Appendix J – HED Toxicological Chapter for Metam Sodium and MITC

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
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OFFICE OF
PREVENTION PESTICIDES AND
TOXIC SUBSTANCES

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Memorandum

SUBJECT: **4th Revised Toxicology Disciplinary Chapter for: *Metam Sodium (PC Code 039003) and Methyl isothiocyanate (MITC, PC Code 068103)***

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Attached is the 4th revised toxicology chapter for Metam Sodium (PC Code 039003) and Methyl isothiocyanate (MITC, PC Code 068103).

METAM SODIUM (PC CODE 039003); METHYL ISOTHIOCYANATE (MITC, PC CODE 068103);

4th Revised Toxicology Disciplinary Chapter for the Risk Assessment

Date completed: May 31, 2005

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1.0 EXPOSURE AND USE INFORMATION

Metam sodium, metam potassium, dazomet, and MITC are each registered as fumigants and are evaluated for risk assessment as 'non-food-use' chemicals. Metam sodium, metam potassium, and dazomet are considered carriers of MITC since they convert to MITC quickly under environmental conditions. It is MITC that performs the fumigating activity. *The primary route of human exposure to MITC is through inhalation in ambient air*. The toxicological and exposures profiles for metam sodium, metam potassium, dazomet, and MITC are intricately related (the present document considers metam sodium and MITC only). HED has previously accepted toxicity data for metam sodium for the registration of metam potassium.

Metam sodium, metam potassium and dazomet are used as agricultural fumigants to control weeds, nematodes, and fungi on a variety of crops. Although dazomet can also be used as a pre-plant soil fumigant before planting residential lawns, no residential exposure to MITC or dazomet is expected. MITC is registered, as an active ingredient, as a sterilization agent on treated wood products (e.g., telephone poles). Metam potassium is also used in sugarcane processing plants to clean process equipment; no residues of metam potassium or MITC are expected in sugar. Metam sodium and metam potassium are both extremely soluble in water and differ only by their cation.

2.0 HAZARD CHARACTERIZATION

Metam sodium, metam potassium, and dazomet are converted to MITC in the environment, particularly in soil after application. It is MITC that performs the fumigating activity. Metam sodium, metam potassium, and dazomet are efficiently converted to MITC *in vivo*. MITC is primarily an irritating compound that produces non-specific systemic effects in oral toxicity studies such as changes in body weight, food consumption, and hematological parameters. 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. 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). Although toxicological databases 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 data gaps are being filled through bridging with the toxicology databases of metam sodium and dazomet. 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. Since the release of EPA's preliminary risk assessment for metam sodium (May 21, 2004), additional ambient air exposure data became available which suggest that chronic exposure are possible. Because of the potential for chronic exposures and the finding of focal squamous cell metaplasia in the respiratory epithelium following 28-days of exposure to MITC in rats EPA is requiring carcinogenicity studies in mice and rats.

No inhalation pharmcokinetic or metabolism studies are available at this time. However, oral pharmacokinetic and metabolism studies in rats for dazomet, metam sodium, and MITC were submitted to support metabolism for metam sodium. Each compound was tested at two dose levels. It was shown that all three were excreted mainly in urine with urinary recoveries over 168 hours of 63-65% for dazomet, 37-58% for metam sodium, and 84-87% for MITC. Excretion via the feces was low–usually ranging from 1.5% to 3.3%. Three different compounds (MITC, CO_2, COS/CS_2) were found to be excreted via the lungs. Total excretion of the 3 products of the lungs over a 73 hour collection period were about 35% and 50% for metam sodium, 22% and 28% for dazomet, and 22% and 9% for MITC at low and high doses, respectively. There were no differences between males and females in amounts excreted via the three excretion routes. Tissue retention at 168 hours was about 2% for all 3 compounds at both dose levels. Total recoveries, including the percentage of the doses excreted and that remaining in the tissues combined after 168 hours, ranged from 92.6% to 106%, indicating virtually complete absorption from the GI tract. By the first 24 hours, 85% or more of each of the 3 compounds at both dose levels had been excreted. All three compounds were also rapidly absorbed from the GI tract with plasma tmax between 0.25 and 1.0 hours. However, plasma half-lives after 24 hours were long, ranging from around 60 to 74 hours for all three compounds. 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.

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 CS_2 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. Therefore, HED has elected to use oral studies and route to route extrapolation using a dermal absorption factor in its risk assessment.

Relating to the inhalation toxicity with these pesticides, two subchronic inhalation studies in MITC, one subchronic inhalation studies in metam sodium, and no inhalation studies in dazomet are available at this time. An eye irritation and odor threshold study in human subjects is also available. 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 existing uncertainty related to the adverse effects following exposure to MITC via the inhalation route, particularly for acute or single day exposures. 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. 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. An acute inhalation neurotoxicity study in MITC with additional measurements to characterize the complete respiratory tract is required at this time. There are no studies available for evaluating the route specific effects of MITC in the young, therefore an inhalation reproductive toxicity study is required at this time. Additional justification for this study come from inhalation developmental studies with MIC, a photolysis degradate of MITC, (Schwetz et al, 1987; Shilohi et al, 1986; Varma, 1987; Varma et al., 1987) which report effects such as pup death and survivability.

There are several toxicologically notable metabolites/degradates of metam sodium, metam potassium, MITC, and dazomet. Methyl isocyanate (MIC) is a photolysis degradate of the MITC. MIC is a toxic and irritating compound which has been detected in ambient air in parts of California. Following soil application of metam sodium, both CS_2 and H_2S can be formed; the relative amounts depend on the pH of the soil. Following oral exposure to metam sodium, rats metabolize approximately 20-25% of the dose (on a molar basis) to CS_2. CS_2 is a neurotoxic agent known to cause a variety of effects such as neuropathology and changes in sensory conduction velocity and peroneal motor conduction velocity. Exposure to H_2S at low levels in humans can result in eye injury, headaches, nausea, and insomnia. Comprehensive reviews of the toxicological profiles of CS_2 and H_2S are available on EPA's IRIS website and are briefly summarized in this document.

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 and dazomet are 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.

Metam sodium was negative in several mutagenicity assays (including the chromosomal aberration, clastogenicity, Salmonella assay, an unscheduled DNA synthesis). A new study on *in vitro* cytogenetics in human lymphocytes was recently submitted. Preliminary review of this study indicates metam sodium may be negative in this assay. Detailed review of this study is on-going; the results of this study will be incorporated into the hazard characterization of metam sodium in the future. Carcinogenic potential was evidenced by statistically significant increases in malignant angiosarcomas in both sexes of the CD-1 mouse. Metam sodium is classified as a 'probable human carcinogen.' For the purpose of risk characterization, a low dose extrapolation model be applied to the animal data for the quantification of human risk (Q,*) , based on the total incidence of angiosarcomas in male mice, at all sites combined.

In *in vitro* studies, dazomet is not mutagenic in the Ames test (bacteria, unacceptable studies), non mutagenic in the Rec assay (bacteria) and negative for inducing DNA damage/repair, and does not cause unscheduled DNA damage in primary rat hepatocytes. It was negative in *in vivo* bone marrow cytogenetic assay, micronucleus assay and in *in vitro* cytogenetic assay with human lymphocytes. It was positive in mammalian cells in culture gene mutation in Chinese hamster ovary (CHO) cells. Carcinogenicity and chronic feeding studies in Wistar rats appeared to be negative for carcinogenicity at doses up to 16.36 mg/kg/day in males and 21.54 mg/kg/day in females. There was lack of tumors in male B6C3F1 mice at doses up to 69.9 mg/kg/day and equivocal evidence for hepatocellular tumors in females at doses up to 21.54 mg/kg/day. Dazomet is currently classified as Group D-not classifiable as to human carcinogenicity.

Several of the MITC mutagenicity studies are considered unacceptable. MITC was positive in the structural chromosomal aberration assay in V79 lung cells. In the absence of appropriate data, the carcinogenic potential of MITC cannot be assessed at this time. The carcinogenic potential of MITC cannot be determined at this time; it is notable that focal squamous cell metaplasia was observed in the 28-day inhalation study with MITC.

3.0 REQUIREMENTS

The requirements (CFR 158.340) for METAM SODIUM and MITC are in Table 1 and 2, respectively. Use of the new guideline numbers does not imply that the new (1998) guideline protocols were used.

3.1 Table 1. Guideline Requirements for the Use Pattern(s) of METAM SODIUM

Test	Technical	
	Required	**Satisfied**
870.1100 Acute Oral Toxicity	yes	yes
870.1200 Acute Dermal Toxicity	yes	yes
870.1300 Acute Inhalation Toxicity	yes	yes
870.2400 Primary Eye Irritation	yes	yes
870.2500 Primary Dermal Irritation	yes	yes
870.2600 Dermal Sensitization	yes	yes
870.3100 Oral Subchronic (rodent)	yes	yes
870.3150 Oral Subchronic (nonrodent)	yes	yes
870.3200 21-Day Dermal	no	-
870.3250 90-Day Dermal	no	-
870.3465 90-Day Inhalation	yes	yes
870.3700a Developmental Toxicity (rodent)	yes	yes
870.3700b Developmental Toxicity (nonrodent)	yes	yes
870.3800 Reproduction	yes	yes
870.4100a Chronic Toxicity (rodent)	a	a
870.4100b Chronic Toxicity (nonrodent)	yes	yes
870.4200a Oncogenicity (rat)	a	a
870.4200b Oncogenicity (mouse)	yes	yes
870.4300 Combined Chronic/Oncogenicity	yes	yes
870.5100 Mutagenicity—Gene Mutation - bacterial	yes	yes
870.5300 Mutagenicity—Gene Mutation - mammalian	yes	yes
870.5xxx Mutagenicity—Structural Chromosomal Aberrations	yes	yes
870.5xxx Mutagenicity—Other Genotoxic Effects	yes	yes
	yes	yes
870.6100a Acute Delayed Neurotox. (hen)	no	-
870.6100b 90-Day Neurotoxicity (hen)	no	-
870.6200a Acute Neurotox. Screening Battery (rat)	yes	yes
870.6200b 90 Day Neuro. Screening Battery (rat)	yes	yes
870.6300 Develop. Neuro	no	-
870.7485 General Metabolism	yes	yes
870.7600 Dermal Penetration	yes	yes
Special Studies for Ocular Effects		
Acute Oral (rat)	no	-
Subchronic Oral (rat)	no	-
Six-month Oral (dog)	no	-

a. Fulfilled by combined chronic/carcinogenicity

3.2 Table 2. Guideline Requirements for the Use Pattern(s) of MITC

Test	Technical	
	Required	**Satisfied**
870.1100 Acute Oral Toxicity	yes	yes
870.1200 Acute Dermal Toxicity	yes	yes
870.1300 Acute Inhalation Toxicity	yes	yes
870.2400 Primary Eye Irritation	yes	yes
870.2500 Primary Dermal Irritation	yes	yes
870.2600 Dermal Sensitization	yes	yes
870.3100 Oral Subchronic (rodent)	no	-
870.3150 Oral Subchronic (nonrodent)	no	-
870.3200 21-Day Dermal	yes	yes
870.3250 90-Day Dermal	no	-
870.3465 90-Day Inhalation	yes	yes
870.3700a Developmental Toxicity (rodent)	yes	yes
870.3700b Developmental Toxicity (nonrodent)	no	-
870.3800 Reproduction	yes[c]	no
870.4100a Chronic Toxicity (rodent)	yes	yes
870.4100b Chronic Toxicity (nonrodent)	yes	yes
870.4200a Oncogenicity (rat)	yes	no
870.4200b Oncogenicity (mouse)	yes	no
870.4300 Chronic/Oncogenicity	yes	yes
870.5100 Mutagenicity—Gene Mutation - bacterial	yes	yes
870.5300 Mutagenicity—Gene Mutation - mammalian	yes	yes
870.5xxx Mutagenicity—Structural Chromosomal Aberrations	yes	yes
870.5xxx Mutagenicity—Other Genotoxic Effects	yes	no [a]
870.6100a Acute Delayed Neurotox. (hen)	no	-
870.6100b 90-Day Neurotoxicity (hen)	no	-
870.6200a Acute Neurotox. Screening Battery (rat)	yes[c]	no
870.6200b 90 Day Neuro. Screening Battery (rat)	no[b]	-
870.6300 Develop. Neuro	no	-
870.7485 General Metabolism	yes	yes
870.7600 Dermal Penetration	no	-
Special Studies for Ocular Effects		
Acute Oral (rat)	no	-
Subchronic Oral (rat)	no	-
Six-month Oral (dog)	no	-

a In vivo cytogenetics and repeat of the unscheduled DNA synthesis assays are required at this time.
b. Subchronic neurotoxicity battery asked for as part of the reproductive toxicity study.
c. Reproductive toxicity and acute neurotoxicity studies should be via inhalation

3.3 Data gaps

3.3.1 Metam Sodium/Metam Potassium

At present time, there are no data gaps for metam sodium or metam potassium.

3.3.2 MITC

The MITC database is incomplete for pesticidal uses of MITC *per se*, and additional data requirements may be imposed. The HIARC has identified following studies on MITC as the 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

4.0 METABOLITES/DEGRADATES

There are several toxicologically notable metabolites/degradates: methyl isocyanate (MIC), carbon disulfide (CS_2) and hydrogen sulfide (H_2S). Specifically, methyl isocyanate (MIC) is a photolysis degradate of the MITC which has been measured in ambient air around agricultural areas of California. Following soil application of metam sodium or metam potassium, both CS_2 and H_2S can be formed; the relative amounts depend on the pH of the soil. Following oral exposure to metam sodium, rats metabolize approximately 20-25% of the dose (on a molar basis) to carbon disulfide (CS_2).

5.0 HAZARD ASSESSMENT

5.1 Toxicity Profile Summary

5.1.1 Table 3. Acute Toxicity Data on Metam Sodium

Acute Toxicity of Metam Sodium (P. C. Code 039003)

Guideline No.	Study Type	MRIDs #	Results	Toxicity Category
81-1	Acute Oral-Rat	41277002	LD_{50} =7 80 mg/kg (male rats) 845 mg/kg (female rats)	III
81-2	Acute Dermal-Rat	41277003 41286005	LD_{50} = >2020 mg/kg	III
81-3	Acute Inhalation-Rat	41277004	LC_{50} = 2.27 mg/L	III
81-4	Primary Eye Irritation	41277005	No corneal/iris involvement; all irritation was absent by 7 days; Slight irritation	III
81-5	Primary Skin Irritation-Rabbit	41277006	non-irritating to the skin of male rabbits	IV
81-6	Dermal Sensitization	43457705	Positive for sensitization in guinea pigs	
81-8	Acute Neurotoxicity-Rat	42977801 and 42977802	The LOAEL of 22 mg/kg is based on reduced ambulatory and total motor activity observed in male & female rats. The NOAEL < 22 mg/kg and was not achieved in this study.	

5.1.2 Table 4. Acute Toxicity Data on MITC

Acute Toxicity of Methyl Isothiocyanate (PC Code 068103)

Guideline No.	Study Type	MRID #(S).	Results	Toxicity Category
81-1	Acute Oral-Rat	00162331	LD_{50} = 82 mg/kg ♂ 55 mg/kg ♀	II
81-2	Acute Dermal-Rat	00162330 42443501	LD_{50} = 136-436 mg/kg ♂ 181 mg/kg ♀	I
81-3	Acute Inhalation-Rat	45919410	LC_{50} = 0.54 mg/L	II
81-4	Primary Eye Irritation	00162328	corrosion of the cornea and conjuctivae	I
81-5	Primary Skin Irritation	00162329	all animals died within one hour	I
81-6	Dermal Sensitization	459194101	positive for sensitization in guinea pig	

5.1.3 Table 5. Subchronic, Chronic, and Other Toxicities on Metam Sodium and MITC

Guideline No./ Study Type	Metam Sodium		MITC	
	MRID No. (year)/ Classification /Doses	Results	MRID No. (year)/ Classification /Doses	Results
870.3100 90-Day oral toxicity rodents (rat)	42117302 (1991) Unacceptable/guideline 0, 0.018, 0.089, 0.443 mg/mL M: 0, 1.7, 8.1, 26.9 mg/kg/day F: 0, 2.5, 9.3, 30.6 mg/kg/day	NOAEL = 1.7M/ 2.5F mg/kg/day LOAEL = 8.1M/9.3 F mg/kg/day based on hematology and decrease absolute body weight.	Not available	
870.3100 90-Day oral toxicity rodents (mouse)	42117301 (1991) Unacceptable/guideline 0, 0.018, 0.088, 0.35, and 0.62 mg/ml M: 0, 2.7, 11.7, 52.4, and 78.7 mg/kg/day F: 0, 3.6, 15.2, 55.4, and 83.8 mg/kg/day	NOAEL = 0.018 mg/mL; 2.7M/3.6 F mg/kg/day LOAEL = 0.088 mg/mL; 11.7 M/15.2 F mg/kg/day based on urinary bladder lesions (eosinophilic granules, cystitits and mucosal hyperplasia) in both sexes and decrease in hematological parameters (hemoglobin, RBC, hematocrit) in female	Not available	

Guideline No./ Study Type	Metam Sodium		MITC	
	MRID No. (year)/ Classification /Doses	Results	MRID No. (year)/ Classification /Doses	Results
870.3150 90-Day oral toxicity in nonrodents (dog)	42600001 (1992) Unacceptable/guideline 0, 1, 5, and 10 mg/kg/day	NOAEL = < 1 mg/kg/day LOAEL = 1 mg/kg/day based on increase in plasma ALT, AST, and alkaline phosphatase, as well as increase incidence of biliary duct proliferation with inflammatory cell infiltration.	Not available	
870.3200 21/28/30-Day dermal toxicity	41106204 (1979) Unacceptable/guideline	Methods unacceptable	00132815 (1983) Unacceptable/guideline 0, 0, 120, 240, or 480 mg/kg/day	NOAEL < 120 mg/kg/day LOAEL = 120 mg/kg/day based on decreased body weight gain and food intake. Severe necrosis and corrosion of the skin.
870.3200 21/28/30-Day dermal toxicity			41221406 (1986) Unacceptable/guideline 0, 1.0, 10.0, and 100 mg/kg/day	NOAEL = 1 mg/kg/day LOAEL = 10 mg/kg/day based on decreased serum albumin and increased globulin values in addition to increased liver weights. Irritation at all doses
870.3250 90-Day dermal toxicity	Not available		Not available	

Guideline No./ Study Type	Metam Sodium		MITC	
	MRID No. (year)/ Classification /Doses	Results	MRID No. (year)/ Classification /Doses	Results
870.3465 28-Day inhalation toxicity	Not available		45314802 (1987) Acceptable/guideline 0, 5.1, 19.9, 100 ug/L	Systemic NOAEL = 5 mg/m^3(1.7 ppm). Systemic LOAEL = 19.9 mg/m^3,(6.8 ppm), based on clinical signs consistent with irritation in both sexes and increased neutrophilic polymorphonuclear granulocytes in the blood of males. ET NOAEL = 19.9 mg/m^3(6.8 ppm) ET LOAEL = 100 mg/m^3,(34 ppm), based on observation of pathological changes of the nasal cavity (metaplasia of respiratory epithelium and atrophy of the olfactory epithelium). TB NOAEL is 19.9 mg/m^3 (6.8 ppm) TB LOAEL = 100 mg/m^3(34 ppm), based on observation of pathological changes (tracheal epithelial proliferation and single cell necrosis, bronchopneumonia and bronchial and bronchiolar epithelial proliferation).

Guideline No./ Study Type	Metam Sodium		MITC	
	MRID No. (year)/ Classification /Doses	Results	MRID No. (year)/ Classification /Doses	Results
870.3465 90-Day inhalation toxicity	00162041 (1983) Acceptable/guideline 0, 6.5, 45 and 160 mg/m^3	NOAEL = 6.5 mg/m^3 ; 1.11 mg/kg/day LOAEL = 45 mg/m^3 ; 7.71 mg/kg/day based on histopathological changes in the nasal passages (ie, mucigenic hyperplasia) and changes in clinical chemistry.	41221407 (1978) Acceptable/guideline 0, 3.16, 30.67, and 137.13 ug/L for 4 hours/day 0, 2.1, 20.6, and 91.9 ug/L extrapolated to 6 hour exposure	NOAEL = 3.16 ug/L LOAEL = 30.67 ug/L based on decreased body weight, food efficiency and blood protein values accompanied by increased water intake.
870.3700a Prenatal developmental in rodents	42983701 (1993) Acceptable/guideline 0, 5, 20, or 60 mg/kg bw/day	**Maternal** NOAEL = 5 mg/kg/day LOAEL = 20 mg/kg/day based on reduced body weight gain and decreased food consumption. **Developmental** NOAEL =5 mg/kg/day LOAEL = 20 mg/kg/day based on the increased incidence of skeletal observations and the increase in total resorptions and resorptions/dam.	44733602 (1998) Acceptable/guideline 0, 3, 10, or 30 mg/kg/day	**Maternal** NOAEL = 3 mg/kg/day LOAEL = 10 mg/kg/day based on salivation and decreased body weight gain. **Developmental** NOAEL =10 mg/kg/day LOAEL = 30 mg/kg/day based on reduced fetal weight and an increased incidence of the skeletal variation of unossified sternebra(e).

Guideline No./ Study Type	Metam Sodium		MITC	
	MRID No. (year)/ Classification /Doses	Results	MRID No. (year)/ Classification /Doses	Results
	41577101 (1987) Acceptable/guideline 0, 4.22, 16.88, and 50.64 mg/kg/day	**Maternal** NOAEL = 4.22 mg/kg/day LOAEL = 16.88 mg/kg/day based on reduced body weight gain and decreased food efficiency. **Developmental** NOAEL = 4.22 mg/kg/day LOAEL = 16.88 mg/kg/day based on the increased incidence in postimplantation loss and decrease in the % of live fetuses/dam.	45919417 (1987) Unacceptable/guideline 0, 3, 10, or 30 mg/kg/day	**Maternal** NOAEL = 10 mg/kg/day LOAEL = 30 mg/kg/day based on decreased body weight gain and food consumption. **Developmental** NOAEL =10 mg/kg/day LOAEL = 30 mg/kg/day based on higher number of runts and reduced placental weights.
870.3700b Prenatal developmental in nonrodents (rabbit)	42963101 (1991) Acceptable/guideline 0, 5, 20, or 60 mg/kg/day	**Maternal** NOAEL = 5 mg/kg/day LOAEL = 20mg/kg/day based on the red uced body weight gain, reduced food consumption and food efficiency. **Developmental** NOAEL = 5 mg/kg/day LOAEL = 20mg/kg/day based on the increased incidence of skeletal observations.	45919418 (1986) Unacceptable/guideline 0, 1, 3 or 10 mg/kg/day	**Maternal** tentative NOAEL = 3 mg/kg/day Tentative LOAEL = 10 mg/kg/day based on reduced body weight gain and food consumption. **Developmental** NOAEL =10 mg/kg/day LOAEL > 10 mg/kg/day
	40330901 (1987) Unacceptable/guideline 0, 4.22, 12.66, 42.2 mg/kg/day	Numerous defiencies		

Guideline No./ Study Type	Metam Sodium		MITC	
	MRID No. (year)/ Classification /Doses	Results	MRID No. (year)/ Classification /Doses	Results
870.3800 Reproduction and fertility effects	43136101 (1993) Acceptable/ guideline 0, 0.01, 0.03, 0.1 mg/mL M: 0, 1.2, 3.2, or 11.5 mg/kg/day F: 0, 1.8, 3.9, or 13.5 mg/kg/day	**Parental/Systemic** NOAEL = 3.2 M/ 3.9 F mg/kg/day LOAEL = 11.5M/ 13.5F mg/kg/day based on pathology of Bowman's gland duct and olfactory epithelium. **Reproductive** NOAEL = 11.5M/13.5F mg/kg/day LOAEL =11.5M/13.5F mg/kg/day (HDT). **Offspring** NOAEL = 3.2M/ 3.9 F mg/kg/day LOAEL = 11.5M/ 13.5F mg/kg/day based on decrease pup weight.	40974601 (1987) Unacceptable/guideline 0, 2, 10, and 50 ppm M P: 0, 0.16, 0.76 and 3.58 mg/kg/day F P: 0, 0.21, 1.01, and 4.76 mg/kg/day M F1 0, 0.15, 0.71, 3.4 mg/kg/day F F1: 0, 0.19, 0.87, 4.22 mg/kg/day	**Parental/Systemic** NOAEL = 10 ppm, 0.71 mg/kg/day LOAEL = 50 ppm, 3.4 mg/kg/day based on decreased body weight gain in F1 males. **Reproductive** NOAEL = 50 ppm, 3.4M/ 4.22F mg/kg/day LOAEL > 50 ppm, 3.4M/ 4.22F mg/kg/day **Offspring** NOAEL = 50 ppm, 3.4M/ 4.22F mg/kg/day LOAEL > 50 ppm, 3.4M/ 4.22F mg/kg/day
870.4100a Chronic toxicity rodents	See combined chronic/carcinogencity		See combined chronic/carcinogencity	
870.4100b Chronic toxicity dogs	43275801 (1994) Acceptable/guideline 0, 0.05, 0.1, and 1.0 mg/kg/day	NOAEL =1M/ 0.1F mg/kg/day LOAEL >1 M/ 1 F mg/kg/day based on increased ALT and microscopic changes in the liver in females.	41240701 (1988) Unacceptable/guideline 0, 0.04, 0.4, 2.0 mg/kg/day	NOAEL = 0.4 mg/kg/day LOAEL = 2.0 mg/kg/day based on excessive salivation, RBC measures, and increased liver weights.

Guideline No./ Study Type	Metam Sodium		MITC	
	MRID No. (year)/ Classification /Doses	Results	MRID No. (year)/ Classification /Doses	Results
870.4300 Combined Chronic/ Carcinogenicity rats	43275802 (1994) Acceptable/guideline 0, 0.019, 0.056, and 0.19 mg/mL M: 0, 1.3, 3.9, and 12.0 mg/kg/day F: 0, 2.3, 6.2, and 16.2 mg/kg/day	NOAEL = 0.056 mg/mL LOAEL =0.19 mg/mL based on the changes in body weight gain, food efficiency, hematologic and clinical chemistry alterations, and macro- and microscopic abnormalities observed at this dose in both sexes.	00150078 (1984) Unacceptable/guideline 0, 2, 10, and 50 ppm 0, 0.2, 1.0 and 5 mg/kg/day	NOAEL = 50 ppm LOAEL = > 50 ppm
870.4300 Chronic/Carcinogenicity mice	43233501 (1994) Acceptable/guideline 0, 0.019, 0.074, and 0.23 mg/mL M: 0, 1.6, 6.5, and 27.7 mg/kg/day F: 0, 2.3, 8.7 and 29.9 mg/kg/day	NOAEL = 1.6 M/ 2.3 F mg/kg/day LOAEL = 6.5 M/ 8.7F mg/kg/day based on significant increase in liver weight, and decrease body weight gain, food and water consumption in male and female mice. Evidence of carcinogenicity	00150075 (1980) Unacceptable/guideline 0, 5, 20, 80, and 200 ppm M: 0, 0.82, 3.30, 11.83, and 25.71 mg/kg/day F: 0, 0.91, 3.66, 13.03, 29.03 mg/kg/day	NOAEL = 20 ppm; 0.82 M/0.91 F mg/kg/day LOAEL = 80 ppm, 3.30 M/ 3.66 F mg/kg/day based on decreased body weight gain throughout the majority of the study and reduced water consumption.
870.6200a Acute neurotoxicity screening battery	42977802 (1993) Acceptable/guideline 0, 22, 324, and 647 mg/kg	NOAEL = < 22 mg/kg LOAEL = 22 mg/kg based on reduced ambulatory and total motor activity observed in male and female rats on day 0, 45 minutes post-dosing.	Not available	

Guideline No./ Study Type	Metam Sodium		MITC	
	MRID No. (year)/ Classification /Doses	Results	MRID No. (year)/ Classification /Doses	Results
870.6200b Subchronic neurotoxicity screening battery	43248801 (1994) Acceptable/guideline 0, 0.02, 0.06,and 0.20 mg/mL M: 0, 1.4, 5.0, and 12.8 mg/kg/day F: 0, 2.3,7.0 and 15.5 mg/kg/day	NOAEL = 1.4 M/ 2.3F mg/kg/day LOAEL = 5.0 M/ 7.0 F mg/kg/day based on decreased body weight gain for male and female rats.	Not available	
870.6300 Developmental neurotoxicity	Not available		Not available	
870.7600 Dermal penetration	42670301 (1992) Acceptable/guideline 0.1, 1, 10 mg/rat	Mean absorbed at 10 hours = 2.52%	Not available	

Guideline No./ Study Type	Metam Sodium		MITC	
	MRID No. (year)/ Classification /Doses	Results	MRID No. (year)/ Classification /Doses	Results
Special Study: Human Eye Irritation and Odor Threshold	Not available		44400401 (1996) Acceptable/non-guideline 0, 0.22, 0.6, 0.8, 1.9, 3.3 ppm	One-minute exposure, the NOAEL for eye irritation is 3.3 ppm due to a lack of response in any parameter tested. 4-14 minutes, the NOAEL for eye irritation is 0.6 ppm based on responses on the Likert subjective scale at 1.9 ppm. 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

5.2 Executive Summaries

5.2.1 Acute Toxicity

Adequacy of data base for acute toxicity: The data base for acute toxicity is considered complete for metam sodium and MITC. No additional studies are required at this time.

The acute toxicity data on metam sodium and MITC are summarized above in Tables 2 and 3.

5.2.1.1. MITC

The following text is summarized from the Data Evaluation Record for MRID no. 44400401 and from the Risk Characterization Document for MITC. Department of Pesticide Regulation, California Environmental Protection Agency July 25, 2003, pp 53-59.

In order to determine the no-observed-adverse-effect-level (NOAEL) for human eye irritation produced by MITC vapors, as well as its odor threshold, human volunteers were exposed to air concentrations of MITC in a laboratory setting at different times of exposure. A specialized olfactometer was used which permitted the operator to dispense the test material through a manifold system. The odor threshold was determined to be 1.7 ppm (5 mg/m^3).

The olfactometer was adjusted to include a goggle system; this was then used to deliver MITC during the eye irritation portion of the study. Five parameters were used to ascertain an irritation response: 1. the subjects' subjective estimation of irritation (using the "Likert" scale); 2. photographs of the subjects' eyes prior to and after exposure; 3. blink rate as measured by electromyography; 4. effect upon visual acuity; 5. tear production. Both a positive control (acetic acid) and a negative control (air) were employed. Baseline responses for each of the assessment parameters were determined under pre-exposure conditions ("zero-time controls") and upon exposure to the negative control ("air-only controls") for the prescribed period. A positive irritation response was based on three criteria: 1. the average response must be quantitatively greater than the pre-exposure response; 2. the average response must be greater than pre-exposure and greater than could be expected statistically from individual to individual differences within the group; 3. the average treated response must be greater than the air-only group's response and greater than could be expected from individual differences observed within the group.

Concerning the ethical conduct of this study, informed consent was asserted in the odor threshold study but not mentioned in the eye irritation study; copies of the actual informed consent forms are not provided in the study report. The study also asserts approval through an ethical review but provides no documentation to support the statement. A detailed consideration of the ethical conduct of this study is provided in a separate memo by J. Carley (1/23/04).

The odor threshold was determined to be 1.7 ppm (5 mg/m^3).

Conclusions from the eye irritation portion of the study include:

- 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

5.2.2 Subchronic Toxicity

5.2.2.1. Metam Sodium

Adequacy of data base for subchronic toxicity: The data base for subchronic toxicity is considered complete for metam sodium. No additional studies are required at this time.

870.3100 90-Day Oral Toxicity - Rat

In a 90-day oral toxicity study (MRID 42117302), Alpk:APfSD (wistar derived) SPF rats (12/sex/group) were given metam sodium (45.13%, Batch No. BAS 005/00N) administered in drinking water at nominal dose levels of 0, 0.018, 0.089, and 0.443 mg/ml [1.7, 8.1, and 26.9 mg/kg/day (0.95, 4.54, and 15.06 mg/kg/day MITC equivalent) in males; 2.5, 9.3, and 30.6 mg/kg/day (1.4, 5.21, and 17.34 mg/kg/day MITC equivalent) in females]. Drinking water was prepared daily and water from the previous day was discarded.

A female at the high dose level was killed for humane reasons on day 5. Necropsy revealed cystitis, granulocytic hyperplasia (sternal marrow), unilateral hydronephrosis, pyelonephrosis, lymphadenitis, gastric hemorrhagic foci, hyperplasia of the ureter, and inverted thymus.

Mean body weights were significantly decreased ($p<0.01$,-22%) during weeks 1-14 in high-dose males and females, and -4% during weeks 5 and 7-14 in mid-dose females, when compared to controls. High-dose animals demonstrated a dramatic decrease in body weight gain of 45% and 63% during weeks 1-7, and 37 and 49% during weeks 1-4 in males and females, respectively when compared to controls.

Significant decreases in mean food consumption were noted throughout the study in high-dose males ($p<0.01$, 20-36%) and females ($p<0.01$, 20-50%), when compared to controls. Water consumption was reduced by 50-70% in both sexes at the high dose group and by 30% in females at the mid dose group throughout the study. There were no changes in water consumption in males at the mid dose level or either sex at the low dose level. Decreased water consumption likely due to poor palatibility.

Qualitative urinalyses demonstrated a slight increase of blood in the urine in some males at all doses. However, the magnitude of this change was not the same for all males, and not all males were affected. There were an increase number of animals (both sexes) exhibiting renal epithelial cells in the urinary sediment at mid-and high-dose, and slightly increased numbers of females (all doses) exhibiting red and white blood cells in urinary sediment.

Kidney appeared to be a target organ, with findings of renal tubular dilatation and basophilia, along with increases in blood, protein, and red blood cells, and renal epithelial cells in urine in treated animals. Other incidences above control values were noted at high dose as hyperplasia in cervical lymph node cells.

Significant decreases ($p\leq 0.05$; 9%) in the platelet counts of high-dose males were noted compared to controls, however, none were found in the high-dose females. Significant decreases in red cell count (all dose level for female and mid and high dose level for male) and hematocrit (all dose level for male and female) was also observed.

Significant decreases in mean absolute organ weight occurred in both male (36%) and female (43%) high dose animals when compared to controls, for all organs weighed, except kidneys(female) and testes. The decreases in absolute organ weight were primarily due to decreased body weight gain, since the relative organ weight remained stable. Furthermore, with the exception of a slight increase in kidney (high-dose females) and liver weights (mid-dose females), there was no significant difference in organ weight adjusted for body weight for any group.

Nasal cavity alterations were noted in high dose animals, as increased incidences of vascuolated Bowman's gland/ducts (olfactory epithelium), vacuolated olfactory epithelium, disorganization of nasal epithelium (both sexes), and increased incidences of necrosis of nasal cavity (females).

The LOAEL is 8.1 mg/kg/day (4.54 mg/kg/day MITC equi.) in males based on hematological changes (kidney) and 9.3 mg/kg/day (5.21 mg/kg/day MITC equi.) in females based on decreased absolute body weight. Nasal cavity pathology are likely due to MITC. The NOAEL is 1.7 mg/kg/day (0.95 mg/kg/day MITC equi.) in males and 2.5 mg/kg/day in females.

This 90-day oral toxicity study in the rat is **unacceptable-guideline** and does **not** satisfy the guideline requirement for a 90-day oral toxicity study (OPPTS 870.3150; OECD 409) in rodent species. A deficiency in the study existed in the collection of food and water consumption data which was not performed for individual animals as per the guidelines. Kidney as a target organ was not examined histologically in low and mid-dose groups as per guidelines; this examination might have clarified possible treatment-related effects. The kidney was also affected in subchronic oral toxicity study in mice at dose levels of 0.35 and 0.62 mg/ml. Analyses of the drinking water were not performed during the study due to "analytical problems." Analyses were performed 6-12 months after completion of the study. Stability of the test material in the water samples were outside of acceptable limits, for all levels tested, with low and mid-dose values <40% of nominal concentrations.

870.3100 90-Day Oral Toxicity - Mouse

In a 90-day oral toxicity study (MRID 42117301) metam sodium (45.13%w/w, Batch No. BAS/005/00N and CLT Reference No. Y06930/007 and Y06930/008) was administered to C57BL/10JfAP/Alpk strain mice (30/sex/dose) in drinking water at the dose levels of 0, 0.018, 0.088, 0.35, and 0.62 mg/ml [0, 2.7, 11.7, 52.4, and 78.7 mg/kg/day (0, 1.51, 6.55, 29.34 and 44.07 mg/kg/day MITC equivalent) for males and 0, 3.6, 15.2, 55.4, and 83.8 mg/kg/day (0, 2.02, 8.51, 31.02 and 46.93 mg/kg/day MITC equivalent) for females] for 90 days. Drinking water was prepared daily, except for on occasions at the start of the study where the control and 0.62 mg/ml dosing preparations were used over a three and two-day period.

No treatment-related mortality or clinical signs of toxicity were observed in any of the treated animals during the 90-day study period. Treatment-related statistically significant decreases in mean body weight were observed in both female and male mice at doses of 0.35 and 0.62 mg/ml as early as weeks 2-3 and persisted throughout most of the remainder of the 13-week study period. A reduction of up to 11% and 13% in female and male respectively, at the 0.62 mg/ml dose level and a reduction of up to 8% and 9% in the female and male respectively, at the 0.35 mg/ml dose level was noted. There were statistically significant decreases in total water consumption during weeks 1-13 in the males at the 0.62 mg/ml (-24%) dose level, and in females at dose levels of 0.35 mg/ml (-27%) and 0.62 mg/ml (-44%), as compared to their respective controls.

At termination of the study treatment-related changes in hematological parameters were

observed at doses as low as 0.088 mg/ml in females and 0.35 mg/ml in males. At dose levels 0.088, 0.35 and 0.62 mg/ml in females, statistically significant dose-related decreases in hemoglobin (HGB), hematocrit (HCT), and red blood cell count (RBC) were observed. At 0.35 and 0.62 mg/ml, dose-related statistically significant decreases were observed in males for RBC and HGB.

Microscopic examination were performed on the interim kill animals from the control and highest dose (0.62 mg/ml) groups. At the 0.62 mg/ml dose level, one male had slight centrilobular hypertrophy of the liver, and two females had minimal inflammatory cell infiltration of the liver which was not observed in any of the control animals. Also, one female at high dose level had a cystic gland in the stomach. This observation was not reported for any control animals.

At terminal sacrifice, there were statistically significant increases for males and females in absolute liver weight at doses of 0.35 mg/ml (↑13% and ↑16%, respectively) and 0.62 mg/ml (↑17% and ↑13%, respectively), and in liver weight adjusted for body weight at doses of 0.088 mg/ml (↑8% and ↑5%, respectively), 0.35 mg/ml (↑22% and ↑21%, respectively) and 0.62 mg/ml (↑21% and ↑19%, respectively, as compared to their respective controls. Also at terminal sacrifice, microscopic findings of the liver consisted of slight periportal hepatocyte vacuolation, slight microvesicular changes in centrilobular hepatocytes, and minimal inflammatory cell infiltration. None of the reported microscopic abnormalities of the liver were considered to be treatment related as the same frequencies of abnormalities were observed in both treated and control animals and no dose-response was seen.

At terminal sacrifice, there were statistically significant increases for males and females in kidney weight adjusted for body weight at doses 0.35 mg/ml (↑10% and ↑9%, respectively) and 0.62 mg/ml (↑9% and ↑10%, respectively, as compared to their respective controls). At termination of the study microscopic findings a polycystic kidney (marked severity) was reported in 1/10 males at a dose of 0.35 mg/ml and 1/10 females at a dose of 0.62 mg/ml.

At termination of the study microscopic findings of the urinary bladder were reported for males and females at doses of 0.088, 0.35, and 0.62 mg/ml. Cystitis was observed in 8/8 females and 10/10 males from the 0.35 mg/ml dose group, and 3/10 females and 8/10 males from the 0.62 mg/ml dose group. Mucosal hyperplasia was observed in 7/8 females and 10/10 males from the 0.35 mg/ml dose group, and 8/10 females and 9/10 males from the 0.62 mg/ml dose group. Eosinophilic granules in the bladder epithelium were reported for 10/10 males and 10/10 females at 0.088 and 0.62 mg/ml, and 7/10 males and 8/8 females at the 0.35 mg/ml dose group. No incidence was reported in the control and 0.018 mg/ml dose groups.

The systemic LOAEL was 0.088 mg/mL [11.7 and 15.2 mg/kg/day (6.55 and 8.51

mg/kg/day MITC equi.) for males and females, respectively] based on urinary bladder lesions (eosinophilic granules, cystitits and mucosal hyperplasia) in both sexes and decrease in hematological parameters (hemoglobin, RBC, hematocrit) in female mice. The systemic NOAEL was 0.018 mg/mL [2.7 and 3.6 mg/kg/day (1.51 and 2.02 mg/kg/day MITC equi.) for males and females, respectively].

This 90-day oral toxicity study in the mouse is **unacceptable-guideline** and does **not** satisfy the guideline requirement for a 90-day oral toxicity study (OPPTS 870.3150; OECD 409) in rodent species. Clinical blood chemistries and ophthamological examinations were not performed during this study (however, clinical chemistry was affected in the chronic mouse study). The significant instability of metam sodium in water after 24 hours, especially at the concentration of 0.018 mg/ml (29.1-31.5% of initial concentration remained after 24 hours), make it not possible to determine the actual amount of test article administered to the animals.

870.3150 90-Day Oral Toxicity - Dog

In a 90-day oral toxicity study (MRID 42600001), metam sodium (Purity 43.15%, Batch No. not stated) was administered to 4 Beagle dogs/sex/dose by gelatin capsules at dose levels of 0, 1, 5, and 10 mg/kg/day(0, 0.56, 2.8 and 5.6 mg/kg/day MITC equivalent) once daily for 13 weeks.

Compound related mortality was observed in this study. One male and one female were sacrificed during weeks 11 and 12, respectively, at the 10 mg/kg/day dose level. The animals were sacrificed due to poor clinical condition such as appearance of jaundice, inappetance and emaciation. No mortality was observed during administration of the test material at lower doses.

Some signs of vomiting were noted in males and females dogs at the 5 and 10 mg/kg/day dose levels. The incidence of this was more evident at the 10 mg/kg/day (75) than the 5 mg/kg/day (9) and it appears that the occurrence was slightly higher in the male (48) than female (36) dogs. One incidence of vomiting occurred in the control group.

Statistically significant decreases (9%) in absolute body weight were noted at the 10 mg/kg/day dose level in male dogs beginning at week 10 of the study and continued through until study termination. Body weight gain was also affected in the male dogs at the 10 mg/kg/day dose level, such that overall weight gain for weeks 1-13 was decreased by 39% vs. control. In female dogs, no significant effects were noted in group mean absolute body weight for the study period.

Results for food consumption showed food residues left by some of the dogs at the 5 and 10 mg/kg/day dose levels. It appeared that the amount of food left by three male dogs at the 10 mg/kg/day dose level increased with increasing duration of treatment 9%-99%).

However, residue measurements were presented only from approximately week 8 until study termination.

Abnormal urine color (orange or orange/brown) was recorded for 3 males and 2 females at the 10 mg/kg/day dose group and for 1 male at the 5 mg/kg/day dose level. An increased presence of urobilinogen and bilirubin was observed in both sexes at 10 mg/kg/day and an increase bilirubin was also present in both sexes at the 5 mg/kg/day dose level.

The observed group mean kidney weight of the male dogs at the 10 mg/kg/day dose level were higher than control group. Also, testes weight was decreased by 24% in comparison to control values for male dogs at the 10 mg/kg/day dose level. Reduced weights of the epididymides were also observed in 2 of th 4 male dogs at the 10 mg/kg/day dose level. The epididymides of 2 dogs were approximately 2g in weight, while those of the affected dogs were approximately 0.95g in weight, a reduction of about 50%.

A slight reduction (5-10%) in the number of red blood cells was noted in male and female dogs at the 5 and 10 mg/kg/day dose levels, but was not labeled as statistically significant. Mean cell volume was significantly increased at the 10 mg/kg/day dose level during week 8 (4% and 4%, male and female dogs, respectively) and during week 13 (7.5% and 11%, male and female dogs, respectively). Similar changes were observed in mean cell hemoglobin, with the exception that a significant increase was not observed in female dogs at week 8 of the study. A statistically significant reduction in mean cell hemoglobin concentration was observed at the 5 mg/kg/day dose level on week 13 (1.5%, female only), and at the 10 mg/kg/day dose level on weeks 8 (2%, males only) and week 13 (3% males and 1.5% females).

The white blood cell differential analysis showed time and dose- related increases in the number of neutrophils and monocytes in both male and female dogs. There was a statistically significant increase in neutrophils at week 4 (32%) and week 8 (17%) at the 1 mg/kg/day dose level in comparison to control. Statistically significance was achieved for the increase in monocytes at the 10 mg/kg/day dose level in both male (71%) and female (61%) dogs at week 13 of the study. There was also a statistically significant increase in prothrombin time in female dogs at the 1 mg/kg/day (6.4%), 5 mg/kg/day (45), and 10 mg/kg/day (11%) dose level during week 4. Significant increase was observed at the 10 mg/kg/day dose level in male dogs during week 8 (15%) and week13 (31%).

Significant increases in AST were evident at the 10 mg/kg/day dose level in male dogs by week 6 (39%), and in female dogs by week 12 (69%). By week 13, AST was increased 454% vs control in male dogs, and by 108% in female dogs.

A statistically significant increase in ALT was noted in males dogs at the 10 mg/kg/day dose level at week 6 (88%) and week 8 (92%) of the study. Also significant increase in ALT (2395% vs. control and 794% vs. control for male and female dogs, respectively) was observed by week 13 at the 10 mg/kg/day dose level. By week 13 ALT activity in female dogs were increased by 351% vs. control at the 1 mg/kg/day dose level.

Statistically significant increases in ALP were evident in male dogs by week 6 and in female dogs on week 4 and at weeks 8 through 13. The increase in ALP were more evident at the 10 mg/kg/day dose level. In male dogs, ALP was elevated by 659% vs. control at week 13, while in female dogs, ALP was elevated by 95% vs. control. The increase in ALP for male and female dogs appeared dose and time-related beginning at the 1 mg/kg/day dose level.

Plasma GGT showed statistically significant increases in male dogs at the10 mg/kg/day and in female dogs at the 5 and 10 mg/kg/day dose levels. In male dogs, the increase in plasma GGT was approximately 470% for weeks 12 and 23, while in female dogs, GGT at 10 mg/kg/day was increased by 187% at week 12 and by 400% on week 13 in comparison to control.

In those dogs surviving to study termination, the most prominent observations from the macroscopic examination were those in the liver. In 2 of the 3 surviving male dogs at the 10 mg/kg/day dose level, an accentuated lobular pattern, depressed red area(s), and pale (yellow) appearance were noted. Also at the 10 mg/kg/day dose level, depressed red areas were noted in 2 of the surviving 3 female dogs and pale appearance of the liver was noted in 1 female dog. At the 5 mg/kg/day dose level, depressed red areas of the liver were noted in 1 male and 1 female dog. Livers of all dogs were reported as macroscopically normal at the 1 mg/kg/day dose level.

***For female dogs,* the LOAEL is 1 mg/kg/day (0.56 mg/kg/day MITC eqvi.) based on increase in plasma ALT, AST, and alkaline phosphatase, as well as increase incidence of biliary duct proliferation with inflammatory cell infiltration. In female dogs, the NOAEL was not established (< 1 mg/kg/day (<0.56 mg/kg/day MITC eqvi.)).**

***For male dogs,* the LOAEL is 5 mg/kg/day (2.8 mg/kg/day MITC eqvi.) based upon statistically significant increases in plasma ALT, AST, and alkaline phosphatase, as well as the increased incidence of hepatitis and bile duct proliferation. The NOAEL is = 1 mg/kg/day (0.56 mg/kg/day MITC eqvi.).**

This subchronic study in the dog is **acceptable, guideline** and **but does *not* satisfy** the guideline requirement for a subchronic oral study [OPPTS 870.4100, OECD 452] in dog due to the lack of establishment of a NOAEL for female dogs.

870.3200 21/28-Day Dermal Toxicity – Rat

The existing subchronic dermal study (MRID no. 41106204) is considered unacceptable due to deficiencies in the methods used.

870.3465 90-Day Inhalation – Rat

In a 90-day inhalation (MRID no. 00162041), 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/m^3 (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/m^3 (0, 0.12, 0.38, 0.98 mg/kg/day) (measured by intrared adsorption).

Clinical signs of salivation, dullness, chromodacryorhea, dehydration, rough coat, and wet coat were noted in males and females of the highest concentration level. There were no treatment related mortalities.

Body weight gain was reduced at the highest concentration level compared to control (-6% and -8% for males and females). Food consumption was decreased compared to control in the mid and highest levels (-8% and -10%).

At the interim measurement, plasma lactate dehydrogenase levels were statistically reduced compared by 50% and 62% ($p< 0.05$) in females in the mid and high dose levels but only the highest dose in males (-18%). At termination, albumin was decreased compared to control (-13% and -22%; $p<0.05$) and alkaline phosphatase increased (+2-fold; $p<0.05$) at the mid and high dose levels in females only.

Although the absolute weights were not affected, significant increases in relative lung (+13% males, +21% females) and kidney (+7% males, +14% females) weights were noted in the highest dose group.

Histopathology indicative of irritation was noted in the nasal passages, lung, and stomach. A dose-dependant increase in the incidence of mucigenic hyperplasia of the nasal passage was noted in all treatment groups for females but only reached statistical significance in the mid and high dose group. This finding (ie, incidence of mucigenic hyperplasia) was increased ($p<0.05$) only in the male high dose group. Mucigenic cysts were noted in 2 females of the highest dose group. A dose-dependant increase in lymphocytic rhinitis was noted in all treatment groups although statistical significance was noted only at the mid and high dose males. In the lungs, histiocytosis was noted in 3/27 high dose males and 2/18 high dose females. In the stomach, erosive gastritus was statistically increased in the high dose males and females (9/17 males, 13/18 females).

Ulcerative gastritis was noted in 2/18 high dose females. Gross pathological changes in stomach were also noted at the high dose in males and females by in an increased incidence in red/black foci or streaks.

The LOAEL in females is 45 mg/m^3 (7.71 mg/kg/day)of metam sodium (based on Na levels; 2.2 mg/m^3 [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/m^3 (27.43 mg/kg/day) of metam sodium (based on Na levels; 5.7 mg/m^3 [0.98 mg/kg/day]) based on histopathological changes in the lungs and nasal passages.

The NOAEL for females is 6.5 mg/m^3 (1.11 mg/kg/day)of metam sodium (based on Na levels; 0.7 mg/m^3 [0.12 mg/kg/day] measured MITC). The NOAEL for males is 45 mg/m^3 (7.71 mg/kg/day)of metam sodium (based on Na levels; 2.2 mg/m^3 [0.38 mg/kg/day] measured MITC).

This subchronic inhalation toxicity study in the rat is **acceptable-guideline** and satisfies the guideline requirement for a subchronic inhalation study OPPTS 870.3465; OECD 413 in the rat.

5.2.2.2. MITC

Adequacy of data base for subchronic toxicity: Although several of the subchronic studies with MITC are unacceptable, no additional subchronic studies are required at this time.

870.3100 90-Day Oral Toxicity - Rat

90-Day oral rat toxicity study with MITC is not available.

870.3100 90-Day Oral Toxicity - Mouse

90-Day oral rat toxicity study with MITC is not available.

870.3150 90-Day Oral Toxicity - Dog

90-Day oral dog toxicity study with MITC is not available.

870.3200 21/28-Day Dermal Toxicity – Rat

In a 30-day dermal toxicity study (MRID 00132815), MITC (% ai, and lot no. not provided) was dissolved in benzol and applied to a 4x4 cm area of skin of 10 Sprague Dawley rats/sex/dose at 0, 0, 120, 240, or 480 mg/kg/day during a 30-day period. Exposure duration (ie, number of hours per day or days/week) is not given in the study. (However, MITC is expected to volatilze quickly).

No changes in urinalysis was noted. Two animals died during the study: one each in the control and low dose groups. A large abscess in the lung was attributed as the cause of death in each case.

At termination, body weight and body weight gain were decreased in all dose groups(-60% to -70% in males and -20% in females). Although no changes in water consumption were noted, decreased food consumption was noted in all treatment groups.

Dermal ulceration was obsereved in all treatment groups within two weeks. The degree ofulceration was dose related and accompanied by severe cornification and necrosis of the exposed area.

The systemic LOAEL is 120 mg/kg/day, based on decreased body weight gain and food intake. The NOAEL was not established (< 120 mg/kg/day).

This 30-day dermal toxicity study in the rat is **unacceptable-guideline** and does **not** satisfy the guideline requirement for a subchronic dermal toxicity study (OPPTS 870.3250 ; OECD 411) in rat. This study has numerous deficiencies and can not be upgraded; a NOAEL was not identified.

870.3200 21/28-Day Dermal Toxicity – Rat

In a 30-day dermal toxicity study (MRID no. 41221406), MITC (95.5%) was applied dermally for a 5 hour daily exposure to 4 groups of 10 rats/sex/dose 7 days a week at 0, 1.0, 10.0, and 100 mg/kg/day. Sesame oil was used as the vehicle.

The 100 mg/kg/day animals exhibited signs of severe pain by vocalizing, jumping, and reaching for the test site. One high dose male died on day 26 the study from "auto-mutilation" presumably from the severe distress caused by pain from MITC at 100 mg/kg/day. Dermal irritation was noted at all treatment levels. At 1 mg/kg/day, yellow-colored desquamation. At 10 mg/kg/day, light-colored desquamation combined with erythema were noted. The affect of dermal exposure to the 100 mg/kg/day dose of MITC is severe erythema and necroses accompanied sclerosis of the adjacent fatty and connective tissues. Seven rats in the highest dose group exhibited minimal reactive epidermal hyperplasia of the area adjacent to application. Animals in the highest group

appeared to be in severe pain.

At the highest dose group, body weight gain was statistically decreased ($p<0.01$) compared to control (-50% for females, males lost 4 g over the study). A decrease in food consumption and and increase in water consumption were observed in males of the 100 mg/kg/day groups ($p< 0.01$; -17% and +20%, respectively)

There were no treatment related effects observed in hematological parameters or in the bone marrow. At 10 and 100 mg/kg/day, dose-related increases in globulin with comparable decreases in albumin were observed in male and female rats. Blood glucose was increased significantly at 100 mg/kg/day.

A significant ($p < 0.01$) increase in relative liver weights of the mid dose females and the absolute and relative liver weights of the high dose females was reported. Male relative liver weights were increased significantly ($p< 0.01$) at the high dose.

The systemic LOAEL is 10.0 mg/kg/day, based on decreased serum albumin and increased globulin values in addition to increased liver weights. The systemic NOAEL is 1.0 mg/kg/day.

This 30-day dermal toxicity study in the rat is **unacceptable-guideline** and **does not** satisfy the guideline requirement for a 30-day dermal toxicity study (OPPTS 870.3250 ; OECD 411) in rat. As stated in the TXR no. 011275 and 003991, individual animal data for all the parameters need to be submitted.

870.3465 28-Day Inhalation – Rat

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/m^3 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.

All animals survived to study termination. Mid and high dose rats demonstrated clinical signs during exposure from the third exposure period day. No clinical signs were observed in the low dose animals. According to the study report,

> "During exposure, the animals of test group 2 showed eyelid closure, somnolence, and ruffled fur from the third day of exposure onwards. On the next morning before exposure nothing abnormal was found in the animals.....At 20 mg/m3 the

animals showed first indications of an irritating effect of the test substance and a slightly deteriorated general state of health."

Additional clinical signs observed at the high exposure concentration included reddish nasal discharge, salivation, eye discharge, and difficulty in breathing or whooping respiration, and stretched posture. In the high dose rats, although signs recovered between exposures at the beginning of the study, towards the end of the study ruffled fur and respiratory sounds were no longer reversible.

Body weight and body weight gain were significantly decreased ($p<0.05$) at the high dose. Food consumption and feed efficiency were not measured. There were decreases in plasma urea, glucose, triglyceride, and albumin the high dose males. In high dose females, urea and glucose were also decreased. In the males of mid exposure group, there was a decrease in urea concentration in the plasma.

At the mid and high exposure concentrations, increase in neutrophilic polymorphonuclear granulocytes in the peripheral blood was observed in males; this was also observed in the high exposure concentration for females.

There was increased lung weight at the high exposure concentration. Histopathology revealed an increase in incidence and severity of rhinitis in the nasal cavity at the high exposure concentration in both sexes (incidence in males: 2/5, 2/5, 2/5, 5/5; females: 0/5, 3/5, 1/5, 5/5). Other histopathologic findings at the high exposure concentration included: atrophy of the olfactory epithelium, metaplasia of the nasal respiratory epithelium (3 males in section plane 1 only, 5 females in section planes 1 and, to a lesser extent, section plane 2), tracheal epithelial proliferation and single cell necrosis (all high exposure concentration),bronchopneumonia and bronchial and bronchiolar epithelial proliferation (5 males, 2 females), and emphysema (3 males, 2 females).

The systemic LOAEL is 19.9 mg/m^3,(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/m^3(1.7 ppm).

The LOAEL for effects in the extrathoracic (ET) region is 100 mg/m^3,(34 ppm), 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/m^3(6.8 ppm).

The LOAEL for effects in the tracheabronchial (TB) region is 100 mg/m^3(34 ppm), 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/m^3(6.8 ppm).

This subchronic toxicity study is **Acceptable but does not satisfy** the guideline requirement for a subchronic inhalation study (82-4) in the rat. The study duration was too short and the number of animals used were inadequate to satisfy the Guideline requirement. Detailed tables of the clinical signs were not provided in the study report.

870.3465 90-Day Inhalation – Rat

In a subchronic inhalation study (MRID no. 41221407) 4 groups of 10 Wistar rats/sex/dose received a nose-only inhalation exposure to MITC (95.69% a.i., Batch no. 26,300) at 0, 3.16, 30.67, and 137.13 ug/L for 4 hours/day, 5 days/week over a 12 to 13 week period (By extrapolation from four to six hours of exposure, the dose levels are 0, 2.1, 20.6, and 91.9 ug/L). There were two control groups of 10 rats/sex/dose, one maintained in the laboratory without inhalation exposure and the other in chamber without MITC.

No effects on urinalysis parameters, gross or microscopic pathology or organ weights were noted at any dose level. Although no clinical signs were noted in the low or middle dose groups, clinical signs of apathetic appearance accompanied with salivation and nasal discharge was observed throughout the study in high dose rats. Six of 20 rats in the high dose exhibited stimulated vocalization during the last 30 days of exposure.

A treatment related decrease in body weight gain was noted in male and females of the middle (11% M and 15% F, not statistically significant) and the high (63% M and 47% F, $p < 0.01$) dose groups. A treatment related increase in water consumption was noted in males and females of the mid dose group (14% and 21%, $p <0.05$) and males of the high dose group (16%, $p<0.05$). Food consumption, however, was decreased ($p < 0.05$) in only the high dose group.

Hematological parameters of leucocyte and neutrophil counts and hematocrit and RBC values were significantly increased in the high dose group only. A significant decrease in total blood protein was noted in males and females of the mid dose group ($p<0.05$) and females of the high dose group. Changes in fasting glucose, alkaline phosphatase, and alanine aminotransferase were also in the high dose females.

Effects reported at the mid dose were decreased body weight, food efficiency and blood protein values accompanied by increased water intake. At the high dose (91.9 ug/L) the animals exhibited apathy, salivation, nasal discharge, and stimulated vocalization. These animals exhibited a decrease in body weight, food intake, and food efficiency accompanied by an increase in water intake. Alterations in clinical chemistry values at this dose included decreased total protein with increased alkaline phosphatase and alanine aminotransferase values.

Overall, the results of this study are questionable for a variety reasons detailed by California Department of Pesticide Regulation. The following text was extracted from California Environmental Protection Agency, (2003) RISK CHARACTERIZATION DOCUMENT Methyl Isothiocyanate (MITC) Following the Agricultural Use of Metam Sodium, Sacramento, California July, 2003.

> It may be asked why the 12-13-week rat nose-only inhalation study of Rosskamp (1978) did not provide the critical subchronic NOEL. In this study, the endpoints used to establish the NOEL of 1 ppm were decrements in weight gain, increased water consumption and decreased serum protein levels, all occurring at the LOEL concentration of 10 ppm. Overt toxicity in the form of salivation / nasal discharge, mild and moderate apathy, vocalization and a much more severe weight gain decrement were detected at the high dose of 45 ppm. However, there was massive uncertainty inherent in the study report, which made it very difficult to rely upon it for risk assessment purposes, particularly as another more adequate study using the same strain of rat was available. The uncertainties are delineated as follows:

1. The toxicologic significance of the three endpoints used to establish the NOEL was not clear. Statistically significant decreases in body weight gain with respect to sham-treated controls only occurred at the high dose of 45 ppm, while a much lower, non-statistically significant decrement was noted at the mid dose (10 ppm). Interestingly, a much larger suppression of body weight gain was evident in the sham-treated controls when compared to the untreated controls than occurred when comparing the sham-treated controls to the 10 ppm animals. This may indicate the presence of a stress effect imposed on the animals as they were fitted into the nose-only apparatus day after day. Individual animal data were not supplied, making it impossible to say with assurance what the effect was on individual animals. In the case of water consumption, the increase that was observed compared to sham-treated controls was statistically significant at both 10 and 45 ppm (in females only at the latter dose), though the values at 45 ppm were not greater than those at 10 ppm. The significant decrease in serum protein in mid and high dose males and high dose females was conceivably a consequence of the increased water consumption. (However, a similar lowering of serum protein was detected in the chronic mouse drinking water study in conjunction with a *decrease* in water consumption [Sato, 1980], raising the possibility that protein levels were suppressed independent of an effect on water consumption, perhaps due to an effect of MITC on the liver.)

2. Insufficient analytic data were provided in the study report to validate the reported chamber concentrations. According to the report, MITC levels were determined at hours 1 and 3 during each 4-hour exposure by withdrawing the chamber air for 10 minutes and routing it to an infra-red analyzer. The reported levels were thus mean values computed from hundreds of separate determinations. Without a report of the daily levels or, at the very least, standard deviations from the mean values, there is an implicit assumption that those mean values were in fact the levels that the animals were actually responding to, and were not in reality much lower or higher for significant periods.

3. Rosskamp (1978) failed to provide a histological examination of the nasal cavity of the exposed rats. As MITC is known to cause irritation of mucus membranes, the lack of nasal examination in that study may have resulted in the assignment of an inappropriately high NOEL value or, at the very least, an appreciation of the importance of irritation to the overall toxic response.

The LOAEL is 30.67 ug/L/day (extraplated to 20.6 ug/L/day for 6 hour exposure), based on decreased body weight, food efficiency and blood protein values accompanied by increased water intake. The NOAEL is 3.16 ug/L/day (extrapolated to 2.1 ug/L/day for 6 hour exposure).

This subchronic inhalation toxicity study in the rat is **acceptable-guideline** and satisfies the guideline requirement for a subchronic inhalation study OPPTS 870.3465; OECD 413 in the rat.

5.2.3 Prenatal Developmental Toxicity

5.2.3.1. Metam Sodium

Adequacy of data base for Prenatal Developmental Toxicity: The data base for prenatal developmental toxicity is considered complete for metam sodium. No additional studies are required at this time.

870.3700a Prenatal Developmental Toxicity Study - Rat
In a developmental toxicity study (MRIDs 41577101, 42170101, and 92097012) 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 (GD). On GD 20, all dams were sacrificed and necropsied, and all fetuses were weighted, sexed, and examined externally for abnormalities.

Maternal toxicity was observed at 16.88 and 50.64 mg/kg/day levels as significantly decreased body weight gain during the dosing period. The corrected maternal body weight gain was significantly reduced (-22% vs. control) at 50.64 mg/kg/day. Although not statistically analyzed, mean maternal feed consumption was reduced during the treatment period. The greatest decrease occurred initially, days 7-8 for the 16.88 and the 50.64 mg/kg/day groups (-16% and -19% vs. control, respectively).

The cesarean section data indicate a significant increase in postimplantation loss (↑146% and ↑103%) and a significant decrease in the % of live fetuses/dam (-11.4% and -8%) at the 4.22 and 50.64 mg/kg/day levels, respectively. Fetal weights were significantly reduced for male and female fetuses in the 50.64 mg/kg/day group (-7% and -8% vs. control, respectively). Examination of the viscera of fetuses that underwent skeletal examination revealed a significant increase in the % fetuses/litter with anomalies, variations, and retardations at the 16.88 mg/kg/day level, which were dose-related (except for anomalies). There were significant increases in the % fetuses/litter with variations and retardations at the 50.64 mg/kg/day level which were dose-related. Meningocele was noted in 2 fetuses (0.51% of the fetuses examined per litter) in 1 litter

(4.55% of litters) at the 50.64 mg/kg/day group.

The maternal LOAEL is 16.88 mg/kg bw/day (9.45 mg/kg/day MITC eqvi.), based on reduced body weight gain and decreased food efficiency. The maternal NOAEL is 4.22 mg/kg bw/day (2.36 mg/kg/day MITC eqvi.).

The developmental LOAEL is 16.88 mg/kg bw/day (2.36 mg/kg/day MITC eqvi.), based on the increased incidence in postimplantation loss and decrease in the % of live fetuses/dam. The developmental NOAEL is 4.22 mg/kg bw/day (2.36 mg/kg/day MITC eqvi.).

This developmental toxicity study in the rat is classified **acceptable-guideline** and satisfies the guideline requirement for a developmental toxicity study (OPPTS 870.3700; OECD 414) in the rat.

870.3700a Prenatal Developmental Toxicity Study - Rat

In a developmental toxicity study (MRID 42983701) metam sodium [43% w/w active ingredient in aqueous solution (525.54 g/l, Batch No. BAS/005/00N) was adjusted for dose levels 0, 5, 20, or 60 mg/kg bw/day (0, 2.8, 11.2 or 33.6 mg/kg bw/day MITC equivalent)] and administered to 24 female Wistar rats/dose in deionized water by gavage from days 6 through 17 of gestation (GD), inclusive. Insemination was by natural means. All animals survived to scheduled termination.

Clinical signs of discharge from the eye, salivation, piloerection, subdued behavior and urinary incontinence was observed at the 60 mg/kg/day dose level. Signs of urinary incontinence were also seen in one dam at 20 mg/kg/day. Vaginal bleeding was seen in three dams in each of the 20 and 60 mg/kg/day groups.

During the treatment period (days 7-16 of gestation), decreases of 23% and 38% were observed in group mean body weight gain compared to control at the 20 and 60 mg/kg/day dose levels, respectively. For the treatment and post-treatment period (days 8-22), a decrease of 13% in body weight gain was observed at the 60 mg/kg/day dose level, while for the overall study period (days 1-22), a decrease of 16% was observed at the 60 mg/kg/day dose level.

During the period of dosing, a dose-related decrease in food consumption was observed in treated groups of pregnant dams. While statistical significance was achieved at the lowest dose level (5 mg/kg/day), the decrease from control at this dose level was only between 5-7%. Decreases of 13-16% compared to control were observed at the 20 mg/kg/day dose level for the period of dosing, while decreases of between 23-34% compared to control were observed at the 60 mg/kg/day dose level for the period of dosing.

No significant differences in group mean body weight gain were observed during the pre-treatment period among pregnant dams. During the period of treatment (days 7-16 gestation), decreases of 23% and 38% were observed in group mean body weight gain at the 20 and 60 mg/kg/day dose levels, respectively. For the treatment and post-treatment period (days 8-22), a decrease of 13% in body weight gain was observed at the 60 mg/kg/day dose levels, while for the overall study period (days 1-22), a decrease of 16% was observed at the 60 mg/kg/day dose level. With the exception of effects observed during days 8-16, body weight gain was affected only at the 60 mg/kg/day dose levels.

Food consumption prior to dosing was unaffected in control and test article treated rats. During the period of dosing, a dose-related decrease in food consumption was observed in treated groups of pregnant dams. While statistical significance was achieved at the lowest dose level (5 mg/kg/day), the decrease from control at this dose level was between 5-7%. Decreases of 13-16% were observed at the 20 mg/kg/day dose level for the period of dosing, while decreases of 23-34% were observed at the 60 mg/kg/day dose level for the period of dosing. Post dosing decreases of 11-15% were present at the 60 mg/kg/day dose level.

Gross findings in dams were limited to an increase in the number of dams with pelvic dilatation of the kidney at the 60 mg/kg/day dose level (4/24 vs. 0/24 in control). There were no significant differences in mean gravid uterus weight among the groups of treated and control dams (78.1-82.0 grams).

The maternal LOAEL is 20 mg/kg bw/day (11.2 mg/kg bw/day MITC equi.), based on reduced body weight gain and decreased food consumption. The maternal NOAEL is 5 mg/kg bw/day (2.8 mg/kg bw/day MITC eqvi).

Developmental toxicity was noted at the 60 mg/kg/day dose levels in the form of an increase in resorptions/dam (57%) at the 60 mg/kg/day dose level compared to control. There was also a noted decrease (4% and 14%) in mean fetal weight at the 20 and 60 mg/kg/day dose levels compared to control, respectively. Cesarean section data reported no changes comparable to controls in premature delivery, corpora lutea/dam, total implantations, total live fetuses and live fetuses/dam.

The fetal and litter incidence of several external/visceral observations were increased slightly at 60 mg/kg/day. There was one incidence of meningocoele noted in one animal and three incidences of internal hydrocephaly noted in three animals. There were no incidences of meningocoele or internal hydrocephaly noted in the low or middle dose levels or the control animals.

Developmental toxicity was also suggested at the 20 and 60 mg/kg/day dose levels in the form of a significant increase in the fetal and litter incidence of unossified centrum of the 4th, 5th, and 6th cervical vertebrae, an increase in the litter incidence of unossified 5th

sternebrae at the 60 mg/kg/day dose level, a significant increase in the fetal incidence of unossified odontoid, centrum of the 2nd cervical vertebrum, ventral tubercle, and calcaneum at the 20 and 60 mg/kg/day dose levels. In addition, litter incidence of unossified odontoid, unossified centrum of the 2nd cervical vertebrum, and unossified ventral tubercle was also significantly increased over control at the 60 mg/kg/day dose level.

The developmental LOAEL is 20 mg/kg bw/day (11.2 mg/kg bw/day MITC equi.), based on the increased incidence of skeletal observations and the increase in total resorptions and resorptions/dam. The developmental NOAEL is 5 mg/kg bw/day (2.8 mg/kg bw/day MITC equi.).

The developmental toxicity study in the rat is classified **acceptable-guideline** and satisfies the guideline requirement for a developmental toxicity study (OPPTS 870.3700; OECD 414) in the rat.

870.3700b Prenatal Developmental Toxicity Study - Rabbit

In a developmental toxicity study (MRID 42963101*)* metam sodium [43.14% w/w active ingredient concentration in liquid form (525.54 g/L, Lot No.90/2, Y06930/007/001 and YA6930/008) was adjusted for dose levels 0, 5, 20, or 60 mg/kg/day (0, 2.8, 11.2 or 33.6 mg/kg/day MITC equivalent)] and administered to 20 presumed pregnant New Zealand white rabbits/group by oral gavage from gestation days 8 through 20, inclusive. Dams were sacrificed on day 30 of gestation and all fetuses were, weighted, sexed, and examined externally.

There were 3 deaths, 1 in the low, mid-, and high dose groups, respectively. The deaths could not be attributed to the test article administration. No specific clinical signs were seen in the animal in the 5 mg/kg/day group, which was found dead on day 26 of the study. The animal in the 20 mg/kg/day group was killed on day 24 for humane reason and that in the 60 mg/kg/day group was killed on day 24, following abortion.

Maternal toxicity was noted in the mid and high dose group in the form of increase incidence of few feces (19 in mid dose/2 in high dose) and red/orange staining (16 in mid dose/1 in high dose) on the cage tray in the 60 mg metam sodium/kg/day group compared with the control group. Treatment related decrease in body weight gain in the mid (66%) and high (63%) dose groups was observed for the duration of the study compared to control. Also, the dosing plus post dosing period and entire gestation period (not including gestation days 0-4) along with the corrected body weight gains for these periods, support this observation.

Food consumption was reduced in the mid (11%) and high (37%) dose groups was observed during the dosing period compared to control, with a rebound in food consumption.

The food efficiency correlated with the bodyweight gain findings and decrease food consumption in the mid and high dose groups.

The maternal LOAEL is 20 mg/kg bw/day (11.2 mg/kg/day MITC eqvi.) based on the reduced body weight gain, reduced food consumption and food efficiency. The maternal NOAEL is 5 mg/kg bw/day (2.8 mg/kg/day MITC eqvi.).

Developmental toxicity was noted in the high dose group in the form of increased resorptions including total litter resorptions in 9/19 pregnancies, a decrease in the number of live fetuses (31%) and mean litter size (36%), and an increase in post-implantation loss (40%) compared to control. There was also a noted decrease (10.5%) in mean fetal body weight of the high dose group.

Developmental toxicity was noted in the mid dose group in the form of increased incidences of sutural bones between the parietals, misshapen hyoid, partially ossified transverse process of the cervical vertebrae, and 27 presacral vertebrae. There was an increased incidence in the high dose group in the 27 presacral vertebrae and 7 sternebrae (usually only 6 present).

The developmental LOAEL is 20 mg/kg bw/day (11.2 mg/kg/day MITC eqvi.) , based on the increased incidence of skeletal observations. The developmental NOAEL is 5 mg/kg bw/day (2.8 mg/kg/day MITC eqvi.).

The developmental toxicity study in the rabbit is classified **acceptable-guideline** and satisfies the guideline requirement for a developmental toxicity study (OPPTS 870.3700; OECD 414) rabbit.

The above findings were in general, similar to what was seen another rabbit development toxicity study conducted with metam-sodium (MRID no. 40330901, *Report on the Study of the Prenatal Toxicity of Metam-Sodium (aqueous solution) in rabbits after Oral Administration (gavage),* BASF Aktiengesellschaft for BASF CORPORATION CHEMICALS DIVISION, Project No. 38R0232/8579, July 15, 1987). MRID no. 40330901 is considered unacceptable-guideline due to numerous deficiencies that are outlined in TXR no.009030.

870.3700b Prenatal Developmental Toxicity Study - Rabbit

In a developmental toxicity study (MRID 40330901) metam sodium (42.2% a.i. aqueous, batch #ZH 130585)was administered to 15 Himalayan rabbits/dose by gavage at dose levels of 0, 4.22, 12.66, and 42.2 mg/kg/day (0, 2.36, 7.09, and 23.63 MITC equivalents) from days 6 through 18 of gestation.

No treatment related mortality or clinical signs were noted during the study. Compared to control animals, the high dose groups exhibited reduced body weight gains and and consumed less food (-8%).

The number of corpora lutea and implantations, mean fetal weight, and the sex ratio did not differ among treatment groups. The total number of live fetuses was decreased and total number of resorptions was increased in the mid and high dose groups. However, the number of fetuses/ dam and resorptions/dam was only statistically significant at the highest dose level.
One observation each of meningocele and spina bifida were noted in the high dose.

The developmental toxicity study in the rabbit is classified **unacceptable-guideline** and does **not** satisfies the guideline requirement for a developmental toxicity study (OPPTS 870.3700; OECD 414) rabbit. MRID no. 40330901 has numerous defiencies that are outlined in TXR no. 009030 The above findings were in general, similar to what was seen another rabbit development toxicity study conducted with metam-sodium (MRID no. 42963101) which is considered acceptable-guideline.

5.2.3.2. MITC

Adequacy of data base for Prenatal Developmental Toxicity: Although several of the developmental toxicity studies with MITC are unacceptable, no additional developmental toxicity studies are required at this time.

870.3700a Prenatal Developmental Toxicity Study - Rat
In a developmental toxicity study (MRID 44733602), methyl isothiocyanate (99.6% a.i.; Lot #: WIL Log No. 3518A) was administered in corn oil by gavage twice daily from gestation day (GDs) 6 through 19 to Crl:CD®(SD)BR rats (25/dose level) at concentrations of 0, 3, 10, or 30 mg/kg/day. It was stated that the twice-daily treatment regimen was used because of the irritative properties of the test substance. Dams were sacrificed on GD 20. No treatment-related findings were noted at 3 mg/kg/day.

No premature deaths occurred during the study interval. Many treatment-related clinical signs of toxicity (Table 2) were observed in the 30 mg/kg group at daily examination, at the time of the first and second daily doses, and 1 hour post-dose of the first and second doses. Treatment related salivation was also noted at 10 mg/kg.

At 30 mg/kg/day, decreased ($p<0.05$ or 0.01) body weight gains were observed as follows: during daily measurements on GDs 15-17 (↓22-33%) and GDs 18-20 (↓36-47%); for the GDs 12-20 interval (↓29%); the overall treatment interval (↓27%, GDs 6-20); and the overall study interval (↓20%, GDs 0-20). At 10 mg/kg/day, body weight

gains were statistically decreased during GD 15-16 and 18-19 (↓20% and ↓32%, respectively) compared to controls. At 30 mg/kg/day, a decrease in gravid uterine weight was observed (↓13%), along with a reduction in corrected (for gravid uterine weight) body weight gain (↓31%, $p<0.01$). Absolute (g/animal/day) and/or relative (g/kg/day) food consumption was reduced in the 30 mg/kg/day group ($p<0.05$ or 0.01) during the daily measurements on GDs 15-20 (↓11-24%), during the GDs 6-9 (↓12-15%) and 12-20 (↓10-11%) intervals, and for the overall treatment interval (↓6-12%, GDs 6-20).

Females of the highest dose group (8/25 treated) exhibited stomach adhesions and one of these eight also had a stomach abscess; neither of these observations were noted in control animals.

The number of implantations/dam, number of resorptions/dam, percent male, and the extent of pre-and post-implantation losses were similar between control and treated groups.

The maternal LOAEL is 10 mg/kg/day, based on salivation and decreased body weight gain. The maternal NOAEL is 3 mg/kg/day.

At 30 mg/kg/day the mean fetal weight was decreased by 8% compared to controls ($p< 0.01$). The reduced fetal weight is associated with decreased body weight gain of the maternal animals at the same dose level. Upon skeletal examination, increased incidence of unossified sternebra(e) #1, #2, #3, and/or #4 was observed at 30 mg/kg [2.6 (27.3)] vs controls [0.28 (4.5)]; the litter incidence of this finding was beyond the historical control range (0.0-22.73). No treatment related effects were observed in the 3 or 10 mg/kg/day groups.

The developmental LOAEL is 30 mg/kg/day, based on reduced fetal weight and an increased incidence of the skeletal variation of unossified sternebra(e).
The developmental NOAEL is 10 mg/kg/day.

This developmental toxicity study is classified **acceptable-guideline** (**§83-3[a]**) and does satisfy the guideline requirement for a developmental toxicity study in the rat.

870.3700a Prenatal Developmental Toxicity Study - Rat
In a developmental toxicity study (MRID 45919417*)* MITC (96.9% a.i., batch# 6205 MK) was administered to 25 female Wistar rats/dose by gavage at dose levels of 0, 3, 10 or 30 mg/kg bw/day from days 6 through 15 of gestation (GD). On GD 20, all dams were sacrificed and necropsied, and all fetuses were weighed, sexed, and examined externally. Homogenecity, stability and concentration analysis of the test article was provided in German.

Maternal toxicity as evidenced by reduced body weights and body weight gain was observed at the high-dose level (30 mg/kg bw/day). In addition, statistically significant decrease in the high-dose group maternal mean body weights was noted on days 6-8 (76%), 8-10 (64%), 10-13 (21%), and 15-17 (23%). A statistically significant decrease in body weight was noted in the mid- dose group (10 mg/kg bw/day) only on days 8-10 (39%). A reduction in food consumption was noted in the dams at the high- dose level (30 mg/kg bw/day) during the dosing period. Food consumption was reduced 21% for days 10-13, 15% for days 13-15, and 18% for days 15-17 of dosing. There were no treatment- related effects on mortality. **The maternal LOAEL is 30 mg/kg bw/day, based on reduced body weight gain and food consumption. The maternal NOAEL is 10 mg/kg bw/day.**

The numbers of corpora lutea, implantation, live fetuses, resorptions, and fetal weights were similar among treated and untreated animals. There were no treatment- related effects found upon visceral and skeletal examinations of the fetuses. However, there was a decrease in the placental weight and an increase in the number of runts at the high dose level. **The developmental LOAEL is 30 mg/kg bw/day, based on the higher number of runts and reduced placental weights. The developmental NOAEL is 10 mg/kg bw/day.**

The developmental toxicity study in the rat is classified **unacceptable /guideline (upgradeable)** and **does not satisfies** the guideline requirement for a developmental toxicity study (OPPTS 870.3700; OECD 414) in the rat. The homogeneity, stability and concentration analyses were provided in German instead of English. Therefore, the concentration of the administrated article could not be verified; these data need to be provided to the Agency.

870.3700b Prenatal Developmental Toxicity Study - Rabbit

In a developmental toxicity study (MRID 45919418) MITC (98% a.i., ZNT-No. 85/231-2)] was administered to 16 female Chinchilla rabbits/dose in corn oil by gavage at dose levels of 0, 1, 3 or 10 mg/kg bw/day from days 6 through 18 of gestation. Insemination was by natural means.

One dam in the high dose group died on GD 11 following weight loss and loss of hindlimb function. No other clinical signs attributed to administration of MITC occurred in this study. No abortions occurred in any group. Variation in body weight and food consumption are large. Because of the large variations, no statistically significant decreases in maternal weight gain and food consumption were noted. However, mean body weight gain and food consumption were decreased compared to the control at the highest dose level.

There were no differences in mean corpora lutea, mean implanatation sites, mean

resorptions, and mean viable fetuses were detected among all dose groups.

In the data provided in the report, the mean measured concentration ranged from 67% to 88% of the nominal concentration. This large range provides uncertainty surrounding the amount of MITC the rabbits recieved.

The tentative maternal LOAEL is 10 mg/kg bw/day, based on reduced body weight gain and food consumption. The tentative maternal NOAEL is 3 mg/kg bw/day.

There were no differences in fetal weights or sex ratio among the treatment groups. There were also no treatment related changes in external, skeletal or visceral examinations following *in utero* exposure to MITC.

The developmental LOAEL was not established. The developmental NOAEL is 10 mg/kg bw/day.

The developmental toxicity study in the rabbit is classified **unacceptable-guideline** and does **not** satisfy the guideline requirement for a developmental toxicity study (OPPTS 870.3700; OECD 414) in rabbit. The homogeneity, stability, and concentration information provided in the study report are inadequate. This study could be upgraded if additional data discussed in the DER are provided.

5.2.4 Reproductive Toxicity

5.2.4.1. Metam Sodium

Adequacy of data base for Reproductive Toxicity: The data base for reproductive toxicity is considered complete for metam sodium. No additional studies are required at this time.

In a two-generation reproduction study (MRID 43136101) metam sodium (43.148% in aqueous solution/ Reference Number BAS/005/00N) was administered to 30 Alpk:APfSD rats/sex/dose continuously in drinking water at dose levels of 0.01, 0.03, and 0.1 mg/ml [approx. 1.2, 3.2, or 11.5 mg/kg/day (0.672, 1.79, or 6.44 mg/kg/day MITC equivalent) for males, and 1.8, 3.9, or 13.5 mg/kg/day (1.01, 2.18, or 7.56 mg/kg/day MITC equivalent) for females, respectively]. The F_o animals were given test article in drinking water for 10 weeks prior to mating. At 21 days of age, pups from the F_o generation was selected to produce F_1 litters (30/sex/group). After weaning, F_1 (30 /sex/dose) animals were selected to become the parents of the F_2 generation and were given the same concentration test article in drinking water as their dam. Drinking water was prepared daily throughout the study.

No significant treatment related signs of clinical toxicity were observed in male and female F_o parent rats during pre-mating, gestation, or lactation. No treatment related effects on mortality of F_o parent male and female were observed occurred during the study.

F_o parent female rats receiving 0.10mg/ml had statistically significant decrease (3%) in body weight than controls. The single statistically significant decrease (2%) in body weight in females at the 0.03mg/ml dose level, after the initial week of test article administration was consistent with palatability effect. Body weight gains were similar to those of controls for both sexed at the 0.01 mg/ml dose level and for males at the 0.03 mg/ml dose level. F_o pregnancy weight gains were reduced 1-5% in rats at the 0.10 mg/ml dose level. There was also a decrease (3%) in pregnancy weight gain of rats at the 0.03 mg/ml dose level. Lactation body weights were reduced (3-6%) in female at the 0.10 mg/ml dose level and 2% at the 0.03 mg/ml dose level, respectively. There was no effect on lactation body weights in females at the 0.01 mg/ml dose level.

F_1 parent pre-mating body weights were reduced in males (3-5%) and females (3-5%) at the 0.10 mg/ml dose level and by 3% in female rats at the 0.01 mg/ml dose level. Pregnancy weights were reduced in males (3-5%) and females (3-5%) at the 0.10 mg/ml dose level. Lactation weights were reduced (3-9%) in females at the 0.10 mg/ml dose level. Lactation weight of female rats at the 0.01 mg/ml and 0.03 dose level where similar to those of the control group.

F_o parent food consumption was reduced in males (6%) and females (7%) at the 0.10 mg/ml dose level. There were no effects at the 0.01 and 0.03 dose level groups. F_1 parent food consumption was reduced in males (6%) and females (7%) at the 0.10 dose level. There were statistically significant reductions in food consumption in females at the 0.01(6%) and 0.03 (7%) dose levels, however, there was no dose response relationship. Food consumption in F_1 parent males at the 0.01 and 0.03 dose levels were similar to those if the control group.

Water consumption was markedly reduced in F_o parent males (20%) and females (42%) at the 0.10 mg/ml dose level. Water consumption was also reduced (20%) in rats at the 0.03 mg/ml dose level. There was no effect on water consumption in rats at the 0.01 mg/ml dose level. Water consumption during pregnancy was reduced (36%) in the 0.10 mg/ml dose group and by (17%) in the 0.03 mg/ml dose group. Water consumption during lactation was reduced in rats at the 0.10 mg/ml dose level (25%) and (11%) at the 0.03mg/ml dose level.

Systemic toxicity was observed at the 0.10 mg/ml dose level in F_o and F_1 parent female rats. This toxicity consisted of Bowman's gland duct hypertrophy with loss of alveolar cells, degeneration/disorganization and/or atrophy of the olfactory epithelium, and dilatation of the Bowman's gland ducts. Bowman's gland duct hypertrophy was mainly confined to the nasal septum and dorsal arch. The change in Bowman's glands was accompanied in all affected animals by degeneration, disorganization, and/or atrophy of the olfactory epithelium. No changes were observed at the 0.01 and 0.03 mg/ml dose levels.

The parental systemic LOAEL is 0.1 mg/ml [11.5 mg/kg/day (6.44 mg/kg/day MITC equi.) in males and 13.5 mg/kg/day (7.56 mg/kg/day MITC equi.) in females], based on Bowman's gland duct hypertrophy and degeneration/disorganization and/or atrophy of the olfactory epithelium . The parental systemic NOAEL is 0.03 mg/ml [3.2 mg/kg/day (1.8 mg/kg/day MITC equi.) in males, and 3.9 mg/kg bw/day (2.18 mg/kg/day MITC equi.) in females].

There were no apparent effects of metam sodium on reproductive performance in precoital interval, gestation period, number of litters, and number of live pups in the F_o or F_1 generations in this study. **The LOAEL for reproductive toxicity is $\geq$ 0.1 mg/ml and the NOAEL for reproductive toxicity is 0.1 mg/ml [13.5 mg/kg/day (7.56 mg/kg/day MITC equi.)].**

In pups, F_{1a} litter weight was lower at the 0.1 mg/ml and 0.03 mg/ml dose levels compared to controls at days 22 and 29, however, the differences were not statistically significant. Total litter weight decreased by 7% and 9% compared to control at the 0.03 and 0.10 mg/ml dose levels on day 22. On day 29, total litter weight was decreased by approximately 9% at both dose levels. In the F_{2a} litter weight decreased by 4% and 14%

on day 22 at the 0.03 and 0.10 mg/ml dose levels compared to control, respectively. On day 29, total litter weight decreased 2% and 11% at the 0.03 and 0.10 mg/ml dose level compared to control. There were also a 16% decrease in body weight gain for male and female pups in the F_{2a} litter at the 1.0 mg/ml dose level.

Data on organ weights in the pups consisted only of the weights of the testes and epididymis in male rats. In the F_{1a} litter, there were noted 8% decrease in testes and epididymis weights at the 0.10 mg/ml dose level. In the F_{2a} litter, noted decrease of 9% compared to control was observed in the testes weight at the 0.10 mg/ml dose level.

The offspring LOAEL is 0.1 mg/ml [11.5 mg/kg/day (6.44 mg/kg/day MITC equi.) in males and 13.5 mg/kg/day (7.56 mg/kg/day MITC equi.) in females), based on decreased pup weight. The offspring NOAEL is 0.03 mg/ml (3.2 mg/kg/day (1.8 mg/kg/day MITC equi.) in males, 3.9 mg/kg bw/day (2.18 mg/kg/day MITC equi.) in females).

This study is **acceptable-guideline** and **satisfies** the guideline requirement for a two-generation reproductive study (OPPTS 870.3800); OECD 416 in rat.

5.2.4.2. MITC

Adequacy of data base for Reproductive Toxicity: The data base for reproductive toxicity is considered incomplete. A two generation reproduction study in rat via inhalation with pathological evaluation of the complete respiratory tract is required at this time. 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.

870.3800 Reproduction and Fertility Effects - Rat

In a two-generation reproduction study (MRID 40974601) MITC (95.8-96.5% a.i., batch # 340178) was administered to 30 parental and 25 F_1 Sprague-Dawley rats /sex/dose in drinking water at dose levels of 0, 2, 10, and 50 ppm (mean intake of MITC in water: 0, 0.16, 0.76, and 3.58 mg/kg/day for parental males; 0, 0.21, 1.01, and 4.76 mg/kg/day for parental females; 0, 0.15, 0.71, 3.40 mg/kg/day for F1 males; 0, 0.19, 0.87, 4.22 mg/kg bw/day for F1 females). Drinking water was prepared with MITC three times a week; solutions were prepared and given to the rats on the next two or three days (for example, solutions prepared on Monday were used on Tuesday and Wednesday). To compensate for anticipated loss of MITC, solutions were over-formulated by 20%.

One litter per generation was tested in this study. The parental generation was treated for 70 days prior to mating. The F1 generation were reared until weaning at which time 25

F1 males and females were selected for mating. Remaining F1 pups were necropsied. F1 generation was treated for 77 days prior to mating. F2 litters were reared to weaning followed by study termination.

No treatment related mortality, clinical signs, or gross pathology were observed in any generation. Although no reduction in body weight was observed in P generation males, males of the F1 generation in the 50 ppm group, exhibited a 29% decrease in body weight gain ($p < 0.05$) compared to control. During the pre-mating phase, gestation and lactation body weight and body weight gain of females were compared among all groups. (Note to the reader: The pre-existing DER lists significant changes in the low and mid groups in P females–these changes have not been confirmed by the current reviewer. See attached sheets). Although sporadic decreases in food intake were observed, food consumption was similar among treatment groups in the P and F1 generations.

In the P and F1 males of 10 and 50 ppm groups, a dose dependant decrease in water consumption was observed (ranging from -3 to -28%; $p< 0.05$) throughout the treatment period. During the premating and lactation phases, P and F1 females of the 10 and 50 ppm groups also exhibited decreased water consumption (ranging from -7% to -37%, $p< 0.05$). Decreased water consumption was attributed by the study director to poor palatability of MITC.

Although no pathological changes were observed in the pituitary gland and the absolute pituitary weights were not changed compared to control, the relative pituitary weights in P females were increased ($p<0.01$) in the 50 ppm P females.

The parental systemic LOAEL is 50 ppm (3.40 and 4.22 mg/kg bw/day in males and females, respectively), based on decreased body weight gain in F1 males. The parental systemic NOAEL is 10 ppm (0.71 and 0.87 mg/kg bw/day in males and females, respectively).

Number of live pups and number of live pups/female were similar among treatment and control groups in both generations. Pup weight were not effected by treatment with MITC in both generations. Time to pinna unfolding, tooth eruption, and eye opening were similar among all groups. Limited functional observations of tail pinch and surface righting were performed on day 1 offspring; air righting was performed on day 17 offspring; grip strength, papillary reflex, visual placing responses, and auditory startle response were performed on day 21 offspring; no treatment related effects were noted.

The offspring LOAEL > 50 ppm (3.40 and 4.22 mg/kg bw/day in males and females, respectively). The offspring NOAEL is 50 ppm (3.40 and 4.22 mg/kg bw/day in males and females, respectively).

No changes in the measured reproductive parameters of mating performance, fertility, reproductive performance and the viability and growth of offspring were observed.

The reproductive LOAEL is > 50 ppm (3.40 and 4.22 mg/kg bw/day in males and females, respectively). The reproductive NOAEL is 50 ppm (3.40 and 4.22 mg/kg bw/day in males and females, respectively).

This study is **unacceptable-guideline** and does not satisfy the guideline requirement for a two-generation reproductive study (OPPTS 870.3800); OECD 416 in rat. Deficiencies listed in the data evaluation record include: lack of tabulation of clinical signs for adult animals; derivation of the actual article intake; and reporting and stability analysis of the actual concentrations instead of the nominal concentrations.

5.2.5 Chronic Toxicity

5.2.5.1. Metam Sodium

Adequacy of data base for chronic toxicity: The data base for chronic toxicity is considered complete for metam sodium. No additional studies are required at this time.

870.4100a (870.4300) Chronic Toxicity – Rat

See below for combined chronic/carcinogenicity study in rat.

870.4100b Chronic Toxicity - Dog

In a chronic toxicity study (MRID 43275801), 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. The study was conducted in two randomized blocks, each comprising two male and two female replicates consisting of one dog per treatment group.

There were no deaths nor treatment-related clinical signs of toxicity. Group mean body weights of the treated animals were comparable to the control group over the course of the study, except for a decrease of 1.5% at week 4 in a male dog at the 0.1 mg/kg/day dose level. There was also a decrease of 9% at week 50 in a female dog at the 0.1 mg/kg/day dose level.

Statistically significant increases in kaolin-cephalin time at the 1.0 mg/kg/day dose level were observed at week 4 (6%), week 13 (7%) and week 26 (10%) in male dogs. Increase

in kaolin-cephalin time at the 1.0 mg/kg/day dose level was also observed in female dogs at week 4 (13%), week 13 (7%) and week 52 (9%). A statistical significant increase (92%) was also note in monocyte count for male dogs at week 13 at all dose levels. There was an increase of 56% compared to control in eosinophil count in male dogs at the 0.05 mg/kg/day dose level at week 13.

Group mean ALT levels at 1.0 mg/kg/day gradually increased in female dogs over the course of the study until study termination, where the mean value was 3x control. However, the increase was due to changes in one female dog whose ALT level spiked during weeks 45 and 52. This animal also had a 15% increase in AST compared to control. Increase in AST was noted in male dogs at week 13 at the 0.05 mg/kg/day (22%) and 0.1 mg/kg/day (30%), and week 52 at the 0.05 mg/kg/day (15%). Increase in AST was also observed in female dogs at week 52 at the 1.0 mg/kg/day (23%).

The only treatment related finding in necropsy was on microscopic examination of the liver of the female from the 1 mg/kg/day dose group with ALT elevation. This animal had a slight increase in hepatocyte and macrophage/Kupffer cell pigmentation, slight mononuclear cell infiltration, slight telangiectasis, and a positive reaction for hemosiderin. However, one control group female also had hepatic changes consisting of monocellular infiltration, minimal hepatocyte pigmentation and increased macrophage/ Kupffer cell pigmentation.

The LOAEL is > 1mg/kg/day (>0.56 mg/kg/day MITC equi.) in males and equal to 1 mg/kg/day (0.56 mg/kg/day MITC equi.) for females, based on increased ALT and microscopic changes in the liver. The NOAEL is $\geq$ 1 mg/kg/day (≥0.56 mg/kg/day MITC equi.) for males and 0.1 mg/kg/day (0.056 mg/kg/day MITC equi.) for females.

This chronic study in the dog is **acceptable-guideline** and satisfies the guideline requirement for a chronic oral study [OPPTS 870.4100, OECD 452] in dog. The registrant reported that the changes seen in the liver were of a similar nature to those observed in previous studies with this compound in dogs but of a reduced severity.

5.2.5.2. MITC

Adequacy of data base for chronic toxicity: Existing chronic studies in rat and dog are unacceptable primarily due to problems with dosing stability and/or concentration analysis. Since the release of EPA's preliminary risk assessment for metam sodium (May 21, 2004), additional ambient air exposure data became available which suggest that chronic exposure are possible. Because of the potential for chronic exposures and the finding of focal squamous cell metaplasia in the respiratory epithelium following 28-days of exposure to MITC in rats EPA is requiring carcinogenicity studies in mice and rats.

870.4100a (870.4300) Chronic Toxicity – Rat

See below, combined chronic/carcinogenicity studies.

870.4100b Chronic Toxicity - Dog

Four groups of six pure-bred beagle dogs/sex/group were dosed orally twice daily with MITC in corn oil at 0, 0.04, 0.4, and 2.0 mg/kg/day for 52 weeks (MRID 41240701). The NOAEL is 0.4 mg/kg/day. The LOAEL is 2.0 mg/kg/day based on excessive salivation, increased platelet count and activated partial thromboplastin time, decreased blood protein and albumin values, and increased liver weight. This study is unacceptable and does not satisfy the guideline data requirement for a nonrodent chronic toxicity study. It is deficient for the lack of information on the purity of the test material and stability of the use dilutions administered.

5.2.6 Carcinogenicity

5.2.6.1. Metam Sodium

Adequacy of data base for Carcinogenicity: The data base for carcinogenicity is considered complete for metam sodium. No additional studies are required at this time.

870.4200a Carcinogenicity Study - rat

In a two year combined chronic toxicity/carcinogenicity study (MRID 43275802), metam sodium technical (43.14% a.i., Sample Reference No. BAS/005/005 90-2) was administered in drinking water to groups of 64 male and female rats for either 52 weeks or 104 weeks at dose levels of 0, 0.019, 0.056, and 0.19 mg/mL (0, 1.3, 3.9, and 12.0 mg/kg/day metam sodium). 12 animals were sacrificed at week 52 of the study. The drinking water was prepared daily throughout the study.

There were no significant effects if treatment on mortality in male and female rats during the study period. However, at week 105, mortality in control male rats appeared unacceptably high (less than 25% alive at week 105). The number of male rats found dead were 7, 3, 2, and 1 for the 0, 0.019, 0.056, and 0.19 mg/ml dose levels, respectively. Mortality in female rats at all dose levels was much less at week 105 in relation to male rats. There were historical control data provided with which to make a comparison of mortality in this strain of rats.

Effects on body weight gain were observed at the 0.19 mg/ml dose level in both male and female rats, where weight gain was decreased by 12-18% in males and 16-20% in females vs control over the course of the study period. At the 0.056 mg/ml dose level, body weight gain was unaffected in male rats, and was decreased by approximately 8-9% in female rats over the course of the study period.

In both male and female rats at the 0.19 mg/ml dose level, food consumption was decreased by 10% relative to the control for weeks 1-13 if the study. At weeks 52 and 104, decreases were also observed in both sexes at the 0.019 mg/ml dose level, ranging from 4-19% below control values. Efficiency of food utilization was decreased in male rats at the high dose for weeks 1-12 of the study. While this was labeled as statistically significant, this represented a decrease of only 3% from control.

Statistically significant decreases in water consumption in both male and female rats at the 0.056 and 0.19 mg/ml dose levels. Female rats appeared to be affected in a greater manner than male rats at these two dose levels. Mean water consumption for weeks 1-13 of the study was decreased in treated male rats by 4.2%, 9.6%, and 37.9% compared to control at the 0.019, 0.056, and 0.19 mg/ml dose levels, respectively. In females, the decreases were 4.8%, 24%, and 54.2% at the 0.019, 0.056, and 0.19 mg/ml dose levels.

Reduction (statistical significance) in urine volume was observed in male (34%) and female (33%) rats at week 78 at the 0.19 mg/ml dose level.

Effects on hematology (decreased red blood cells(RBC), hemoglobin (HGB), hematocrit (HCT)) and clinical chemistry (decreased cholesterol and triglycerides) was observed in both sexes. At the 0.19 mg/ml dose level, both male and female rats showed a consistent decrease of 3 to 4% form control in mean HGB and RBC throughout the study. The largest decrease in these parameters occurred at week 105, where HGB was decreased 12% high dose males and 5% in high dose females, with HCT and RBC following a similar pattern. At weeks 79 and 105, both plasma cholesterol and triglycerides were decreased in female and male rats at the 0.19 mg/ml dose level. For cholesterol, the decreases ranged from 4-10% in males, and 17-19% in females. For triglycerides, the decrease ranged from 22-43% in females, and 18-32% in males. These changes in hematology parameters did not always achieved statistical significance, were isolated and inconsistent and therefore considered not to be of biological significance.

At both the interim sacrifice and terminal kill time, organ weight changes were noted in the adrenal glands and kidneys. The effects on organ weight were not consistent between sexes. Adrenal weight in male rats at the 0.19 mg/ml dose level from the interim sacrifice group was decreased by 10% compared to control, while adrenal weight in female rats at the same dose level and time point was increased by 36% from control. At the terminal sacrifice time, no significant changes were observed in adrenal weight. Kidney weight was noted to be decreased significantly in male rats at the 0.19 mg/ml dose level from the interim sacrifice time point (decrease of 12% from control), but no effects were observed in female rats. At the terminal sacrifice time point, the same percentage decrease was observed in male rats at the 0.019 mg/ml dose level, but was not considered to be statistically significant.

Increased number of liver masses and increased incidence of fat vacuolation of the liver

were observed in male rats at the 0.19 mg/ml dose level, as was increased incidence of wasting of voluntary muscle.

Microscopic abnormalities of the nasal cavity (increased incidence of rhinitis, hypertrophy of Bowman's ducts/glands, atrophy and adenitis of Steno's gland, and olfactory epithelium hyperplasia and degeneration), heart and aorta (decreased mineralization), liver (spongiosis/ peliosis hepatitis with altered hepatocytes) voluntary muscle (increased severity of degenerative myopathy), and sciatic nerve (increased severity of degeneration) were observed in male and/or female rats at the 0.19 mg/ml dose level.

The changes observed in the adrenal gland, aorta, heart, and liver were confined primarily in the male rats, while the remaining changes were observed in both sexes.

The LOAEL is 0.19 mg/ml [12.0 and 16.2 mg/kg/day (6.72 and 9.07 mg/kg/day MITC eqvi.) for males and females, respectively], based on the changes in body weight gain, food efficiency, hematologic and clinical chemistry alterations, and macro- and microscopic abnormalities observed at this dose in both sexes.

The NOAEL is 0.056 mg/ml [3.9 and 6.2 mg/kg/day (2.18 and 3.47 mg/kg/day MITC eqvi.) for males and females, respectively].

At the doses tested, there were no treatment-related increases in tumor incidences when compared to test and control groups in females. The CPRC report discusses incidence of angiosarcomas in male rats; these did not exhibit a significant trend but the intermediate-dose incidences show a statistically significant pairwise comparison with controls. The angiosarcomas in male rats were considered to support the overall weight of evidence for a B2 call since the same type of tumor was appearing in both rats and mice. Dosing was considered adequate based on microscopic abnormalities of the nasal cavity, heart and aorta, voluntary muscle, and sciatic nerve at the high- dose level.

This chronic/carcinogenicity study in the rat is **acceptable-guideline** and **satisfies** the guideline requirement for a chronic/ carcinogenicity study OPPTS 870.4300); OECD 453] in rat

870.4200b Carcinogenicity (feeding) - Mouse

In a two-year carcinogenicity study in mice (MRID 43233501), metam sodium (43.15% w/w active ingredient concentration in liquid form (525.54 g/L, Sample Reference No. BAS/005/00N 90-2) was administered to C57BL/10JfCD-1/Alpk mice (55/sex/dose) in drinking water for 104 weeks at nominal dose levels of 0, 0.019, 0.074, and 0.23 mg/ml (1.6, 6.5, and 27.7 mg/kg (0.896, 3.64 and 15.51 mg/kg MITC equivalent) for male mice

and 2.3, 8.7, and 29.9 mg/kg(1.29, 4.87 and 16.74 mg/kg MITC equivalent) for female mice. Drinking water was daily in batches of 2.5 or 5 liters.

There were no apparent treatment related effects on mortality in either male or female mice in this study. The decrease in the number of female mice alive between weeks 1 and 27 at the 0.074 mg/ml dose level was due to accidental death of 5 female mice at week 25. The cause of the accident was not stated.

Group mean body weight gain was reduced at the high dose level for both sexes of mice. The decrease was more pronounced in the male mice than the female mice, as shown by the 14% decrease for weeks 1-13 at the 0.23 mg/ml dose level and the 20% decrease for the entire study period. The decrease in females did not exceed 10% of the control.

In male mice, significant food consumption decreases were observed during the first 13 weeks (2, 5, and 7 through 11) of the study at the 0.23 mg/ml dose level. These decreases, while identified as statistically significant, were on the average of 5%. In females, no significant decreases in food consumption were recorded for the first 13 weeks of the study. Total food consumption for both male and female mice for the first 13 weeks of the study was not affected in treated compare to control mice.

Water consumption in male and female mice was decreased during the first week of the study, and was statistically significant at the 0.23 mg/ml dose level for both sexes, and at all dose levels for the male mice. This trend continued in male mice for the first 2 weeks of the study, and then by week 9, was increased at the 0.23 mg/ml dose level. In female mice, water consumption at eh 0.23 mg/ml dose level tend to decrease relative to control, but statistical significance was not consistently achieved.

At 0.074 and 0.23 mg/ml dose levels, statistically significant increases in absolute liver weight were observed in both the male and female mice. The increase in liver weight for male mice was 111% and 135% of control at the 0.074 and 0.23 mg/ml dose levels, respectively, while the increase for female mice was 119% and 122% of control at the same dose levels. Kidney weight was decreased by 9% in male mice at the 0.074 and 0.23 mg/ml dose levels and was increased by approximately the same percentage in female mice at these dose levels. There were no other significant organ weight changes reported in the study.

Increases in the incidence of macroscopic pathology were observed in the liver (accentuated lobular pattern, pale appearance) and urinary bladder (wall thickening) at the 0.23 mg/ml dose level. Non-neoplastic pathology in male and female mice was increased at 0.23 mg/ml, and included increases in extramedullary hemopoiesis of the spleen and several alterations in the urinary bladder, including epithelial hyperplasia, eosinophilic/hyaline cytoplasmic inclusions, increased submucosal connective tissue, and submucosal hyalinization.

Carcinogenic potential was evidenced in this study from the microscopic pathology which noted an increase in the incidence of angiosarcoma of the liver, spleen, and subcutaneous tissue as well as the presence of a transitional cell papilloma in a single high dose male, and a transitional cell carcinoma in a single high dose female. An increase incidence of angiosarcoma was observed in the liver for male mice at all dose levels in comparison to concurrent controls. Also in the liver, an increased incidence of hepatocyte fat vacuolation was observed in both sexes at this dose in both male and female mice.

Female showed an increased incidence of this neoplasm at the 0.23 mg/ml dose level only. Increase incidence of angiosarcoma was observed in the spleen at the 0.074 and 0.23 mg/ml dose levels for both male and female mice. At the 0.074 mg/ml dose level, 8/55 male mice (14.5%) and 3/55 (5%) of female mice were observed with this lesion, compared to 9% of male mice and 0% of female mice. At 0.23 mg/ml, 15/55 male mice (27%) and 4/55 female mice (7%) were observed with angiosarcoma of the spleen. Increase incidence of angiosarcoma was also observed in the subcutaneous tissue of male and female mice at the 0.23 mg/ml dose level, where 3/55 mice (5%) per sex were observed with this lesion vs. 0% in controls.

The LOAEL is 0.074 mg/ml [6.5 mg/kg (3.64 mg/kg MITC equi.) in males, 8.7 mg/kg (4.76 mg/kg MITC equi.) in females], based upon the significant increase in liver weight, and decrease body weight gain, food and water consumption in male and female mice. The NOAEL is 0.019 mg/ml [1.6 mg/kg in males (.89 mg/kg MITC equi.), and 2.3 mg/kg (1.29 mg/kg MITC equi.) in females].

Dosing was considered adequate in male mice based upon the decrease in body weight gain and increase in liver weight observed at the 0.23 mg/ml dose level. In March 1995, the HED Carcinogenicity Peer Review Committee estimated a unit risk, Q_1^* $(mg/kg/day)^{-1}$ of $1.98x10^{-1}$ in human equivalents, for metam sodium based upon angiosarcoma rates in male mice. The Q_1^* was converted from animal to human equivalent by the use of weights of 0.030 kg for the mice and 70 kg for the human and the 3/4's scaling factor for interspecies extrapolation (Tox_Risk program, version 3.5- K. Crump).

This carcinogenicity study in the mice is **acceptable/guideline** and satisfies the guideline requirement for a carcinogenicity study [OPPTS 870.4200; OECD 451] in mice.

5.2.6.2. MITC

Adequacy of data base for carcinogenicity: Existing studies in rat and dog are unacceptable primarily due to problems with dosing stability and/or concentration analysis. Since the release of EPA's preliminary risk assessment for metam sodium (May 21, 2004), additional ambient air exposure data became available which suggest that

chronic exposure are possible. Because of the potential for chronic exposures and the finding of focal squamous cell metaplasia in the respiratory epithelium following 28-days of exposure to MITC in rats EPA is requiring carcinogenicity studies in mice and rats.

870.4200a Carcinogenicity Study - rat

In a chronic/ carcinogenicity toxicity study (MRID 00150078) [MITC (95-96% a.i., batch #s 28.166 and 29.482) was administered to 60 Sprague Dawley CD rats/sex/dose in drinking water at dose levels of 0, 2, 10, and 50 ppm (equivalent to 0, 0.2, 1.0 and 5 mg/kg bw/day) for 102 weeks. Ten rats/sex of the control and high dose were sacrificed after one year. Of this group 5/sex/group were placed on untreated water for 4 weeks to assess reversibility. Drinking water solutions were prepared every two or three days.

Survival after 102 weeks among the control, 2, 10, and 50 ppm levels was comparable; the percent alive for males was 65, 63, 58, and 64, respectively and the percent alive for females was 42, 33, 53, and 53, respectively. Treatment related clinical signs were not observed.

No dose related effects on body weight gain or food intake as compared to controls were reported. Reduced water intake at the high dose was associated with the 'pungent odor and its known to irritate mucous membranes.' No dose related affects on hematology, clinical chemistry, urinalysis, or organ weights were reported as compared to control values.

No compound or dose related effects on the incidence of non-neoplastic or neoplastic lesions were reported from ingestion of MITC at doses up to 50 ppm. A maximum tolerated dose was not demonstrated.

A LOAEL was not established in this study. The NOAEL is the highest dose tested, 50 ppm (5 mg/kg/day).

This chronic/ carcinogenicity study in the rat is **unacceptable-guideline** and **does *not* satisfy** the guideline requirement for a carcinogenicity study [OPPTS 870.4200; OECD 451] in rats. This study cannot be upgraded due to inadequate concentration and stability analysis of MITC in drinking water.

870.4200b Carcinogenicity (feeding) - Mouse

In a chronic/ carcinogenicity toxicity study (MRID 00150075) MITC (93.14% ai., Lot no. MS25206) was administered to 70 ICR:JCL albino mice/sex/dose in drinking water at dose levels of 0, 5, 20, 80, and 200 ppm (approximately equivalent to 0, 0.82, 3.30, 11.83, and 25.71 mg/kg bw/day in males and 0, 0.91, 3.66, 13.03, 29.03 mg/kg/day in females) for 106 weeks. Drinking water solutions were prepared daily. Six mice/sex/group were sacrificed at 26 and 52 weeks for determination of clinical and

histopathological parameters.

Survival after 106 weeks among the control, 5, 20, 80, and 200 ppm levels were comparable for male and female mice (35%, 25%, 29%, 28%, and 37 % alive for males; 37%, 38%, 37%, 39%, and 37%, for females).

Body weight gain was decreased significantly at the 80 and 200 ppm level in male mice and at the 200 ppm level in female mice periodically throughout the study up to week 98. From week 98-termination, the mean body weights were comparable for all treatment groups. Approximately 15% and 30% less water was consumed at the 80 and 200 ppm levels, respectively, by male and female mice.

Changes in hematological and clinical chemistry parameters were sporadic and inconsistent. RBC count decreased for males at the 80 and 200 ppm was accompanied by an increase in reticulocytes for males at the 200 ppm level during week 52, but not at week 106. Total blood protein decreased for males and females at the 80 and 200 ppm levels during week 26 accompanied by decreased blood urea nitrogen values for males at the 80 and 200 ppm levels. Cholesterol values were decreased for females at the 200 ppm level also during week 26. By week 106, female aspartate aminotransferase values were increased at the 200 ppm level.

Relative and absolute pituitary weights for the 200 ppm level were increased for females at the interim sacrifices at weeks 26 (relative only), 52 and 106 and for males during week 52. Relative and absolute thyroid weights increased at the 80 and 200 ppm levels in males and females at week 52 and females only at termination.

There were treatment related gross pathological effects observed by the authors. A dose-dependant increase in the incidence of cystic ovaries was observed. An increase in tumors was not observed in treated animals. The DER lists several tissues (most notably the female mammary gland, colon, and rectum) which were not examined pathologically. Also, the mice in the study exhibit minimal toxicity which is indicative that a maximum tolerated dose was not achieved. It is difficult to determine MITC's carcinogenic potential based on the results of this study.

The LOAEL is 80 ppm (3.30 and 3.66 mg/kg/day for males and females, respectively), based on decreased body weight gain throughout the majority of the study and reduced water consumption. The NOAEL is 20 ppm (0.82 and 0.91 mg/kg/day for males and females, respectively).

This carcinogenicity study in the mice is **unacceptable/guideline** and does **not** satisfy guideline requirement for a carcinogenicity study [OPPTS 870.4200; OECD 451] in mice. Although the study provides well-conducted stability studies of MITC in water, the study does not provide actual analytical results of the concentration of MITC actually

provided to the mice or concentration of MITC in the drinking water at the time of removal from the cages.

5.2.7 Mutagenicity

5.2.7.1. Metam Sodium

Adequacy of data base for Mutagenicity: The data base for mutagenicity is considered adequate for metam sodium.

Metam sodium was tested in the unscheduled DNA synthesis using primary rat hepatocytes at concentrations of 0.5, 1.0, 2.5, 5.0, 10.0, 50.0, 100.0, and 250.0 nl/ml. Results of this study showed that metam sodium caused no significant changes in nuclear labeling of primary rat hepatocytes at the concentrations tested (MRID No. 40305601).

Metam sodium was tested in the Rec-Assay with Bacillus subtilis strains H17 and M45 in the absence and presence of metabolic activation (rat liver S-9) at doses up to 150.0 µl/plate. Metam sodium failed to induce differential toxicity in Bacillus subtilis strains H17 and M45 at the concentrations tested (MRID No. 40305602).

Metam sodium was non-mutagenic in the Ames Assay using Salmonella typhimurium strains TA92, TA98, TA100, TA1535, TA1537, and TA1538 in the absence or presence of metabolic activation (rat liver S-9) at doses up to 2500 µg/plate (MRID No. 40305603).

Metam sodium did not induce chromosomal aberration in the In Vitro cytogenic assay using human lymphocytes in the presence or absence of metabolic activation at doses up to 20 µg/ml (MRID No. 40305604).

A new study on *in vitro* cytogenetics in human lymphocytes (MRID No. 44276401) was recently submitted. Preliminary review of this study indicates that metam sodium did not induce chromosomal aberration, however, a more detailed review is on going. The results of this study will be incorporated into the hazard characterization of metam sodium in the future.

Metam Sodium was tested for clastogenicity in Chinese hamsters after single oral doses of 150, 300, and 600 mg/kg. Five animals per sex were sacrificed at 6, 24, and 48 hours post-dose for examination of bone marrow cells. At the dose levels tested, metam sodium was not positive for clastogenicity in Chinese hamster bone marrow (MRID No. 40305605).

4.2.7.2. MITC

Adequacy of data base for Mutagenicity: The data base for mutagenicity is considered inadequate. An in vivo cytogenetics assay needs to be performed as a follow-up to the positive in-vitro results. Also a repeat of the unscheduled DNA synthesis assay is necessary to satisfy the data gap in other genotoxic effects category.

The structural chromosomal aberration assay in V79 lung cells (84-2b, MRID No. 00150074) was classified as acceptable study. The study was positive in the presence of a metabolic activating system at concentrations as low as 1 µg/ml and in the absence of metabolic activation at concentrations as low as 2.5 µg/ml. The response increased slightly at 12 hours, but clearly increased at 28 hours after the initiation of treatment.

The gene mutation test in the Salmonella and E. coli WP2 uvrA gene mutation assays,(84-2a, MRID No. 41221410) was classified as acceptable study. The study was negative up to 100 µg/disc, the highest concentration tested.

The unscheduled DNA synthesis (UDS) in primary rat hepatocytes (84-4**,** MRID No. 00150072) for other genotoxic effects was classified as the unacceptable study. The study was negative up to 15.2 µg/ml, the highest dose tested, but no raw data were provided to confirm the results. In addition there were also problems with the positive control.

The V79/hgprt assay for gene mutation (84-2a, MRID No. 00150073) was classified as unacceptable study. The study was negative up to 1 µg/ml without metabolic activation and 2.5 µg/ml with metabolic activation, the highest concentrations tested. It was determined from the limited toxicities that higher concentrations could have been used.

The DNA damage assay in B. subtilis (84-4, MRID No. 41221410) was classified as unacceptable study. The study was negative up to 2000 µg/disc, the highest concentration tested. However, no toxicity was observed at the highest dose tested, no precautions were taken against compound loss (volatile compound), only single plates were used, and the chemical was not tested under activated conditions.

The sister chromatid exchange assay in V79 cells (84-2b, MRID #41221412) was classified as unacceptable study. The test was negative up to 3.5 µg/ml without metabolic activation and 5 µg/ml with metabolic activation, the highest concentrations used; but higher concentrations could have been used since it did not attain appropriate toxicity levels.

5.2.8 Neurotoxicity

5.2.8.1. Metam Sodium

Adequacy of data base for Neurotoxicity: The database of neurotoxicity studies for metam sodium is adequate at this time.

870.6100 Delayed Neurotoxicity Study - Hen

Not available and not required.

870.6200 Acute Neurotoxicity Screening Battery

In an acute neurotoxicity study (MRID 42977802), groups of non-fasted 43 day old Sprague-Dawley rats were given a single oral dose of **metam sodium** (43.1% a.i., batch/lot #098465) in water at doses of 0, 50 mg/kg, 750 mg/kg (12 rats/sex/dose), and 1500 mg/kg (16 rats/sex/ high dose). Based on percent active ingredient of 43.1%, actual doses of metam sodium were 0, 22, 324, and 647 mg/kg. Peak time of effect after administration was estimated to be within 45 minutes post- dosing in rats determined in a range finding study where groups of 2 male and 2 female Sprague-Dawley rats received single oral doses of 150, 300, 600, 800, 1250, and 1500 mg/kg metam sodium (43.1% a.i.), while single male and female rats received single oral doses of 2000 mg/kg. In the main study, observations of viability, clinical signs, and body weights evaluations were performed. Neurobehavioral assessment (functional observational battery [FOB] and motor activity testing) was performed in 11-13 animals/sex/group at days 0 (45 minutes post-dosing), 7, and 14. At study termination, brain weights and brain dimensions were determined for all animals. At the scheduled necropsy, all animals were perfused in situ; 5 animals/sex from the control and high dose groups were randomly selected for neuropathological examination.

No treatment related changes to brain weight, brain dimensions, or neuropathology were noted in the study.

Mortality was observed at the highest dose level, where a total of 5 males and 3 females were found dead during the course of the study. No treatment related clinical signs were noted at lowest dose. At the mid dose one female experienced abnormal gait on day 0. At the highest dose level, clinical signs such as alterations in gait, hypothermia, hypoactivity, and ptosis were noted at the highest dose level. Red, yellow, or orange material was observed on various body parts of most or all of the animals in the mid and high dose groups. Abnormal excreta were observed in 3 females at the mid dose and 5 males and 10 females of the high dose group for 1-5 days post-dosing.

Body weight gain and mean body weights were statistically ($p<0.05$) reduced compared to controls in male and females of the mid and high dose groups at the 7 and 14 day observations. Body weight or body weight gain was not affected at lowest dose level.

In the FOB and motor activity observations noted treatment related effects occurred on day 0, approximately 45 minutes post-dosing. FOB or motor activity effects did not persist until the day 7 or 14 observation. No treatment related FOB effects were noted in the lowest dose level. Various effects were noted at the mid and highest dose levels. Some of these included: alterations in posture and palpebral closure, increased

lacrimation and salivation, alterations in respiratory rate, decreased arousal, increased time to first step, lack of response to approach, lack of olfactory and pupil responses, and absent or reduced tail pinch response. Reduced hindlimb strength and decreased body temperature were also noted at mid and high dose groups. Statistically significant reductions in mean ambulatory and total motor activity were observed in male and female rats at all dose levels, including the lowest dose, at day 0. (At pretest, no differences in motor activity counts were noted among groups or compared to controls.)

Based on the effects seen in this study, the acute LOAEL for *metam sodium* was 22 mg/kg (12.32 mg/kg equivalents of MITC) based on reduced ambulatory and total motor activity observed in male and female rats on day 0, 45 minutes post-dosing. The acute NOAEL for *metam sodium* was not established (< 22 mg/kg; < 12.32 equivalents of MITC).

This neurotoxicity study is classified as **acceptable-guideline** and **satisfies** the guideline requirement for an acute neurotoxicity study in rats (870.6200; OECD 424) because a NOAEL for acute neurotoxicity was not established.

870.6200 Subchronic Neurotoxicity Screening Battery

In a subchronic neurotoxicity study (MRID 43248801) **metam sodium** (43.15%, CTL Ref. No. Y06930/008) was administered in drinking water to 12 Sprague-Dawley rats/sex/dose/group at dose levels of 0, 0.02, 0.06, and 0.2 mg/ml (equivalent to 0, 1.4, 5.0, and 12.8 mg/kg bw/day for males and 0, 2.3, 7.0 and 15.5 mg/kg bw/day for females) for 13 weeks.

Neurobehavioral assessment (FOB and motor activity testing) was performed in all animals/sex/group at Weeks -1, 5, 9, and 14. At study termination, 6 animals/sex/group were euthanized and perfused in situ for neuropathological examination. The tissue (brain, vertebral column, etc.) from the perfused animals were subjected to histopathological evaluation of brain and peripheral nervous system tissues.

No mortalities occurred during the study. Statistically significant decreases in body weight for male and female rats at the 0.2 mg/ml dose level were usually between 7-9% of control. In male rats, body weight gain for both the 1-7 study week period was well as the 1-13 week period was decrease to 86% of control at 0.2 mg/ml dose level. There was no effect on body weight gain in male rats at lower dose levels. In female rats, body weight gain at the 0.2 mg/ml dose level was deceased to 79% of control for weeks 1-7, and decrease to 82% of control for weeks 1-13. At the 0.06 mg/ml dose level, body weight gain for weeks 1-7 and weeks 1-13 was decreased to 86% of control. Body weight gain was statistically significant decreases (3-7%) in female rats at all dose level during week 13 of the study.

Food consumption was statistically significant decreased (3-7%) in all female rats at all dose levels during week 13 of the study. Food efficiency (5-7%) decreased in males and females at 0.2 mg/ml. Water consumption was significantly decreased (8%, 7% and 41% at the 0.02, 0.06 and 0.2 mg/ml dose level, respectively; $p<0.05$) in male rats. Water consumption was also significantly decreased ($p<0.05$; 27%, 38% and 68%) at the 0.02, 0.06 and 0.2 mg/ml dose levels, respectively, in females rats.

There appeared to be a mild effect at the 0.2 mg/ml dose level on time to tail flick in male rats, but this was not statistically significant. There were no other significant findings to report from the FOB. During week 5, a significant increase (29%) was observed in overall motor activity for female rats at the 0.06 mg/ml dose level, but subsequent measurements showed no significant alterations in motor activity. Males showed no significant changes in motor activity over the study period.

The systemic LOAEL for *metam sodium* is 5.0 mg/kg/day (2.8 mg/kg/day MITC

equi.) for male rats and 7.0 mg/kg/day (3.92 mg/kg/day MITC equi.) for female rats based on decreased body weight gain. The systemic NOAEL for *metam sodium* is 1.4 mg/kg/day (0.44 mg/kg/day MITC equi.) (decreased body weight gain) for male rats and 2.3 mg/kg/day (1.29 mg/kg/day MITC equi.) for female rats (decreased body weight gain).

There was no evidence of a neurotoxic effect for metam sodium in this study *at the doses tested*.

The study is classified as **acceptable-guideline** and **satisfies** the guideline requirement for a subchronic neurotoxicity study in rats (870.6200b).

870.6300 Developmental Neurotoxicity Study
A development neurotoxicity study is not available for metam sodium. This study is not required at this time.

5.2.8.2. MITC

Acute and subchronic neurotoxicity studies by any route of administration are not available for MITC. An acute neurotoxicity study in rat via inhalation with pathological evaluation of the complete respiratory tract is required at time. (Subchronic neurotoxicity see Section 5.2.42).

870.6100 Delayed Neurotoxicity Study - Hen
Not available and not required.

870.6200 Acute Neurotoxicity Screening Battery
An acute neurotoxicity study is required at this time for MITC (See Section 3.3.2).

870.6200 Subchronic Neurotoxicity Screening Battery
A subchronic neurotoxicity study is required at this time for MITC (See Section 3.3.2).

870.6300 Developmental Neurotoxicity Study
A developmental neurotoxicity study via the inhalation route is not required at this time for MITC. (See Section 3.3.2)

5.2.9 Metabolism

Adequacy of data base for metabolism: The data base for metabolism is considered to be complete for metam sodium and MITC. No additional studies are required at this time.

870.7485 Metabolism - Rat

Pharmacokinetic and metabolism studies in rats for dazomet, metam sodium, and MITC were submitted to support metabolism for metam sodium. Each compound was tested at two dose levels. It was shown that all three were excreted mainly in urine with urinary recoveries over 168 hours of 63-65% for dazomet, 37-58% for metam sodium, and 84-87% for MITC. Excretion via the feces was low–usually ranging from 1.5% to 3.3%. Three different compounds (MITC, CO_2, COS/CS_2) were found to be excreted via the lungs. Total excretion of the 3 products of the lungs over a 73 hour collection period were about 35% and 50% for metam sodium, 22% and 28% for dazomet, and 22% and 9% for MITC at low and high doses, respectively. There were no differences between males and females in amounts excreted via the three excretion routes. Tissue retention at 168 hours was about 2% for all 3 compounds at both dose levels. Total recoveries, including the percentage of the doses excreted and that remaining in the tissues combined after 168 hours, ranged from 92.6% to 106%, indicating virtually complete absorption from the GI tract. By the first 24 hours, 85% or more of each of the 3 compounds at both dose levels had been excreted. All three compounds were also rapidly absorbed from the GI tract with plasma t_{max} between 0.25 and 1.0 hours. However, plasma half-lives after 24 hours were long, ranging from around 60 to 74 hours for all three compounds. Tissue and plasma levels at all time periods, and plasma AUCs were consistently higher in females than in males by a substantial amount. The tissue with the highest uptake for all three compounds was the thyroid gland. 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.

870.7600 Dermal Absorption - Rat

^{14}C-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 cm^2 on the back (MRID no. 42670301). 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).

5.2.10 Other Metabolites/Degradates

1. Carbon Disulfide

Rat Developmental Toxicity Study (MRID NA; TXR NO. 011691)

Under the conditions of the study, dose levels of 0, 100, 20, and 400 mg and 600 of **carbon disulfide** CS_2 (>99%)/kg of body weight/day administered to pregnant (COBS) CD (SD) rats per group during days 6-15 of gestation resulted in decreased body-weight gain at the three highest dose levels during both the dosing period (71%, 43%, and 16%, respectively).

Treatment related clinical signs (lethary, ataxia, rough or erect coat, abnormal posture-arched back were observed mainly at the 400 and 600 mg/kg/day dose levels. There were no statistically significant differences in the number of implantations/dam, live fetuses/dam, resorptions/dam, dead fetuses/dam, or in post-implantation losses. Fetal body weight was decreased at the 400 and 600 mg/kg/day groups (84% of control). Male and female fetal body weights, when considered separately were decreased significantly at the three highest dose levels (94% to 83% of control). There were no apparent differences among the groups with respect to the incidence of malformations.

The maternal LOAEL for CS_2 is 200 mg/kg bw/day, based on clinical signs and decreased body weight. The maternal NOAEL for CS_2 is 100 mg/kg bw/day.

The developmental LOAEL for CS_2 is 200 mg/kg bw/day, based on decreased fetal body weight in both sexes. The developmental NOAEL for CS_2 is 100 mg/kg bw/day.

Rabbit Developmental Toxicity Study (MRID NA; TXR NO. 011691)

Under the conditions of the study, dose levels of 0, 25, 75, and 100 mg/kg/day of **carbon disulfide** was (>99%) administered to 23-2 pregnant female rabbits per group during Days 6-19 gestation resulted in 1) decreased maternal body weight at the high dose (92% of control); 2) negative body-weight gain at the mid and high-dose levels during the dosing period and at the high dose overall; 3) treatment related clinical signs (hyperactivity, convulsions, circling, and trembling) at the mid and high dose levels; 4) dose related increase in maternal liver weight; 5) dose-related increase in the number and percent of resorptions, resorptions/litter, and nonliving fetuses/litter, litters with nonlive fetuses, and postimplantation loss; 6) dose related decrease in % of litters with live fetuses, fetal body weight, and gravid uterine weight, ; and 7) increases in gross malformations/litter, the # of malformed/litter, % fetuses malformed/litter at the

high dose.

The maternal LOAEL for CS_2 is 75 mg/kg bw/day, based on clinical signs and decreased body weight. The maternal NOAEL for CS_2 is 25 mg/kg bw/day.

The developmental LOAEL for CS_2 is 100 mg/kg bw/day, based on decreased fetal body weight in both sexes. The developmental NOAEL for CS_2 is 75 mg/kg bw/day.

Other relevant information: CS_2

The following text was extracted from EPA's Integrated Risk Information System (IRIS) database.

Rats and rabbits were exposed to 20 ppm or 62.3 mg/m^3 (recommended occupational exposure limit) and 40 ppm or 124.6 mg/m^3 of carbon disulfide (CS_2) during the entire length of the pregnancy period and also 34 weeks before breeding to simulate occupational exposure.

Hardin et al. (1981) observed no effects on fetal development in rats or rabbits following inhalation exposure to 62.3 or 124.6 mg/m^3 which corresponds to estimated equivalent oral dosages of 5 and 10 mg/kg for rats, and 11 and 22 mg/kg for rabbits. The highest NOEL from this study, 22 mg/kg for the rabbit, should not be used for an RfD estimate because adverse effects were seen in rabbit fetuses following oral exposure of pregnant does to 25 mg/kg (Jones-Price et al., 1984a,b). Therefore, the highest NOAEL that is below an effect level is the estimated low dose from the Hardin et al. (1981) inhalation study using rabbits. This dose level, 11 mg/kg, is the most appropriate basis for RfD derivation.

A NCTR-NTP oral study (Jones-Price et al., 1984a,b) observed 25 mg/kg/day in rabbits as an FEL (fetal resorption). Fetotoxicity and fetal malformations in this study were not observed in rats at the lowest level (100 mg/kg/day) of CS_2 exposure. The data from this study also suggest that the rabbit fetus is more sensitive than the rat fetus to CS_2-induced toxicity. Johnson et al. (1983) reported an epidemiologic study that employed a wide range of exposure with CS_2, such as 0.04-5 ppm (mean: 1.2 ppm, low, exposure), 0.04-33.9 ppm (mean: 5.1 ppm, medium exposure) and 0.04-216 ppm (mean: 12.6 ppm, high exposure). In this study the entire population was exposed to a combined exposure of 7.3 ppm over a period of 12 or more years. Of the several clinical findings, the exposed population showed significant alterations in sensory conduction velocity and peroneal motor conduction velocity. However, the data indicated, in the opinion of the authors, that minimal neurotoxicity was evident, since the reduction in

nerve conduction velocity was still within a range of clinically normal values and thus not associated with specific health consequences. Additionally, the exposed population had blood lead levels <40 mg/dL and the exposed air alone contained H_2S, H_2SO_4 and tin oxide. Therefore the 7.3 ppm CS_2 can be considered as a NOAEL for neurotoxicity. This dose, when extrapolated to an oral dose of 10 mg/kg/day, lends support to the animal NOAEL of 11 mg/kg/day.

2. Hydrogen Sulfide

The following text was extracted from EPA's IRIS database.

No data on human developmental effects of inhaled hydrogen sulfide were found, but, based on the limited information available in laboratory animals, hydrogen sulfide does not appear to induce developmental effects. In a preliminary study, Saillenfait et al. (1989) administered 0, 50, 100, or 150 ppm hydrogen sulfide (0, 69.7, 139, or 209 mg/m^3, respectively) 6 hours/day to pregnant rats (n = 7-9) during gestational days 6-20. Maternal body weight gain was reduced significantly at 150 ppm, and fetal body weight was reduced slightly (4-7%) in all exposed groups. In dams exposed to 100 or 150 ppm, reduced absolute weight gain and increased implantations and live fetuses were observed. In a follow-up experiment, 20 pregnant females were exposed to 100 ppm for 6 hours/day on days 6-20 of gestation. Fetal weights, number of live and dead fetuses, number of implantation sites and resorptions, and external malformations were recorded. Viable fetuses were then prepared for soft tissue and skeletal examination. No maternal toxicity or adverse effects on the developing embryo or fetus were observed. The preliminary study identifies a LOAEL of 50 ppm for maternal weight gain. Because of the larger number of animals in the main study, a NOAEL of 100 ppm for maternal effects and developmental effects is identified [NOAEL(HEC) calculated for extrarespiratory effect = 139 mg/m^3].

3. Methylisocyanate

The following was extracted from California's Department of Pesticide Regulation Hazard Assessment of MITC (2002):

Following the Bhopal MIC disaster of December, 1984, which killed 2500-5000 people and injured up to 200,000.....[human] fetal loss rose precipitously after the accident, from an estimated background incidence of 6-10% to 43% in the exposed population, with a disproportionate rise in first trimester spontaneous abortions (Varma, 1987). Fourteen percent of live-born infants exposed *in utero* died within 30 days of birth, an increase of over 4-fold compared to background rates (Varma, 1987). Gynecological effects (increased leukorrhea, irregular menses, menorrhagia [excessive menstrual bleeding at menstruation] and

excessive vaginal discharge with, in many cases, inflammation) were common at 15 weeks post exposure (Shilotri *et al.*, 1986). Exposure of pregnant mice to MIC for 6 hours per day on gestation days 14-17 led to increased mortalities over controls in fetuses at 1 and 3 ppm (dead fetuses at increasing doses: 0.4%, 3.3%* and 6.4%* , *$p<0.05$), and in neonates at 3 ppm (neonatal deaths between days 0-4: 2.0%, 0.8% and 11.3%*, *$p<0.05$) (Schwetz *et al*, 1987). Exposure of pregnant mice to 9 and 15 ppm MIC for 3 hours on gestation day 8 resulted in greater than 80% resorptions, suppressed fetal skeletal growth, induced persistent diestrus, decreased female fertility and male reproductive performance (Varma *et al.*, 1987).

Ambient air exposure studies have been performed in California which include measurements of MIC levels. These data indicate that both MITC and MIC can be measured in ambient air following the application of metam sodium.

6.0 REFERENCES

6.1 Metam Sodium

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