profile

Note to Reader: 3rd Revised Toxicology Disciplinary Chapter for: Metam Sodium (PC Code 039003) and Methyl isothiocyanate (MITC, PC Code 068103)
August 19, 2004. TXR No.: 0050771

Appendix B: Methodologies for Inhalation Risk Calculations and Human Equivalent Concentration Arrays

Note to Reader: Inhalation risk calculations are found in "Toxicity endpoint selection and inhalation dosimetry calculations for metam sodium, dazomet, and MITC. August 19, 2004." TXR No: 0051475. Array tables from this document are provided below.

Table 1a RfC Array for MITC NON-OCCUPATIONAL RISK ASSESSMENTS

Relevant Study	LOAEL ^b (ppm)	NOAEL ^c (ppm)	Da ^d	Dh ^e	Wa ^f	Wh ^g	RGDR ^{h,i}	HEC ⁱ (ppm)	Inter	Intra	Other UF	HEC/JFs (ppm)
Short- & Intermediate- Term												
28-day inhalation study in rat	Systemic	6.8	1.7	6	24	5	7	1	3	10	NA	0.01
	Local	34	6.8	6	24	5	7	0.17	3	10	NA	0.001
	TB	34	6.8	6	24	5	7	1.46	3	10	NA	0.058
Long- Term												
28-day inhalation study in rat	Systemic	6.8	1.7	6	24	5	7	1	3	10	10 ^a	0.001
	Local	34	6.8	6	24	5	7	0.17	3	10	10 ^a	0.001
	TB	34	6.8	6	24	5	7	1.46	3	10	10 ^a	0.0058

a Subchronic to chronic uncertainty factor
 b LOAEL: Lowest-observed-adverse-effect level
 c NOAEL: No-observed-adverse-effect level
 d Da: Duration (hours) of exposure to laboratory animals
 e Dh: Duration (hours) of exposure to humans
 f Wa: Number of days/week for animal exposures during the study
 g Wh: Number of days/week for expected human exposures
 h RGDR: Regional gas-dose ratio
 i HEC: Human equivalent concentration
 j RGDRs based on equations and defaults (when appropriate) in USEPA (1994), mean body weight for male and female Wistar rats.

58

Table 1b RfC Array for MITC OCCUPATIONAL RISK ASSESSMENTS

Relevant Study	LOAEL ^b (ppm)	NOAEL ^c (ppm)	Da ^d	Dh ^e	Wa ^f	Wh ^g	RGDR ^h	HEC ⁱ (ppm)	Inter	Intra	Other UF	HEC/UFs (ppm)
Short- & Intermediate- Term												
28-day inhalation study in rat	Systemic	6.8	1.7	6	8	5	5	1	3	10	NA	0.043
	Local	34	6.8	6	8	5	5	0.68	3	10	NA	0.024
Long- Term												
28-day inhalation study in rat	Systemic	6.8	1.7	6	8	5	5	1	3	10	10 ^a	0.0043
	Local	34	6.8	6	8	5	5	0.68	3	10	10 ^a	0.024

a Subchronic to chronic uncertainty factor
 b LOAEL: Lowest-observed-adverse-effect level
 c NOAEL: No-observed-adverse-effect level
 d Da: Duration (hours) of exposure to laboratory animals
 e Dh: Duration (hours) of exposure to humans
 f Wa: Number of days/week for animal exposures during the study
 g Wh: Number of days/week for expected human exposures
 h RGDR: Regional gas-dose ratio
 i HEC: Human equivalent concentration
 j RGDRs based on equations and defaults (when appropriate) in USEPA (1994), mean body weight for male and female Wistar rats.

59

Appendix C: Bibliography Of Metam Sodium Exposure Data

Note to Reader: For a detailed description of studies used in this assessment, see Section 4.0 of the August 19, 2004 ORE RED Chapter (Steven Weiss, D293328).

Appendix D: Summary Datasheets For Single Agricultural Field Fumigation Events

Note to Reader: For a detailed description of the field volatility data used in this assessment, see Appendices (A through C, E, F) of the August 19, 2004 ORE RED Chapter (Steven Weiss, D293328).

**Appendix E: Downwind MITC Air
Concentrations from Metam Sodium
Applications Estimated with ISCST3 for Pre-
Plant Agricultural Uses**

Appendix F: Occupational Risks Associated With Agricultural Fumigations

Note to Reader: For a detailed description of the field volatility data used in this assessment, see Appendices (A through C for metam sodium, E for MITC) of the August 19, 2004 ORE RED Chapter (Steven Weiss, D293328).

**Appendix G: Downwind MITC Air
Concentrations from Metam Sodium
Applications Estimated with ISCST3 for Pre-
Plant Agricultural Uses (Used to Calculate
Re-entry Risks)**