

ESTIMATION OF EXPOSURE OF PERSONS IN CALIFORNIA TO METAM-SODIUM DURING SOIL APPLICATIONS OF PRODUCTS CONTAINING METAM-SODIUM

by

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EXECUTIVE SUMMARY

Metam-sodium has been used extensively in California to control weeds, soil-borne diseases, and nematodes in preplant soil. The average amount of annual use from 1998 to 2002 was 14.1 million pounds. The annual average (1990-2002) of illnesses/injuries associated with exposure to metam-sodium/methyl isothiocyanate was 60.7. Illnesses/injuries were also classified according to activities and symptoms experienced by affected persons. Illnesses/injuries (occupational and nonoccupational) caused by drift following metam-sodium applications accounted for 669 cases from 1990 to 2002. Within the same period, 78 illness/injury cases resulted from fumigation activities. The major degradates of this chemical are methyl isothiocyanate and carbon disulfide. The dermal absorption obtained from a study using rats was 2.5 percent for the dermal dose of $8.6 \mu\text{g}/\text{cm}^2$. This dermal absorption was employed to determine absorbed dosages.

Exposure to metam-sodium was determined for workers or handlers and was not estimated for residents or bystanders. A worker exposure study using metam-sodium is not available. A worker exposure study using cesium ions, mixed with sodium tetrathiocarbonate, was used as surrogate study for the estimation of worker exposure to metam-sodium during shank injection (SI), sprinkler chemigation (SC), rotary tiller injection (RTI), oak root fungus (ORF) control, and reentry (R) into treated fields. For SI, SC, RTI, or R task, a commercial pest control operator may apply metam-sodium up to 200 workdays per year, whereas a grower may apply metam-sodium up to 23 workdays per year. The maximum estimated workdays for the control of oak root fungus are five days per season and 15 days per year. The exposure estimates for adult workers expressed as absorbed daily dosage (ADD) ($\mu\text{g}/\text{kg}$ body weight/day) were 1.52 for SI, SC, or R task, 1.65 for RTI, and 2.95 for ORF control. Seasonal average daily dosages for these

tasks were assumed to be the same as absorbed daily dosages, except for the control of ORF, which was not estimated. Annual and lifetime exposures were also calculated for SI, SC, RTI, and R tasks, except for the control of oak root fungus. Potential health concerns for the latter relating to seasonal, annual, or lifetime exposures were not expected and these values were not estimated. Dermal exposure to metam-sodium was also estimated based on the amount per unit of skin area. The exposure estimates for adult workers expressed as daily dermal exposure ($\mu\text{g}/\text{cm}^2$) were 0.27 for SI, SC, or R task, 0.30 for RTI, and 0.53 for ORF control. Seasonal daily dermal exposures ($\mu\text{g}/\text{cm}^2$) were assumed to be the same as daily dermal exposures, except for the control of ORF, which was not estimated. Metam-sodium is in risk assessment because studies with experimental animals have shown that it may cause liver damage and embryotoxicity. In addition, it is tumorigenic and genotoxic.

This report was prepared as part of the Department's risk assessment process for metam-sodium. A separate exposure assessment has been prepared for methyl isothiocyanate (MITC) and considers exposure to MITC from metam-sodium use.

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California Environmental Protection Agency
Department of Pesticide Regulation
Worker Health and Safety Branch
Exposure Assessment and Mitigation Program

Metam-sodium

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INTRODUCTION

Metam-sodium (sodium N-methyldithiocarbamate) is a general soil sterilant used to control weeds, nematodes, and soil fungi. Metam-sodium is available as an alkaline solution of the salt that can be directly injected into soil or metered into irrigation systems (chemigation), as a preplant incorporated biocide to prepare fallow fields for planting (Wofford *et al.*, 1994).

Human exposure assessment provides essential information for risk assessment of metam-sodium. This document was prepared as part of the Department's risk assessment process of this chemical. It will also be used as a basis for developing mitigation proposals if exposures to metam-sodium are found to cause excessive risks.

After application, metam-sodium is readily transformed to methyl isothiocyanate (MITC), carbon disulfide (CS₂), and other products. It is difficult to collect and handle metam-sodium samples in a worker exposure study. Exposure monitoring of mixer/loaders and applicators to metam-sodium is not available at this time. Therefore, surrogate data from a study using sodium tetrathiocarbonate (Enzone[®]) mixed with cesium ions was employed in the estimation of exposure of pest control operators to metam-sodium.

In addition to exposure estimates, presentation of other properties of metam-sodium are necessary for a better understanding of its nature, usage, and effects. These additional categories are: physical and chemical properties, regulatory history, formulations/label precautions, usage, worker illnesses/injuries, dermal toxicity/eye irritation, dermal absorption, and animal metabolism/pharmacokinetics.

In June 2004, this exposure document was revised as follows: a) Page 9 - Updated usage; b) Pages 10-11, Tables 1-3 - Updated illness/injury data; c) Page 16, Table 5 – Added a column showing excreted dose from the 72-hour sacrifice time and footnote "b"; d) Page 17, First and last paragraphs - Defined absorption and revised the conclusion for the *in vitro* dermal absorption study; e) Page 22, paragraph 4 – Added information explaining why metam-sodium products have high vapor pressure; f) Page 23, paragraph 2 – Added information to indicate that workers did not enter the treated area; g) Page 24 - Re-estimated workdays for pest control operators; h) Page 25, Table 10 – Recalculated exposures; i) Page 26, Exposure Appraisal – Deleted a

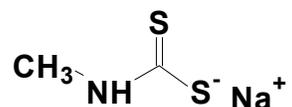
statement regarding the likelihood of underestimation of workdays; j) Page 27, paragraph 2 – Revised a statement on the *in vitro* absorption study to indicate that data do not support a lower or higher value than 2.5%.

A separate exposure assessment document was prepared for MITC and considered exposure to MITC from metam-sodium use.

PHYSICAL AND CHEMICAL PROPERTIES

Physical and chemical properties of technical grade active ingredient (TGAI) (metam-sodium dihydrate; solid) and end-use product (24.9-44% aqueous metam-sodium; liquid) are as follows:

1. Chemical Name: Sodium N-methyldithiocarbamate
Methyldithiocabamic acid sodium salt
Methylcarbomodithioic acid sodium salt
2. Common Name: Metam-sodium
3. Trade Name: Amvac Metam, Busan 1020, Busan 1236, Busan 1236W, Metham, Metam 426, Metam CLR 42%, Metam-sodium, Metam-sodium Manufacture's Concentrate, Nemasol 426, Pole Fume, Rid-A-Vec II, SMDC-Fume, Sonafoam[®], Vaporooter[®] II, Sectagon 42, SeweRout[™], VAPAM, VAPAM HL Soil Fumigant, VAPAM Manufacturing Concentrate, Woodfume.
4. CAS Registry No.: 137-42-8
5. Structural Formula:



6. Empirical Formula: C₂H₄NNaS₂
7. Molecular Weight: 129.18
8. Physical State: TGAI: Solid, colorless crystalline dihydrate (Tomlin, 1997)
End-use: Liquid, colorless to faint yellow-green (Myers and Johnson, 1985)
9. Density: End-use: 1.1648 g/cm³ @ 20 °C (Myers and Johnson, 1985)
10. Odor: TGAI: Acrid garlic-like
End-use: "Rotten egg," mercaptan-like (Myers and Johnson, 1985)
11. Boiling Point: End-use: 111 °C at 783 mm Hg (Myers and Johnson, 1985)
12. Melting Point: TGAI: Decompose without melting (Tomlin, 1997)
End-use: not applicable (n/a)
13. pH: TGAI: n/a
End-use: 9.0-10.5 (OR-CAL, 1987)
14. Specific Gravity: End-use: 1.16-1.18 at 68/68 °F (20/20 °C) (OR-CAL, 1987)

15. Stability: End-use: Stable at pH range above 8.8. Below pH 7 conversion to carbon disulfide and amine salts may begin. If acidified, may form hydrogen sulfide gas. Stable at ambient temperatures and atmospheric pressure. Heating will cause decomposition to form MITC and CS₂. Prolonged exposure to air will result in gradual decomposition to form MITC (OR-CAL, 1987).
16. Flash Point: End-use: Did not produce a flash point at the highest temperature obtainable (110 °C) with the apparatus (Myers and Johnson, 1985).
17. Solubility: 722 g/L H₂O at 20 °C. In acetone, ethanol, kerosene, xylene: <5g/L. Practically insoluble in other organic solvents (Tomlin, 1997).
18. Vapor Pressure: TGAI: Nonvolatile (Tomlin, 1997)
End-use: 21 mm Hg at 77 °F/25 °C (OR-CAL, 1987; Myers and Johnson, 1985.)
19. Octanol/Water
Partition Coefficient: TGAI: <10 (Tomlin, 1997)
(K_{ow}) End-use: Test done at 2 concentrations (525 and 46 ppm), K_{ow} <0.036 (Myers and Johnson, 1985).
20. Henry's Law
Constant: End-use: 4.3 x 10⁻⁶ atm-m³/g-mol (Myers, 1987).
8 x 10⁻⁶ atm-m³/g-mol (Tseng, 1986)
21. Corrosion
Characteristics: End-use: Corrosive to brass, copper, zinc, and aluminum. May soften or discolor iron (OR-CAL, 1987).

REGULATORY HISTORY

Metam-sodium was originally registered for use in the United States in 1954 (U.S. EPA, 1994). On June 2, 2004, the U.S. EPA announced in the Federal Register (Vol. 69, No. 106, pages 31104-31106) the availability of risk assessments for metam-sodium. The risk assessments include metam-potassium, dazomet, and methyl isothiocyanate. These documents were developed as part of EPA's process for making pesticide reregistration eligibility decisions.

On July 5, 1994, following an interim evaluation of human risk from agricultural use, the Department of Pesticide Regulation (DPR), and the Office of Administrative Law listed metam-sodium as a restricted pesticide (CCR, 1994). DPR placed metam-sodium and MITC on the restricted use pesticide list because it was considered to pose a danger either to public health or to farm workers, animals, crops or the environment. Thus, the county agricultural commissioner must issue a use permit after consideration of the proposed application site and use practices. Restrictions requiring buffer zones, reduced application rates and acreage limitations may be required based on the specific conditions under consideration.

FORMULATIONS/LABEL PRECAUTIONS

Formulations:

As of June 2004, there are 21 registered metam-sodium products in California (DPR, 2004a). Metam-sodium concentrations in these products range between 24.9 and 44%. Two of these products, namely SeweRout™ and Sanafoam® Vaporooter® II, contain 2.2% and 25% 2,6-dichlorobenzonitrile (or dichlobenil), respectively (DPR, 2004a). Metam-sodium products are formulated as solution/liquid (ready-to-use) (9 products), aqueous concentrate (8 products), and emulsifiable concentrate (6 products).

Label Precautions:

Product labels of metam-sodium or metam-sodium in combination with another chemical have a signal word DANGER (Toxicity Category I). Product labels of metam-sodium show the following precautionary statements: "Corrosive: causes skin damage. May be fatal if absorbed through the skin. Do not get on skin or clothing. Prolonged or frequently repeated contact with this chemical may cause allergic reactions in some individuals. Harmful if swallowed. Harmful if inhaled. Irritating to eye, nose, and throat. Avoiding breathing vapor or spray mist."

The Metam Sodium Task Force (MSTF) issued a technical bulletin as guidelines for all application methods for metam-sodium in California. The guidelines were intended to minimize off-site movement of odors when applying metam-sodium. This bulletin stresses the responsibility of the applicator to minimize any off-site movement of odors. General instructions concern use of closed systems, notice of intent, soil conditions, field monitoring, equipment cleaning, and specific instructions for soil injection, soil covering methods (bed-over), and sprinkler irrigation methods.

Requirements of personal protective equipment (PPE):

- a) Applicators and other handlers performing direct-contact activities must wear:
 1. Coveralls over long-sleeved shirt and long pants.
 2. Waterproof gloves.
 3. Chemical-resistant footwear plus socks.
 4. Chemical-resistant headgear for overhead exposure.
 5. Chemical-resistant apron when cleaning equipment, or when mixing, loading, or transferring without dry-disconnect fittings.
 6. Face-sealing goggles, unless full-face respirator is worn.
 7. A respirator either with an organic-vapor-removing cartridge with a prefilter approved for pesticides (MSHA/NIOSH approval number prefix TC-23C), or a canister approved for pesticides (MSHA/NIOSH approval number prefix TC-14G).

- b) Applicators and other handlers in enclosed cabs must wear:

Coveralls, shoes plus socks.

Plus, if pungent, rotten-egg odor of the metam-sodium product can be detected inside the enclosed cab, the handlers in the cab must wear: Face-sealing goggles, unless full-face respirator is worn. A respirator either with an organic-vapor-removing cartridge with a prefilter approved for pesticides (MSHA/NIOSH approval number prefix TC-23C), or a

canister approved for pesticides (MSHA/NIOSH approval number prefix TC-14G). In addition, the PPE specified in (a) for direct-contact activities must be immediately available in the enclosed cab and must be worn if the handler leaves the enclosed cab to perform any direct-contact activity.

- c) Handlers in treated areas while entry is restricted. The following handling tasks may be performed in a treated area outdoors: assessing/adjusting the soil seal; assessing pest control, application technique, or application efficacy; operating ventilation equipment; and sampling air or soil for this product. Handlers must wear:
1. Coveralls over long-sleeved shirt and long pants.
 2. Waterproof gloves.
 3. Chemical-resistant footwear plus socks.
- Plus: Handlers must wear (1) in a treated greenhouse before ventilation criteria have been met or (2) if pungent, rotten-egg odor of the metam-sodium product can be detected outdoors or in a treated greenhouse after ventilation criteria have been met: Face-sealing goggles, unless full-face respirator is worn, and a respirator either with an organic-vapor-removing cartridge with a prefilter approved for pesticides (MSHA/NIOSH approval number prefix TC-23C), or a canister approved for pesticides (MSHA/NIOSH approval number prefix TC-14G).

USAGE

Metam-sodium products are intended for use as antimicrobials, bactericides, fungicides, herbicides, insecticides, and nematicides. In California, the annual use of metam-sodium from 1998 to 2002 averaged 14.1 million pounds (lbs) (DPR, 2000a, 2000b, 2001, 2002, 2003). From the same period, the highest use was in 1999 totaled 17.3 million lbs (DPR, 2000b) and the lowest use was in 2001 totaled 11.3 million lbs (DPR, 2002). The four highest uses in 1999 were reported for carrots (6.6 million lbs), tomatoes (4.1 million lbs), potatoes (2.1 million lbs), and cotton (0.7 million lbs) (DPR, 2000b).

Wales (2000) analyzed the historical metam-sodium use from 1990 to 1998. A graph was presented to show the use of metam-sodium in each month of the year. There were two distinctive peak use periods (seasons), which were from January to April and July to October. The two low use periods were from May to June and November to December. Also, the graph indicated that metam-sodium was used year-round in California. A use season in California was assumed to be four months or 120 days.

Metam-sodium is typically applied through rotary tiller injection or by injection into a sprinkler irrigation system 14 to 21 days before planting. Once metam-sodium is in the soil, it will degrade to MITC and other degradates. MITC is the principal active ingredient (AI) in controlling various pests in the soil.

ILLNESS/INJURY DATA

In California, there was no separate classification of illnesses/injuries resulting from exposure to metam-sodium. It was assumed that the majority of illnesses/injuries were caused by exposure to MITC because it is the major degradate of metam-sodium after application to soil and MITC is volatile in the environment. From 1990 to 2002, there were 790 illnesses/injuries (annual average was 60.7 cases) attributed to exposure to metam-sodium/MITC as reported in California (Mehler, 2004) (Table 1). These illnesses/injuries were classified according to relationship to exposure. The majority of illness/injury cases from 1990 to 2002 occurred to workers during field fumigation and to residents classified as non-occupational exposure (Table 2). These illness/injury cases were also grouped according to symptoms experienced by affected persons (Table 3). These cases excluded illnesses/injuries as a result of the Cantara spill in 1991 where a train tanker spilled metam-sodium into the Sacramento River, and 38 cases in 2002 where 15 cases could not be classified because affected workers were not interviewed, 21 cases remained asymptomatic because the questionnaires indicated that these workers denied experiencing symptoms, and 2 cases could not be evaluated because illness symptoms could not be determined from the questionnaires.

Table 1. Case reports received by the California Pesticide Illness Surveillance Program in which health effects were attributed to exposure to metam-sodium/MITC (1990-2002): Classified according to relationship to exposure.^a

Year	Illness/injury relationship			Total
	Definite ^b	Probable ^c	Possible ^d	
1990	6	6	8	20
1991	2	2	9	13
1992	1	9	8	18
1993	14	4	0	18
1994	4	5	1	10
1995	27	20	1	48
1996	9	43	4	56
1997	5	12	3	20
1998	0	2	2	4
1999	1	149	33	183
2000	2	6	2	10
2001	0	5	2	7
2002 ^e	1	377	5	383
Total	72	640	78	790
Average	5.5	49.2	6.0	60.7

^a In 1993, there were two illnesses/injuries attributed to exposure to metam-sodium/MITC in combination with other pesticides. Thus, there were altogether 792 illness/injury cases from 1990 to 2002. These cases excluded illnesses/injuries as a result of the Cantara spill in 1991 where a train tanker spilled metam-sodium into the Sacramento River.

^b The "definite" means the signs and symptoms exhibited by the affected person are such that would be expected to result from the exposure described.

^c The "probable" means that there is close correspondence between the exposure and the illness experienced.

^d The "possible" means some correspondence between the exposure described and the illness/injury experienced.

^e Illness/injury cases do not include these cases: 15 (fieldworkers) – could not be classified; 21 (residents) – remained asymptomatic; 2 (residents) – could not be evaluated (See text for explanation).

Table 2. Case reports received by the California Pesticide Illness Surveillance Program in which health effects were attributed to exposure to metam-sodium/MITC (1990-2002): Classified according to activities.^a

Activity	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	Total
Loader	0	1	1	3	3	3	3	5	0	0	1	0	0	20
Applicator	1	0	0	2	0	1	3	2	2	0	3	5	0	19
Fumigation, field	14	7	1	1	3	0	0	5	1	2	0	0	5	39
Drift: Occupational	2	0	0	0	0	0	2	0	0	8	0	0	123	135
Non-occup.	0	0	11	11	0	40	48	0	1	167	6	0	250	534
All others	3	5	5	1	4	4	0	8	0	6	0	2	5	43
Total	20	13	18	18	10	48	56	20	4	183	10	7	383 ^b	790

^a In 1993, there were two illnesses/injuries attributed to exposure to metam-sodium/MITC in combination with other pesticides. Thus, there were altogether 792 illness/injury cases from 1990 to 2002. These cases excluded illnesses/injuries as a result of the Cantara spill in 1991 where a train tanker spilled metam-sodium into the Sacramento River.

^b Illness/injury cases do not include these cases: 15 (fieldworkers) – could not be classified; 21 (residents) – remained asymptomatic; 2 (residents) – could not be evaluated (See text for explanation).

Table 3. Case reports received by the California Pesticide Illness Surveillance Program in which health effects were attributed to exposure to metam-sodium/MITC (1990-2002): Classified according to symptoms.^{a, b}

Year	Systemic	Skin	Eye & Eye/skin	Respiratory & Respiratory/eye	Total
1990	8	11	1	0	20
1991	4	6	1	2	13
1992	8	4	5	1	18
1993	10	6	2	0	18
1994	3	6	1	0	10
1995	40	2	6	0	48
1996	22	6	28	0	56
1997	10	9	1	0	20
1998	2	1	1	0	4
1999	161	18	4	0	183
2000	7	1	2	0	10
2001	4	3	0	0	7
2002 ^c	1	2	2	378	383
Total	280	75	54	381	790
Average	21.5	5.8	4.2	29.3	60.7

^a In 1993, there were two illnesses/injuries attributed to exposure to metam-sodium/MITC in combination with other pesticides. Thus, there were altogether 792 illness/injury cases from 1990 to 2002. These cases excluded illnesses/injuries as a result of the Cantara spill in 1991 where a train tanker spilled metam-sodium into the Sacramento River.

^b Examples of reported symptoms were: eye - watery, burning, itchy, blurred vision; skin - rash, burns, redness, swelling; systemic - nausea, chest pain, scratchy throat, diarrhea, weakness, dizziness, headache, malaise, salivation, vomiting; respiratory - cough, shortness of breath.

^c Illness/injury cases do not include these cases: 15 (fieldworkers) – could not be classified; 21 (residents) – remained asymptomatic; 2 (residents) – could not be evaluated (See text for explanation).

DERMAL TOXICITY AND EYE IRRITATION

Dermal/eye irritation:

There were several submissions of primary dermal and eye irritation studies for metam-sodium products. For example, the results indicated that metam-sodium can cause mild eye and mild to severe (corrosive) skin irritation in New Zealand white rabbits (Stauffer Chemical, 1987; ICI Americas, 1988a). The Risk Characterization Document for metam-sodium contains complete results of primary dermal and eye irritation studies for metam-sodium products.

Dermal sensitization:

Most product labels of metam-sodium indicate that this chemical has the potential to cause dermal sensitization or allergic reactions if exposure is prolonged or frequent. Some metam-sodium products were used in dermal sensitization studies. The results showed that metam-sodium has the potential to be a sensitizer under the conditions of the studies.

The dermal sensitization potential of Vapam[®] Technical (32.9% a.i.) was tested in young adult male, Hartley strain guinea pigs. In the definitive phase of the study, animals were divided into three groups: positive control, negative control, and test material group. Animals were induced dermally with 0.1% DNCB (dinitro-chlorobenzene) in 70% ethanolic water as a positive control group. For test material group, animals were induced with nonirritating doses of Vapam[®] Technical (1% in deionized water). Water was used for the negative control group. Animals in these three groups were challenged, where appropriate, on days 35, 42 and 49 using 0.1 and 1.0% Vapam[®] Technical in deionized water, 0.1% DNCB in acetone, and 0.1% MITC in acetone. Reactions of the skin (e.g., erythema, edema) were observed and scored. The results indicated Vapam[®] Technical at a nonirritating concentration of 1% has the potential to elicit dermal sensitization reactions. MITC at a nonirritating concentration of 0.1% has the potential to produce dermal sensitization reactions after the animals were induced with 1% Vapam[®] Technical (ICI Americas, 1988b).

Similar evidence of mild hypersensitivity reactions was observed when tested with metam-sodium using female albino guinea pigs of Dunkin/Hartley strain (UCB Chemicals, 1992). The test and control animals were challenged topically two weeks after the topical induction using metam-sodium, 1% and 0.5% (v/v) in distilled water. Nineteen out of 20 animals showed positive reactions. However, sensitizing reactions were not shown when male guinea pigs were induced with 10% metam-sodium and challenged with 1% metam-sodium (Amvac, 1992). In another study, metam-sodium had the potential to be a contact sensitizer when male Hartley albino guinea pigs were induced with irritating doses of metam-sodium and rechallenged with nonirritating dose of 0.5% metam-sodium in deionized water (OR-CAL, 1993).

DERMAL ABSORPTION

The MSTF in care of ICI Americas (ICI Americas, 1993) submitted a dermal absorption study. There are two separate studies in this submitted document. The first study describes stability determination of aqueous solutions, which was conducted by Zeneca Central Toxicology Laboratory. The second study describes *in vivo* dermal absorption in the rat. The latter was performed by Hazleton UK. The first study was conducted to determine the appropriate dose levels prior to the dermal absorption study of metam-sodium in rats. Both studies were performed in compliance with U.S. EPA Good Laboratory Practice Standards (40 CFR, Part 160). Also, Zeneca Central Toxicology conducted an *in vitro* dermal absorption study using rat and human skin (Clowes, 1993). All studies were reviewed and reported (Thongsinthusak, 1993, 2000). Summary of the three studies is shown below.

A. Stability determination of aqueous solutions:

Stability of metam-sodium in water was conducted prior to the dermal absorption study in the rat. A mixture of high purity ^{14}C -metam-sodium (between 94.4 and 97.4%) and nonlabeled metam-sodium (99.4%) were used in *in vivo* and *in vitro* dermal absorption studies. The labeled position of [^{14}C] was at the carbonyl carbon. ^{14}C -metam-sodium (7.66 mg) was mixed with nonlabeled metam-sodium (193.85 mg), evacuated, and dissolved in degassed HPLC grade water at about 200 mL to make a solution of 200 mg/mL. Dilutions were also done to prepare concentrations of 20, 2, and 0.2 mg/mL. All of the solutions were stored under nitrogen environment at room temperature in the dark. At different time intervals after the preparation of the solutions, samples were analyzed by HPLC using UV absorption at 241 nm with concurrent radioactivity analysis.

The results showed that the 0.2 mg/mL solution was not stable because less than 63% of its initial analyzed concentration remained after three hours. For the 2 mg/mL solution, more than 93% of its initial concentration remained one hour after its preparation and 86% three hours after its preparation. Solutions of 200 and 20 mg/mL appeared to be stable for at least 20 hours. Due to the instability of the lowest concentration solution of 0.2 mg/mL, this concentration was not used in the dermal absorption study in rats.

B. *In vivo* dermal absorption study using rats:

Six to ten-week old Charles River Crl:CD(SD)BR strain rats were used in the dermal absorption study. Body weights of these rats ranged from 178 to 274 grams. These animals were acclimatized 4-12 days prior to the study. An area of the dorso-lumbar skin was clipped free of hair using veterinary clippers, without abrading the skin. The shaved skin sites were washed with acetone. The treated skin site with an area of 11.6 cm² was enclosed with a glass saddle. The animals were placed in individual all glass metabolism cages that allowed the separate collection of urine, feces, and expired air.

The test material was prepared as an aqueous solution in degassed HPLC grade water to give a nominal volume of 0.05 mL per animal. Three dose levels at nominal concentrations of 0.1, 1, and 10 mg/animal (equivalent to 8.6, 86.2, and 862 $\mu\text{g}/\text{cm}^2$) were applied dermally. Four animals were used per sacrifice time of each dose level. After administration of the dosing

solution, an activated charcoal filter, resting between two glass sinters, was placed in the saddle. The charcoal and sinters were secured by a foam disc, cotton gauze, and an elastic band.

The sacrifice times were 1, 2, 10, 24, and 72 hours which corresponded to the exposure times 1, 2, 10, 24, and 10 hours, respectively. For the 72-hour sacrifice time, the treated skin sites and the inside of the glass saddles were swabbed thoroughly with liquid Ivory[®] soap solution and water at the end of the 10-hour exposure period, and the animals were returned to the metabolism cages. Urine, feces, and cage washings of animals for the 72-hour sacrifice time were collected at 10, 24, 48, and 72 hours. Samples collected for analysis were: nonocclusive cover (charcoal, charcoal washings, and sinter washings), treated and untreated skin sites, cage washings, carcass, urine, feces, blood, air traps, and cage debris.

Results of the dermal absorption study are shown in Table 4. The results indicated that metam-sodium and/or its degradates are absorbed rapidly into the skin. Absorption in one hour after exposure is similar to that with longer exposure time. There is no obvious indication that absorption is dose or time dependent. This may be due to metam-sodium being rapidly degraded and the degradate(s) volatilized and are trapped in the charcoal or limited absorption of a radiolabeled impurity. The percentage of dose absorbed for 1, 2, 10, and 24-hour sacrifice times can be calculated by addition of percent dose in treated skin, urine, feces, carcass, cage washings, air traps, and blood. However, these dermal absorption values were not used for worker exposure estimates because bioavailability of bound skin residues can be estimated from the 72-hour sacrifice time group.

In order to resolve the issue of bound skin residues, the cumulative percentage of doses in urine, feces, and cage washings for different time intervals up to 72 hours were used for estimating the asymptote by employing an exponential saturation model with lag time. An equation representing this model is: $Y = A \times (1 - \text{EXP}(-B \times (X - C)))$ or $\text{Recov} = \text{Max} \times (1 - \text{EXP}(-\text{Rate} \times (\text{Time} - \text{Lag})))$ (Thongsinthusak *et al.*, 1999). The dermal absorption value is the sum of the percentage of dose excreted at asymptote (maximum or "A" term) and percent of dose recovered in carcass, blood, and air traps. Table 5 summarizes the dermal absorption values for low, medium and high doses used in this study. The percentages of doses excreted after administration are similar, ranging from 0.89 to 1.18 percent. The corrected dermal absorption values are from 2.48%, 3.48% and 4.20% for the low (8.6 $\mu\text{g}/\text{cm}^2$), mid (86.2 $\mu\text{g}/\text{cm}^2$) and high dose (862 $\mu\text{g}/\text{cm}^2$), respectively.

Table 4. Percentage recovery of administered dose of metam-sodium.

Dose	Sacrifice Time (h)	% of dose									
		Unab-sorbed ^a	Cage debris	Treated skin ^b	Urine	Feces	Carcass	CW	Air traps ^c	Blood ^d	Total Recovery
0.1 mg/rat (8.6 µg/cm ²)	1	92.8	0	2.7	0.000	0	0	0	1.791	0	97.3
	2	87.6	0	3.6	0.018	0	0	0	2.161	0	93.4
	10	91.7	0	7.7	0.451	0	0	0.081	0.824	0	100.8
	24	71.3	0	8.4	1.002	0.035	0	0.015	1.930	0	82.7
	72	93.0	0	2.8	1.049	0.006	0	0.1	1.276	0	98.2
1.0 mg/rat (86.2 µg/cm ²)	1	82.7	0	3.6	0.011	0	0.144	0.022	1.707	0.06	88.3
	2	78.2	0	6.8	0.044	0	0.266	0.000	2.777	0.07	88.2
	10	90.2	0	4.3	0.749	0.026	0.000	0.087	2.823	0.02	98.2
	24	76.4	0	4.1	1.321	0.701	0.815	0.161	1.725	0.02	85.2
	72	87.7	0	1.6	0.697	0.016	0.000	0.129	2.325	0.00	92.5
10 mg/rat (862 µg/cm ²)	1	64.1	0	14.9	0.000	0	0	0.064	0.324	0.05	79.4
	2	79.3	0.03	1.8	0.079	0.044	0.432	0.062	0.682	0.04	82.5
	10	80.8	0	1.3	0.489	0.021	0.342	0.106	0.556	0.03	83.7
	24	80.1	0	2.5	0.753	0.459	0.541	0.157	0.325	0.02	84.8
	72	79.1	0	0.7	0.942	0.109	1.217	0.145	1.101	0.00	83.3

CW is cage washing

^a Application site washing + charcoal + charcoal washings + sinter washings.

^b Included untreated skin around the treated skin site.

^c Trap (1) 2-ethoxyethanol to trap MITC + trap (2) ethanolamine:2-ethoxyethanol (91:3, v/v) to trap CO₂ + trap (3) ethanol:diethylamine:triethanolamine (1000:1:20, v/v) to trap CS₂. Due to unusually high percentage of dose recovered in trap (2) for 24-hour (0.1 mg/animal) and 2-hour (10 mg/animal) sacrifice times, an average of the percentage of dose from trap (2) of other four sacrifice times of the same dose group was used.

^d Percentage of dose in blood was calculated based upon the assumption that one animal has 15 grams of whole blood.

Table 5. Summary: Dermal absorption of metam-sodium in male rats.

Dose mg/animal ($\mu\text{g}/\text{cm}^2$)	% of dose							Total ^c
	Excreted (U+F+CW) ^a	Excreted ^b	Blood	Carcass	Expired air	Sub-total	Recovery	
0.1 (8.6)	1.16	1.15	0	0	1.28	2.43	98.2	2.48
1.0 (86.2)	0.84	0.89	0	0	2.33	3.22	92.5	3.48
10 (862)	1.20	1.18	0	1.22	1.10	3.50	83.3	4.20

^a % of dose in urine (U), feces (F), and cage washing (CW) for the 72-hour sacrifice time as shown in Table 4.

^b Represent maximum excretion of the dose obtained from the asymptotic plot or analysis of cumulative excretion in urine, feces, and cage washings by using the exponential saturation model with lag time. The exposure time for animals was 10 hours for all dose groups. The samples collection times were 10, 24, 48, and 72 hours after dosing.

^c Corrected for the percentage of recovery.

C. *In vitro* dermal absorption study using rat and human skin:

In 1993, Zeneca Central Toxicology Laboratory in United Kingdom conducted an *in vitro* dermal absorption study using rat and human skin (Clowes, 1993). Results of the study were reviewed and reported (Thongsinthusak, 2000).

The dosing solution was prepared by mixing unlabeled and ¹⁴C-labeled metam-sodium in the HPLC grade water. Two dose levels of metam-sodium employed in the study were 940 and 94 $\mu\text{g}/\text{cm}^2$. This study utilized full thickness (epidermis + dermis) of rat and human skin. The rat skin samples (dorsal and flank region) were obtained from 28-day old male rats, Wistar strain. Human skin samples were prepared from human abdominal skin (female) obtained post mortem from subjects of varying ages. The rat and human skin samples were checked for integrity by using tritiated water.

Glass diffusion cells in which the skin forms a horizontal membrane separating donor (outer) and receptor chambers were used for measuring skin absorption. An area of 2.54 cm^2 of skin was available for absorption and all experiments were conducted with the diffusion cell placed in a water bath at 30 ± 1 °C. Receptor solutions were stirred for the duration of the experiment.

The aqueous solution of the dose was spread over the skin surface and the donor chambers covered with two porous carbon filter discs to trap any evaporating dose. Physiological saline (0.9% NaCl) was used as a receptor fluid. The exposure time was 10 hours. Samples of receptor fluid were taken at 0.5, 1, 2, 4, 6, and 10 hours to follow the absorption patterns for different exposure times. Each sample taken was replaced by equal volume of receptor fluid to maintain the same volume in the receptor chamber. At the end of the exposure period, the skin was rinsed with 5 mL aliquots of a detergent (3% TEEPOL L in water). Samples collected for analysis are shown in Table 6. The radioactivity from those samples was analyzed by liquid scintillation spectrophotometers.

It appears that the study was appropriate for the purpose of deriving the ratio of metam-sodium absorption between the rat and human skin based on the procedure provided by Thongsinthusak *et al.* (1993). The absorption is the sum of % dose in receptor fluid and washed skin (not adjusted for the total recovery). Results of the study reveal the total absorption of metam-sodium in the human skin is dose dependent. However, the total percentage of dermal absorption in rats for the two doses tested were fairly similar. The mean absorption values of metam-sodium in rat and human skin are shown in Table 6.

Table 6. Distribution of applied doses in various samples and the mean absorption value following *in vitro* application to human and rat skin.

1) Rat skin

Dose ($\mu\text{g}/\text{cm}^2$)	% Dose						
	Receptor fluid	Skin wash	Washed skin	Donor rinse	Filter	Total recovery	Absorbed ^a
940	21.3	62.8	3.66	8.58	5.65	102	25.0
94	19.4	50.2	8.23	6.28	10.3	94.4	27.6

2) Human skin

Dose ($\mu\text{g}/\text{cm}^2$)	% Dose						
	Receptor fluid	Skin wash	Washed skin	Donor rinse	Filter	Total recovery	Absorbed ^a
940	2.19	75.7	3.86	21.2	3.75	107	6.05
94	12.2	55.3	6.91	19.5	7.74	102	19.1

^a Sum of % dose in receptor fluid and washed skin (not adjusted for the total recovery).

The ratios of *in vitro* dermal absorption of the rat and human skin are dose dependent (Table 7). The ratio for the high dose ($940 \mu\text{g}/\text{cm}^2$) was 4.1 and that for the low dose ($94 \mu\text{g}/\text{cm}^2$) was 1.4 or 1.0 (rounded). A lower dose, e.g., $8.6 \mu\text{g}/\text{cm}^2$, was not used in the study to confirm if the ratio is 1.0 or closest to 1.0. There would be no difference in absorption between the rat and human skin if the ratio were 1.0. Since there are inadequate data to support the change of *in vivo* dermal absorption, the dermal absorption of 2.5% is used in exposure assessment of metam-sodium.

Table 7. Ratios of *in vitro* dermal absorption of metam-sodium in rat and human skin.

Dose ($\mu\text{g}/\text{cm}^2$)	% Dose absorbed (rat/human) ^a	Ratio (rat/human)
940	25.0/6.05	4.1
94	27.6/19.1	1.4

^a Sum of % dose in receptor fluid and washed skin (not adjusted for the total recovery).

ANIMAL METABOLISM/PHARMACOKINETICS

While no FIFRA (Federal Insecticide, Fungicide and Rodenticide Act) guideline standard metabolism studies were submitted by the registrants, an oral-dose metabolism study in rats (Hawkins *et al.*, 1987) and an intraperitoneal-dose metabolism study in rats and mice (Lam *et al.*, 1993) were available. In addition, a single-dose dermal absorption study in rats was also examined (ICI Americas, 1993). In the environment, and after oral administration to animals, the major metam-sodium degradate is MITC. For this reason, a study of both metam-sodium and MITC was undertaken.

The oral-dose metabolism study compared the absorption, retention, tissue distribution, and excretion of metam-sodium and MITC (Hawkins *et al.*, 1987). Rats were given radiolabeled metam-sodium (>99%) at 10 or 100 mg/kg, or MITC at 4.4 or 33 mg/kg by gastric gavage. Feces were collected at 24-hour intervals up to 7 days. Expired air was collected at 24-hour intervals up to 3 days, passing through a series of 3 traps containing 2-ethoxyethanol (to trap MITC), 20% aqueous sodium hydroxide (to trap CO₂), and Viles' reagent (to trap carbonyl sulphide and CS₂). Tissue levels were also determined at the end of the study. Recovery of excreted metam and its metabolites (% of dose) is summarized in Table 8.

A. Absorption, oral exposure:

Using urinary and expired air levels to estimate absorption after oral exposure (Note: these are minimal estimates, *i.e.*, estimates that do not consider contributions from tissue-bound or fecal fractions), the data indicate that over 80% of the administered doses of metam-sodium were absorbed within 24 hours. About 90% was absorbed within 168 hours. MITC appeared to be even more readily absorbed; by 24 hours 88-96% of the dose was absorbed and by 168 hours 94-100% was absorbed (again, these are minimal estimates).

B. Absorption, dermal exposure:

The extent of absorption of metam-sodium after dermal exposure was examined in the rat in a separate study (ICI Americas, 1993). A detailed analysis of this study is provided in the dermal absorption section of this document. The corrected dermal absorption value of 2.5% for the lowest dose (8.6 µg/cm²) was considered appropriate for use in the worker exposure estimates because this dose should be more representative of exposure experienced by agricultural workers than the mid and high dose levels. As shown later in the exposure assessment section, the estimated dermal exposures range from 0.27 to 0.53 µg/cm². Actual dermal exposure of specific areas of certain body regions to the field strength dilution of metam-sodium may be higher than this range. However, specific exposure levels (*i.e.*, not normalized to a body region or the whole body) are not useful for the determination of dose levels for a dermal absorption study.

Table 8. Absorption, excretion and retention of radioactivity (% of dose) following metam-sodium or MITC oral gavage to rats (n = 5 per dose).

	Dose							
	Metam-sodium ^a				MITC ^a			
	10 mg/kg		100 mg/kg		4.4 mg/kg		33 mg/kg	
	M	F	M	F	M	F	M	F
Urine								
0-8 hrs	24.19	26.04	17.83	19.17	71.43	73.65	58.76	54.62
0-24 hrs	46.49	53.34	33.83	38.34	80.68	82.45	81.69	80.13
0-168 hrs	52.02	58.09	37.34	42.42	84.43	86.36	87.09	85.57
Expired air (Trap 1: MITC)								
0-24 hrs	0.37	1.12	23.91	23.39	0.69	1.24	0.49	1.20
0-168 hrs	0.45	1.26	24.53	24.04	0.95	1.51	0.72	1.67
Expired air (Trap 2: CO ₂)								
0-24 hrs	18.44	17.03	6.68	5.00	15.24	14.09	6.78	6.53
0-168 hrs	19.56	18.13	7.20	5.53	16.08	14.88	7.32	7.23
Expired air (Trap 3: COS & CS ₂)								
0-24 hrs	17.99	13.55	20.41	17.00	0.04	0.04	0.29	0.33
0-168 hrs	18.35	13.80	21.34	17.63	0.05	0.04	0.43	0.48
Amount absorbed (minimal estimate ^b)								
0-24 hrs	83.29	85.04	84.83	83.73	96.65	97.82	89.25	88.19
0-168 hrs	90.38	91.28	90.41	89.62	101.5	102.8	95.56	94.95
Feces								
0-24 hrs	2.98	0.83	0.96	0.66	1.99	0.66	1.13	0.93
0-168 hrs	4.48	2.88	1.87	1.57	2.74	1.45	1.93	1.83
Cage washings (total)	0.10	0.05	0.06	0.04	0.15	0.07	0.18	0.15
Tissues (168 hrs)	2.01	1.75	1.17	1.32	2.20	1.86	1.71	2.29
Total recovery	96.96	95.95	93.50	92.55	106.6	106.2	99.37	99.22

^a Results in % of dose.

^b These values are considered minimal estimates of absorption because they take into account only the radioactivity in urine and expired air. Tissue levels are not included because no 24-hr data were available. Fecal levels are not included because there was no attempt to discern which fraction of the fecal radioactivity was excreted into the gut from circulating (*i.e.*, absorbed) pools.

C. Distribution:

For metam-sodium, tissue content was highest in the thyroid on a µg/g basis at 168 hours after oral exposure (Hawkins *et al.*, 1987). Kidneys and liver were among the sites with the highest retention of radioactivity, and, along with the thyroid, were thought to be the tissues responsible for metabolism and excretion. Lung (particularly in females), adrenals, and ovaries were also sites of relatively high accumulation. Whole blood accumulated a relatively high proportion of label at the high dose. The investigators concluded that the absorption was similar at both doses, but exhibited a somewhat different pattern of metabolism and excretion.

Similar to metam-sodium, tissue content following MITC administration was highest in the thyroid at 168 hours, with liver, kidneys, whole blood, and adrenals comprising relatively high secondary sites of accumulation. Female lungs at the high dose were also important sites.

Total tissue levels at 168 hours did not exceed 2.3% of the administered dose of metam-sodium or MITC at either the low or high doses.

D. Biotransformation:

The same urinary metabolites were identified for both compounds although there were some differences in the relative proportions. Neither parent compound was present in the urine. A single major metabolite (M5) represented 16-25% of the dose for metam-sodium and 56-66% of the dose for MITC. There was only one other metabolite (M4) formed in appreciable amounts from both compounds, and represented 5-10% of the dose. There was no evidence for the presence of glucuronide or sulfate conjugates. The major metabolite was identified as N-acetyl-S-(N-methylthiocarbamoyl)-L-cysteine. The other metabolite was shown to chromatographically match to the corresponding cysteine conjugate. It was suggested that the metam-sodium underwent acid hydrolysis in the stomach to form MITC and CS₂, but that a portion of the metam-sodium may have been absorbed intact. That would explain the slower excretion and the dose-dependent excretion compared with MITC (Wagner, 1989).

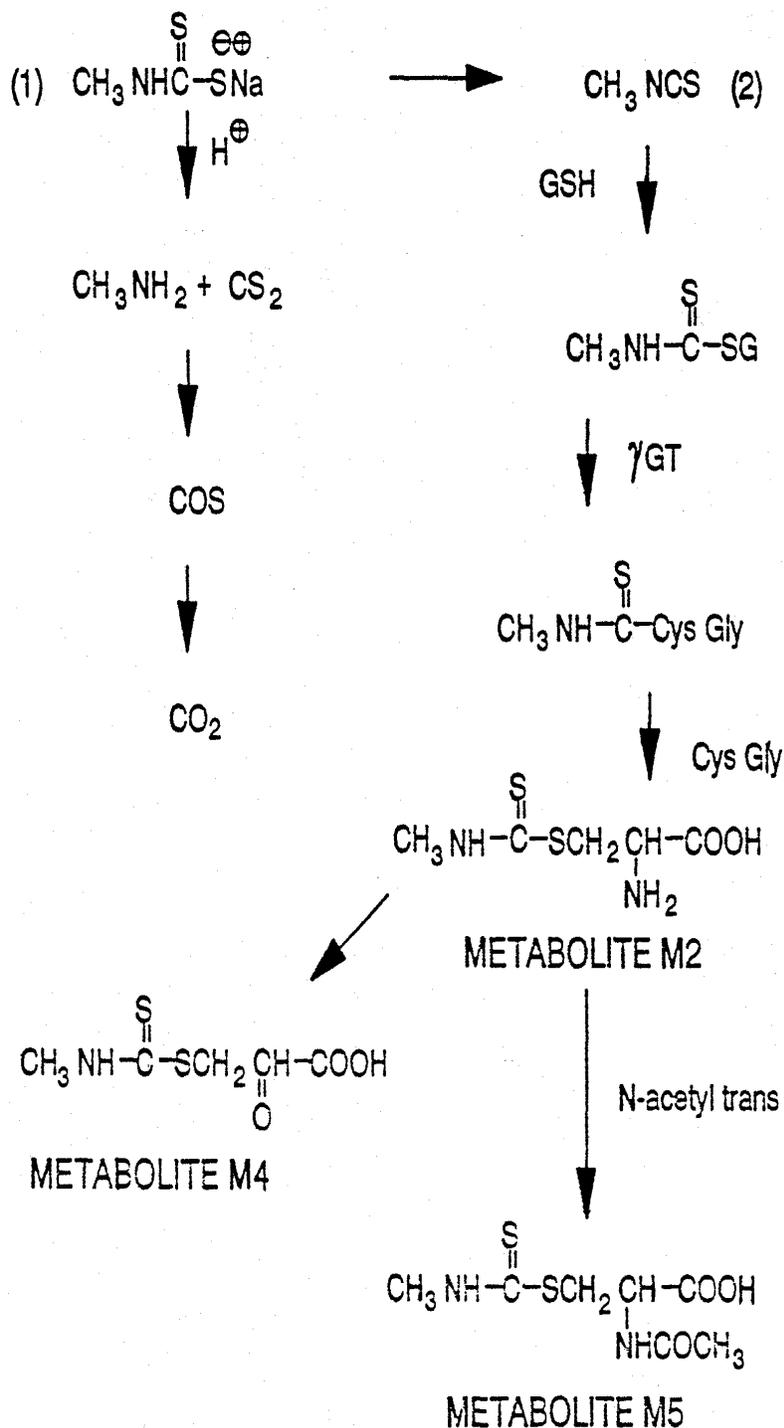
E. Excretion:

Following doses of MITC the radioactivity was principally eliminated in urine (see below) and in the expired air (as CO₂). With metam-sodium, 52-58% of the low dose and 37-42% of the high dose was recovered in the urine. Expired air accounted for 33-38% of the low dose and 47-53% of the high dose. Much of the increase at the high dose was accounted for by a marked increase in the excretion of MITC (however, MITC was not recovered in a similar trap following direct MITC administration to rats (Wagner, 1989)), but, it should be noted, there was a decrease in the relative amounts appearing as CO₂. Other expired metabolites included CS₂ and carbonyl sulfide. Proposed degradation/metabolic pathways for metam-sodium and MITC are shown in Figure 1 (adopted from Rose, 1989).

Urinary elimination occurred mainly during the first 8 hours following MITC administration and over the first 24 hours following administration of metam-sodium. The difference in excretion rate was mirrored by a slower initial rate of elimination of radioactivity from the plasma of metam-sodium-dosed animals.

As indicated above, the Hawkins study did not completely satisfy FIFRA guidelines (no multiple dosing regime was conducted); however, the study did provide useful information on the pharmacokinetics of metam-sodium/MITC in rats.

Figure 1. Proposed degradation/metabolic pathways for metam-sodium (1) and MITC (2).



Abbreviations: GSH is Glutathione S-transferase; γGT is γ -Glutamyltranspeptidase; N-acetyl trans is N-acetyltransferase; Cys Gly is Cysteinylglycinase.

F. Rats and mice, intraperitoneal injection:

Another study from the open literature (Lam *et al.*, 1993) determined the fate of radiolabeled metam-sodium and MITC following intraperitoneal injection into mice (Swiss-Webster, male) and rats (Sprague-Dawley, male). A mean value of 58% of the metam-sodium and 80% of the MITC was excreted in mouse urine by 48 hours. Feces, expired CO₂ and carcass accounted for 6, 5, and 7.5% of the total metam-sodium dose, respectively, and 5, 4, and 6% of the total MITC dose in mice. While widely distributed among tissues, liver, kidney, and hair, accounted for the largest proportions of the tissue fraction for both metam-sodium and MITC. Metabolite studies identified the conversion to the GSH conjugate as common to both compounds, resulting in mercapturates in the urine. Methylamine and other (unidentified) products were also detected in urine. Quantitative differences in the relative proportions of mercapturate, methylamine, unidentified polar metabolites and other unidentified metabolites were observed between mice and rats.

EXPOSURE ASSESSMENT

Metam-sodium is readily converted to its volatile metabolites such as MITC, carbon disulphide, and hydrogen sulfide after application into soil. It is unlikely that metam-sodium can be dispersed in the environment for a long distance and prolonged period of time because metam-sodium has very low vapor pressure. Exposure of residents and bystanders to technical grade metam-sodium is not a major concern at this time. Metam-sodium exposures are, therefore, estimated for workers or handlers only.

A. Worker exposure assessment:

At the present, a worker exposure study using metam-sodium has not been conducted. A surrogate study for metam-sodium exposure assessment is the worker exposure study using sodium tetrathiocarbonate mixed with cesium ions. This surrogate study was used to estimate dermal exposure of pest control operators (mixer/loaders and applicators) to metam-sodium during shank injection, sprinkler chemigation, rotary tiller injection, oak root fungus control, and to reentry workers. This surrogate study was selected because both metam-sodium and sodium tetrathiocarbonate (Enzone[®]) are salts and water-soluble. Both chemicals are applied to soil. After application, sodium tetrathiocarbonate will release carbon disulfide, whereas metam-sodium will release MITC and other gases. Foliar applied pesticides such as those used in the Pesticide Handler Exposure Database (PHED, 2001) are not suitable to be used as surrogate chemicals because of the difference in mode of application and the intended use. Inhalation exposure to metam-sodium was not estimated because technical grade metam-sodium is nonvolatile (Tomlin, 1997) and would not enter the vapor phase.

OR-CAL (1987) showed the vapor pressure of sodium methyldithiocarbamate (32.7% AI) at 77 °F or 25 °C to be 21 mm Hg. The test procedures were not included in the submitted report. Myers and Johnson (1985) measured vapor pressure of VAPAM[®] (sodium methyldithiocarbamate, 33.4% AI) by using an isoteniscopic procedure (ASTM Method No. D 2879-75), with several slight modifications. The modified test procedures were not included in

the report. The vapor pressure of VAPAM[®] at 25°C was determined to be 21.4 torr or 21.4 mm Hg. The high vapor pressure of the end-use product could result from the presence of degradates, such as MITC. The exposure of handlers to MITC during handling of the metam-sodium end-use product was determined and reported in a separate document (Thongsinthusak, 2003).

Exposure data for sodium tetrathiocarbonate (Haskell, 1994a, 1994b) was used as surrogate data for metam-sodium. Sodium tetrathiocarbonate (Enzone[®]) was applied at three sites. Methods of applications were application of sodium tetrathiocarbonate from the nurse tanks into furrows, above ground drip, and mini-sprinklers. The average application rate for these sites was 136 lbs AI per acre (A). Injection of sodium tetrathiocarbonate into an irrigation system was done using a closed system. Three workers were involved with the pretreatment water application and the Enzone[®] application at each site. One worker loaded the nurse tank with water for the pretreatment water application and then loaded Enzone[®] at the storage site and transported the nurse tank to the application site. Two other workers, acting as applicators, attached the nurse tank to the irrigation system with hoses, pumps and metering devices. They applied the Enzone[®] by injection into the irrigation system, then rinsed the nurse tank and injected the rinsate into the irrigation system. These workers then detached the pump and hoses from the nurse tank. Therefore, even though these individuals were applicators, they did not enter the treated area during the application at any of the sites.

The mixers/loaders wore coveralls over normal work clothing, rubber or neoprene boots, and rubber or neoprene gloves, whereas, applicators wore normal work clothing, rubber or neoprene boots, and rubber or neoprene gloves. These requirements on clothing protection are similar to those required for loaders of metam-sodium. A mixer/loader of metam-sodium is also required to wear a properly fit-tested MSHA/NIOSH-approved half-face respirator with organic vapor cartridges plus nonventing chemical goggles, or an MSHA/NIOSH-approved full-face respirator with organic vapor cartridges. Under the work clothing, workers wore long underwear, which served, as the dermal sampling matrix. At each site, there were two applicators and one mixer/loader. The application time ranged from 5.75 to 11.33 hours averaging 8.31 hours per day.

Sodium tetrathiocarbonate like metam-sodium is unstable in the environment after application. Collection of residue samples for analysis was impractical, if not impossible. Therefore, a surrogate chemical, cesium ion in the form of cesium chloride, was added to the product before application at a rate of 0.0975% by weight. Estimation of dermal exposure per day was based on the amount of sodium tetrathiocarbonate that was proportional to the amount of detected cesium ion. Almost all samples collected for analysis showed that residues of cesium ion were either below the limit of detection (LOD) or the limit of quantitation (LOQ). When cesium was not detected in the underwear sample, the value observed was assumed 1/2 LOD and values that were above the LOD but were too low to be quantified were expressed as 1/2(LOD+LOQ). All hand wash sample results were estimated using the LOD. Standard deviation was not presented because of undetectability of residues by methods used in the estimation. Exposure of workers to metam-sodium was then estimated based on the label rates of 318 (shank injection, sprinkler chemigation, reentry), 346 (rotary tiller injection), and 618 (oak root fungus control) lbs AI per

acre. These rates are the maximum label rates for those work tasks. Results are shown in Table 9.

Table 9. Dermal exposure estimates of adult pest control operators to metam-sodium during preplant applications.

Sodium tetrathiocarbonate		Work task ^b	Metam-sodium	
Rate (lbs AI/A)	Dermal exposure ^a (mg/person/day)		Rate (lbs AI/A)	Dermal exposure ^c (mg/person/day)
136	2.27	SI, SC, R	318	5.3
		RTI	346	5.8
		ORF	618	10.3

^a An average dermal exposure from nine workers (Haskell, 1994a, 1994b).

^b Shank injection (SI), sprinkler chemigation (SC), reentry (R), rotary tiller injection (RTI), oak root fungus (ORF) control.

^c Assumed dermal exposure is proportional to application rate.

It is necessary to determine the length of a use season in which exposure estimates can be compared with an appropriate toxicity endpoint. According to Wales (2000), there were two distinctive peak use periods (seasons) in California. The peaks were from January to April and July to October. A season of general use in California should last for a period of each of the two peak use seasons, which is 120 days. In 2002, Sullivan indicated that a custom shank injection applicator might work on the order of 30-40 weeks per year, which would constitute up to 200 days per year (Sullivan, 2002). It is assumed that a pest control operator (or custom applicator) may apply metam-sodium in a certain county and in adjacent counties. An average use of metam-sodium from 2000 to 2002 in carrots, the highest use crop, accounted for 41% of total use. Within the same period, Kern County had the most carrots acreage, totaling 42% of carrots grown in California. The pesticide use data from 2000 to 2002 (DPR, 2004b) showed that the use of metam-sodium in Kern and adjacent counties (Kings, Los Angeles, San Luis Obispo) in carrots is considered continuous (use in each month was greater than 5% of annual use) for eight months. Other crops are also grown in these counties that require metam-sodium for pest control. The use data, particularly in carrots, supports the contention that a pest control operator may apply metam-sodium for up to 200 days per year. Haskell (1994c) revealed that the maximum workdays for a grower who had both carrots and potatoes were 15 workdays/year for a 12-hour shift equivalent to 23 workdays/year for an eight-hour shift.

The maximum estimated workdays for the control of oak root fungus are five days in a 120-day season and 15 days per year. Therefore, potential health concerns relating to seasonal, annual, or lifetime exposures were not expected and these values were not estimated. Absorbed dosages for short-, intermediate-, and long-term exposures are shown in Table 10.

An upper bound exposure is estimated for short-term exposure, whereas an average of short-term exposures is determined for seasonal exposure (Andrews, 2001). Most dermal exposures to metam-sodium were estimated from LOD and/or LOQ of a surrogate study and standard deviations were not presented. Therefore, an upper bound exposure value was not calculated,

and that the ADD represents an average value. SADD is essentially the same as ADD because the latter is the average exposure. The estimated workdays for the control of oak root fungus are five workdays in a 120-day season and 15 workdays per year. These workdays are relatively short. Therefore, SADD, AADD, and LADD are not presented.

Daily and seasonal dermal exposures based on the amount per unit of skin area ($\mu\text{g}/\text{cm}^2$) were also estimated. A median body surface area of $19,400 \text{ cm}^2$ for adult male workers (U.S. EPA, 1997), with a median body weight of 76 kg, was used to calculate dermal exposures. This is because the actual surface areas of workers who participated in the study could not be determined because the heights of these workers were not known. The estimated daily and seasonal dermal exposures are shown in Table 11.

Table 10. Short-, intermediate-, and long-term exposures of adult pest control operators to metam-sodium.

Work task ^a	Adjusted dermal exposure ^b (mg/person/day)	ADD ^c ($\mu\text{g}/\text{kg}/\text{day}$)	Seasonal exposure ^d	SADD ^e ($\mu\text{g}/\text{kg}/\text{day}$)	Workdays /year ^f	AADD ^g ($\mu\text{g}/\text{kg}/\text{day}$)	LADD ^h
SI, SC, R	5.3	1.52	Yes	1.52	200	0.83	0.44
RTI	5.8	1.65	Yes	1.65	200	0.90	0.48
ORF	10.3	2.95	No	N/A	15	N/A	N/A

^a Shank injection (SI), sprinkler chemigation (SC), reentry (R), rotary tiller injection (RTI), oak root fungus (ORF) control.

^b Dermal exposure was adjusted to reflect the maximum recommended label rate for metam-sodium.

^c Absorbed daily dosage (ADD) was calculated using the dermal absorption of 2.5% and the average body weight of 87.5 kg for adult workers, who participated in the study (n=9). Standard deviations are not presented because most values were estimated from LOD and/or LOQ of a surrogate study. Therefore, an upper bound exposure value was not calculated, and that the ADD represents an average value.

^d Seasonal exposure should last about 8 months based on the use of metam-sodium in carrots in Kern and adjacent counties (DPR, 2004b). It was assumed that there was no seasonal exposure for the control of oak root fungus because the estimated workdays are only five days in a 120-day period.

^e Seasonal exposure represents an average of short-term exposures (Andrews, 2001). For metam-sodium exposure, SADD is the same as ADD because ADD is the average exposure. N/A is not applicable.

^f Annual workdays for pest control operators, except for the control of oak root fungus, are 200 days (Sullivan, 2002). The annual workdays are supported by the Pesticide Use Data (DPR, 2004b). A pest control operator is assumed to treat more than one crop with metam-sodium in one or more counties.

^g $\text{AADD} = (\text{ADD} \times \text{workdays}/\text{year}) \div 365 \text{ days}/\text{year}$. The estimated annual workdays for the control of oak root fungus are 15 days, which is a short-time period. Therefore, AADD was not calculated.

^h $\text{LADD} = (\text{AADD} \times 40 \text{ years of employment}) \div 75\text{-year lifetime}$. LADD for the control of oak root fungus was not calculated because the estimated annual workdays were 15 days, which is a short-time period.

Table 11. Estimated daily and seasonal dermal exposures of adult pest control operators during preplant applications.

Work task ^a	Adjusted dermal exposure ^b (mg/person/day)	Daily dermal exposure ^c ($\mu\text{g}/\text{cm}^2$)	Seasonal exposure	Seasonal dermal exposure ^d ($\mu\text{g}/\text{cm}^2$)
SI, SC, R	5.3	0.27	Yes	0.27
RTI	5.8	0.30	Yes	0.30
ORF	10.3	0.53	No	N/A

^a Shank injection (SI), sprinkler chemigation (SC), reentry (R), rotary tiller injection (RTI), oak root fungus (ORF) control.

^b Dermal exposure was adjusted to reflect the maximum recommended label rate of metam-sodium.

^c Calculated based on a surface area of 19,400 cm^2 for adult male worker. These values are average exposures. Daily dermal exposure represents an average exposure.

^d Seasonal exposures represent an average value of the short-term exposures (Andrews, 2001). Seasonal dermal exposures are the same as daily dermal exposures.

B. The use of metam-sodium for treating sewer systems

Three metam-sodium products, Sanafoam[®] Vaporooter[®] II, SeweRout[™], and SeweRout II[™] are used to control roots in sewer mains, drain lines, and other conduits. Use of these products, according to the labels, was previously reviewed by Donahue (1993). In essence, a 1% solution or foam is applied to an isolated section of a sewer system for an hour to destroy infiltrating roots. This type of use is considered minor usage compared to agricultural use. After an application, metam-sodium is contained within the plumbing system treated and should not pose any excessive exposure problem, provided the system has been adequately isolated. At the end of the treatment period, the treating solution is released into the main sewer system and the treated system flushed with water.

It is assumed that MITC and other degradates are formed during the treatment period, like those degradates formed during a soil application. These gases may leak from the system and may be hazardous to unprotected persons in the treated area if ventilation is not adequate. It is believed that sewer workers are aware of the potential for dangerous levels of various gases that may be present in the confining areas in and around the treatment sites. The product labels indicate, "Do not use in confined areas without adequate ventilation." There is no worker exposure monitoring available at this time for sewer use of any chemical.

EXPOSURE APPRAISAL

A field exposure study using metam-sodium has not been conducted. Because metam-sodium is unstable on human skin and in the environment, use of this chemical for an exposure study is difficult, if not possible. There is a limited choice of surrogate data for metam-sodium based upon the chemical properties and the purpose of use. The selected surrogate chemical for metam-sodium is by itself unstable on human skin and in the environment. A stable compound was incorporated into the surrogate chemical preparation. However, the exposure data are

questionable because most residues were below the LOD or LOQ. Foliar applied pesticides such as those used in the Pesticide Handler Exposure Database are not suitable to be used as surrogate chemicals because of the difference in mode of application and the intended use. The best approach would be to design a study method that metam-sodium can be used.

The dermal absorption of 2.5% determined from the lowest dose (8.6 $\mu\text{g}/\text{cm}^2$) used in the study is appropriate for use in the calculation of absorbed dosages of metam-sodium. Results from an *in vitro* dermal absorption study of the rat and human skin do not support a lower or higher human dermal absorption value than 2.5%.

The exposure estimates as presented in this document could be over or under estimated. The degree of over or under estimation could not be quantified because of the lack of specific information. It is desirable to have an exposure study using metam-sodium instead of using a surrogate chemical. Also, an *in vivo* dermal absorption study should be conducted using a dose level lower than 8.6 $\mu\text{g}/\text{cm}^2$ because the normalized dermal exposures are lower than this dose.

Inhalation exposure to metam-sodium was not estimated because metam-sodium end-use products have very low vapor pressure. The possibility of inhaling metam-sodium was assumed to be insignificant compared to dermal exposure.

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