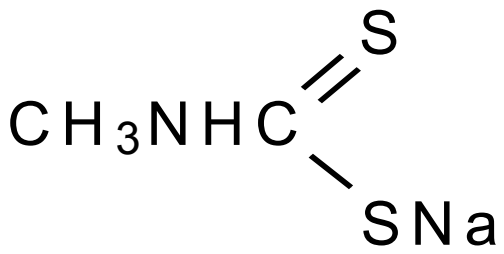
Metam Sodium (Sodium N-Methyldithiocarbamate)

RISK CHARACTERIZATION DOCUMENT



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I. SUMMARY

Introduction

Metam sodium (sodium N-methyldithiocarbamate) is a fumigant used primarily in agriculture as a preplant treatment to kill soil fungi, nematodes, weed seeds and soil insects. Adverse developmental, oncogenic and genotoxic effects of metam sodium in laboratory animals triggered the current human health risk assessment. Along with its degradation product methyl isothiocyanate (MITC), metam sodium was designated as a "restricted use" pesticide in 1994 because of its potential danger to farm workers, the general public, animals, crops or the environment. As a consequence, a use permit must be issued by the county agricultural commissioner after consideration of the proposed application site and use practices. In June 2003, both metam sodium and MITC were designated as Toxic Air Contaminants under the AB 1807 Toxic Air Contaminants Act.

"Technical" metam sodium exists only in aqueous formulations, ranging in concentration between 32% and 44% (the pure solid form of metam, referred to in the text as the "technical grade active ingredient", is unstable). Formulations registered in California containing less than 32-44% metam may also contain other pesticidal active ingredients; these will not be considered further in this report.

Pharmacokinetics

The metabolic fates of metam sodium and its chief degradate, MITC, were assessed in an oral exposure study in rats. 83-86% of the metam sodium and 88-96% of the MITC was absorbed within 24 hours. In that time period, urinary excretion accounted for 33-54% of the metam dose, with <1-3% excreted in the feces, <1-24% in the expired air as MITC (the amounts increasing with the dose of metam sodium), 5-19% in the expired air as CO_2 (the amounts decreasing with the dose), and 13-18% in the expired air as carbonyl sulfide + carbon disulfide. Tissue binding accounted for 1-2% of the dose at 168 hours. For MITC, by 24 hours 80-83% was excreted in the urine, <1-2% in the feces and 6-16% in the expired air (as CO_2). The rest was excreted in the expired air as unmetabolized MITC (<1-2%) or carbonyl sulfide + carbon disulfide (<1%), or remained bound to tissues (1-3% after 168 hours). Thyroid, liver, kidneys, whole blood and adrenals were sites of tissue distribution. The major metabolites in the urine were N-acetyl-cysteine and cysteine conjugates.

A separate study showed that for a metam sodium dermal dose of 8.6 μg/cm^2 in rats, ~2.5% was absorbed by 1 hour. This was considered an appropriate value for use in the worker exposure estimates for metam sodium. However, the precise chemical nature of the absorbed compound(s) was not clear.

Acute toxicity

Acute oral exposure to high doses of metam sodium resulted in what resembled cholinergic signs, with rat LD_{50}s as low as 781 mg/kg. Exposure of rabbits by the dermal route yielded LD_{50}s as low as 1050 mg/kg and clear local and systemic pathology and clinical signs. Four-hour LC_{50} values as low as 2.20 mg/L were obtained in rat acute inhalation studies, again accompanied by local and systemic pathology and clinical signs. Metam sodium had mild eye irritating properties in some rabbit studies (corneal involvement or irritation for 1-7 days using 0.1 ml/eye), and was a dermal sensitizer in guinea pigs.

The critical acute LED_{01} was **1 mg/kg**, established in a Himalayan rabbit developmental toxicity study. It was based on a dose dependent increase in early resorptions, which resulted in a LOEL determination at the low dose of 4.2 mg/kg. Benchmark dose methodology was applied to estimate the 1% response level (the ED_{01}) and its associated lower bound (the LED_{01}). The 1% response level was chosen because early resorption, as a form of embryonic death, was considered to be a severe endpoint. The acute nature of the response was inferred by the fact that these were *early* resorptions, having occurred soon after the commencement of dosing, without evidence of fetal development.

A parallel study in New Zealand White rabbits also reported an increase in early resorptions, though the LOEL was 60 mg/kg, not 4.2 mg/kg as in the Himalayan rabbit study. In addition, weaker evidence for resorptions was available in the Wistar rat developmental toxicity study, though the precise dose level was not clear. These data were supportive of the critical study findings.

Further empirical support was garnered from a study in Wistar-derived Alpk:APfSD rats, which established an acute NOEL of 5 mg/kg based on acute maternal and developmental effects at a LOEL dose of 20 mg/kg. The maternal effects included clinical signs (salivation, vaginal bleeding and oral staining) and decrements in body weight gain and food consumption. The acute nature of these signs was inferred by their rapid development after the onset of dosing on gestation day 7. The developmental effects included suppression of fetal body weights and numerous skeletal developmental delays. As these growth effects were considered to be functions of the acute maternal growth effects, they were also likely to result from acute or short-term exposures.

Based on current use scenarios, occupational dermal exposure was the sole projected exposure route. An occupational acute dermal exposure study utilizing sodium tetrathiocarbonate as a surrogate was used to estimate exposure to metam sodium for several occupational tasks. The surrogate acute data were amortized to provide estimates of seasonal and lifetime exposures. These considerations emphasize that the exposure estimates, along with their attendant risk calculations, should be interpreted with great care, as direct measurements of metam sodium exposure were not made. That said, the mean 24-hour dermal absorbed dose for workers predicted by the surrogate study ranged from 1.5 to 2.9 μg/kg/day. Using the critical LED_{01} of 1 mg/kg, these exposure estimates resulted in acute systemic margins of exposure (MOEs) ranging from 345 - 667. By convention, MOEs greater than 100 are not considered to constitute a human health risk when (as in this case) the toxicity endpoint derives from an animal study.

Developmental toxicity

Six developmental toxicity studies, 4 in rats and 2 in rabbits, were examined for this document. All utilized the oral route of exposure. In both rabbit studies, metam sodium induced early resorptions. In Himalayan rabbits, resorptions were induced at the sub-maternally toxic dose of 4.2 mg/kg/day. Fetal malformations (meningocele + spina bifida) occurred at the slightly maternally toxic dose of 42.2 mg/kg/day. In New Zealand White rabbits, resorption incidence was overwhelming at the high dose of 60 mg/kg/day, which was only slightly maternally toxic. In the Wistar-derived Alpk:APfSD rat, malformations (meningocele, microphthalmia, anophthalmia, skull malformation, hydrocephaly and abnormal zygomatic arch) were noted at the maternally toxic dose of 60 mg/kg/day.

Dermal irritation

The risk of acute occupational dermal irritation was assessed because primary dermal irritation studies in animals as well as incident reports in the California Pesticide Illness Surveillance Program indicated that metam is corrosive and may have caused irritation in the field. A 21-day dermal toxicity study in rabbits produced a local irritation NOEL of 31.25 mg/kg/day, based on a finding of erythema, edema and dermatitis in a majority of animals at 62.5 mg/kg/day. Conversion to units of local concentration produced critical NOEL and LOEL values of **360 and 720 μg/cm^2/day**, respectively. Using estimated dermal exposure rates based on various work tasks in the surrogate acute dermal study mentioned above, acute dermal irritation MOEs were calculated. The lowest MOE was 679 for oakroot fungus control operations. Values as high as 1333 were calculated for other work tasks. Note, however, that the NOEL value was derived in what amounted to a "sub-acute" study (*i.e.*, exposures were longer than one day, but shorter than a conventional subchronic exposure regime), where dermal irritation at the LOEL dose of 720 μg/cm^2/day was not observed until day 4 (irritation was observed on day 1 at the high dose of 1440 μg/cm^2/day). In all probability the dermal irritation NOEL would be higher under a truly acute exposure scenario, raising the corresponding MOE.

Subchronic toxicity

The critical subchronic LED_{10} was **0.2 mg/kg**, established in a dog 90-day oral gavage study. It was based on a dose dependent increase in liver / bile duct damage, which resulted in the establishment of a LOEL at the low dose of 1 mg/kg. Benchmark dose methodology was applied to estimate the 10% response level (the ED_{10}) and its associated lower bound (the LED_{10}). The 10% response level was chosen because the bile duct proliferation / inflammatory cell infiltration and elevated plasma alanine aminotransferase activity in 1/4 females noted at the low dose was "minimal" (even less severe than "slight") and occurred in only a single animal. However, these signs were considered progenitors of the severe hepatitis (hepatocyte degeneration and necrosis, inflammation, and increased pigmentation, collapse of hepatic cords with an influx of blood, and biliary proliferation) present in all animals at 10 mg/kg/day, and the similar, but less severe hepatitis present at 5 mg/kg/day. The primary effects observed at necropsy were related to the liver. These included the accentuated lobular pattern, pale coloration, and red depressed areas indicative of collapsed hepatic cords with an influx of blood at 10 mg/kg. The latter sign was also noted at 5 mg/kg. Designation of 0.2 mg/kg/day and 1 mg/kg/day as the critical LED_{10} and LOEL, respectively, was directly supported by similar findings in the 1-year dog oral gavage study - one female treated at 1 mg/kg/day (the high dose) exhibited an ~8-fold rise in alanine aminotransferase at weeks 26, 32, 39, 45 and 52. The same individual exhibited signs of hepatotoxicity (a slight increase in hepatocyte and macrophage / Kupffer cell pigmentation, slight mononuclear cell infiltration, slight telangiectasis). Some beagle dogs thus exhibit sensitivity in hepatic responsiveness to relatively low doses of metam sodium.

A 90-day mouse drinking water study established a NOEL of 0.79 mg/kg/day. This was calculated from a nominal concentration of 0.018 mg/ml using measurements of the maximum metam degradation rate in water bottles. The NOEL determination was based on a reduction in hemoglobin, hematocrit, and red blood cell numbers (an anemic effect), increased liver weights, and eosinophilic granules in transitional epithelial cells of the urinary bladder, all at the mid-low dose of 4.48 mg/kg/day. The effects on liver weight may have been related to necropsy findings of livers with pale or accentuated lobular patterns noted at the top two doses (36.05 and 60.36 mg/kg/day). The appearance of eosinophilic granules in the urinary bladder was predictive of clearer bladder toxicity (cystitis and mucosal hyperplasia) at the top two doses. The hematologic evidence for anemia at the top 3 doses may have underestimated the actual effect; the

suppression of water consumption at those doses, an effect possibly due to decreased palatability, may have resulted in dehydration.

A 90-day rat inhalation toxicity study established a NOEL of 1.11 mg/kg/day (6.5 mg/m^3) based on apparent liver effects at 7.71 mg/kg/day (45 mg/m^3). Irritation of the nasal passages, stomach, and lungs was apparent at the high dose of 27.43 mg/kg/day (160 mg/m^3), with some nasal irritation evident at the mid dose (45 mg/m^3). Mean air concentrations of MITC, which due to its corrosive properties could be implicated in some of the irritative effects, were also determined. These were 0, 0.7, 2.2 or 5.7 mg/m^3 (0, 0.23, 0.74, and 1.90 ppm).

Mean seasonal average daily doses for metam sodium were calculated from the surrogate acute dermal exposure study mentioned above (the interpretive caveats mentioned there are applicable here as well). Under the various work categories, metam sodium exposure ranged from 1.5 to 1.7 μg/kg/day. These resulted in seasonal MOE values between 118 and 133. Clearly these values were close to, but still exceeded, the benchmark MOE value of 100, below which a human health concern would be indicated.

Chronic toxicity

A critical NOEL of **0.1 mg/kg/day** for chronic toxicity was obtained in a 1-year dog study. Four beagles/sex/dose were administered 0, 0.05, 0.1 or 1 mg/kg/day by gelatin capsules. Mean plasma alanine aminotransferase activities were elevated in high dose females. This was due to an ~8-fold rise in one individual recorded in weeks 26, 32, 39, 45, and 52. The same individual exhibited signs of hepatotoxicity (a slight increase in hepatocyte and macrophage/Kupffer cell pigmentation, slight mononuclear cell infiltration, slight telangiectasis) that, in view of similar results in the dog 90-day study, was probably test article-related. Other observations, including an increase in mean alkaline phosphatase activities (up to 47%, both sexes, mostly high dose) and a reduction in mean plasma triglycerides (up to 34%, females, high dose) may also indicate liver dysfunction. An increase in kaolin-cephalin time (also known as activated partial thromboplastin time) of up to 15% in both sexes at the high dose indicates some interference with blood clotting.

Mean annual average daily doses for metam sodium were calculated from the surrogate acute dermal exposure study mentioned above (the interpretive caveats mentioned there are applicable here as well). Under the various work categories, metam sodium exposure ranged from 0.8 to 0.9 μg/kg/day. These resulted in annual MOE values between 111 and 125. Again, these values were close to, but did not indicate, a human health concern.

Genotoxicity

Metam sodium is a clastogen both *in vivo* (hamsters) and *in vitro* (human lymphocytes). Other assays for genotoxicity, including gene mutation, DNA damage and micronucleus induction, were either negative or equivocal.

Oncogenic effects

Incidence of angiosarcoma, a malignant vascular tumor, following exposure of male mice to metam sodium in the drinking water for 2 years was 7/53, 12/53, 12/55, and 27/53 at internal doses of 0, 1.9, 7.2, and 28.9 mg/kg/day, respectively. Incidence at the high dose was highly significant compared to controls ($p<0.001$, Fisher Exact Test). The incidence curve was also positive for trend ($p<0.001$, Cochran-Armitage trend test) Incidence in females was 4/55, 2/55, 6/46, and 10/52 at internal doses of 0, 2.6, 9.6, and 31.2 mg/kg/day, respectively. While Fisher

Exact tests in females were not significant at any dose ($p>0.05$), the incidence curve was significant in a Cochran-Armitage trend test ($p<0.01$). The increase in angiosarcomas in males was reflected in several organ systems, including liver, spleen and subcutaneous tissues. Incidences in the former two systems were increased over controls by statistically significant margins.

Angiosarcoma was the major contributor to death among male mice that had these tumors. However, there was no statistically significant evidence it decreased the overall survival time or that death from angiosarcoma among high dose animals occurred sooner than death from angiosarcoma among control animals. For these reasons, the oncogenic potency was calculated using the linearized multistage model of tumor development (GLOBAL 86) instead of the Weibull time-to-tumor method. Extrapolation of the mouse doses to humans was done by multiplying the doses by the relative body weights using an interspecies scaling factor: $(BWt_A / BWt_H)^{0.25} = (0.03 \text{ kg} / 70 \text{ kg})^{0.25} = 0.144$. The estimated oncogenic potency using the incidence rate for all "at risk" male mice (that is, all mice surviving for at least 1 year of exposure) ranged from a $Q_1 = 8.56 \times 10^{-2}$ $(\text{mg/kg/day})^{-1}$ (the maximum likelihood estimate or MLE) to a $Q_1^* = 1.85 \times 10^{-1}$ $(\text{mg/kg/day})^{-1}$ (the 95% upper bound or 95% UB).

The risk of oncogenic effects was calculated as the product of the oncogenic potency and the highest lifetime average daily dose (LADD). This value is normally calculated from chronic exposure estimates. As no such estimates were available for metam, LADDs were calculated using seasonal exposure data. (*Note*: The seasonal exposure data were themselves derived from the acute exposure study that employed sodium tetrathiocarbonate as a surrogate. The manifold weaknesses of estimating LADDs by this approach are therefore fully recognized. The corresponding cancer risk values should also be viewed with caution.) The highest LADD of 0.5 μg/kg/day over a 75-year lifetime (assuming a dermal absorption of 2.5%) occurred in rotary tiller operators. The risk to workers for development of angiosarcoma was 3.42×10^{-5} - 4.28×10^{-5} when expressed as the maximum likelihood estimate and 7.40×10^{-5} - 9.25×10^{-5} when expressed as the 95% upper bound estimate. These estimates, derived as they were from the GLOBAL86 approach, were based on assumptions that the tumorigenic process was multistaged and non-threshold-dependent.

As a vascular tissue disease, it is not unexpected that angiosarcomas were found in several different mouse organs including liver (where they may have been responsible for the increase in palpable masses), subcutaneous tissues and, especially, spleen. Interestingly, non-neoplastic histopathology included findings of increased hepatocytic fat vacuolization and splenic hemosiderosis at the high dose.

Support for a role for metam sodium in the induction of angiosarcomas in male mice came from a 2-year drinking water study in rats. Incidence of hemangiosarcoma, a subcategory of angiosarcoma, was 0/50, 3/50, 8/51, and 3/51 at internal doses of 0, 1.5, 4.3, and 12.5 mg/kg/day, respectively. Incidence at the mid dose was statistically significant compared to controls ($p<0.01$, Fisher Exact test), though neither the low or high dose incidences achieved statistical significance. These data were considered ambiguous with regard to a role for metam sodium in the induction of hemangiosarcoma in rats. However, in recognition of the similarity of this tumor to that induced in mice, along with the observation that incidence rates were higher at all doses compared to controls, the rat data were considered to enhance the level of concern over metam sodium as a potential vascular oncogen.

Breakdown products

Upon application, metam sodium breaks down into several volatile compounds. Brief toxicologic and risk profiles for these compounds are provided:

Methyl isothiocyanate (MITC). A complete Risk Characterization document for MITC, the primary pesticidal breakdown product of metam sodium, has been developed by DPR. Field applications of metam sodium are expected to result in measurable inhalation exposure to MITC. MITC is very irritating to ocular and respiratory tissues, a characteristic evident in animal studies and in studies of people exposed both after the 1991 Sacramento River metam sodium spill and after agricultural use. A human study using specially designed goggles resulted in a critical acute eye irritation NOEL of 220 ppb (LOEL = 800 ppb). A subchronic LOEL concentration of 1.7 ppm based on nasal epithelial atrophy was established from a 28-day rat inhalation toxicity study. Severe pulmonary histopathology and clinical signs were observed at the high dose of 34 ppm. The critical subchronic NOEL of 100 ppb was calculated from the LOEL by invoking Haber's Law to convert the 5-days/week, 6-hours/day experimental exposure regimen to a 7-days/week, 24-hours/day regimen and applying an uncertainty factor of 3. As no chronic inhalation studies were submitted, an uncertainty factor of 10 was imposed on the estimated subchronic NOEL to generate a critical estimated chronic NOEL value of 10 ppb. A chronic oral NOEL in dogs was set at 0.4 mg/kg/day based on a plethora of irritative and systemic signs. MITC was not clearly genotoxic, nor did it appear to be a reproductive or developmental toxicant. There was weak evidence that it induced mammary fibroadenomas and carcinomas in female rats in a chronic drinking water study. A similar study in mice produced evidence for induction of cutaneous fibrosarcomas in both sexes. However, none of these data were sufficient to trigger a quantitative oncogenic risk evaluation. Reference exposure levels for acute, subchronic, and chronic exposure were 22, 1, and 0.1 ppb, respectively.

Monitoring of MITC levels under occupational scenarios in towns from regions of heavy agricultural metam sodium use ("ambient" levels) and near fields that were recently treated ("application site" levels) demonstrated the potential for exposure of workers and the general public. While occupational and application site air levels were generally higher than ambient levels (thus generating lower MOEs), MOE values calculated under all three scenarios indicated the potential for human health impacts under acute, seasonal, and chronic exposure conditions. The calculated reference exposure levels were also frequently exceeded.

Methyl isocyanate (MIC). Human exposure to methyl isocyanate (MIC) may occur following metam sodium applications due to photolysis of the metam sodium breakdown product MITC. MIC, the chemical responsible for the deaths of up to 5000 people in the aftermath of the 1984 factory disaster in Bhopal, India, is a severe pulmonary irritant with LC_{50} levels in animals in the 6-12 ppm region. A host of toxicologic effects on other tissues and organ systems were evident both in studies on Bhopal victims and on laboratory animals. Evidence of pulmonary sensitization from exposure to other isocyanates makes it at least possible that, despite the lack of direct experimental or epidemiologic evidence, such an effect could result from MIC exposure. Calculations carried out in this document based on a human study generated a conditional acute 1-hour REL value of 0.98 ppb. Preliminary measurement of MIC after agricultural use of metam sodium in Kern County revealed levels between 0.09 and 2.5 ppb. The potential highest level of MIC to be found under the conditions of this study, estimated by correcting for application rate and recovery similarly to MITC, was 5 ppb. This exceeded by about 5-fold the 1-hour acute REL calculated above. However, it was below the ACGIH 8-hr Threshold Limit Value (TLV) and the Cal OSHA Permissible Exposure Limit (PEL) of 20 ppb.

Hydrogen sulfide (H_2S). H_2S is formed as part of the same monomolecular cleavage reaction that produces MITC from metam sodium under dilute aqueous conditions. It is also a photolytic breakdown product of airborne MITC. Like cyanide, H_2S disrupts intracellular electron transport by inhibiting cytochrome oxidase. In addition, it is a mucus membrane and respiratory irritant. Symptoms commonly reported after accidental human exposures include dyspnea, sore throat, coughing, chest pain and signs of pulmonary obstruction. The geometric mean human odor threshold is 0.008 ppm (range, 0.00007 - 1.4 ppm). The mean 4-hour LC_{50} in rats is 440 ppm. Measurements of H_2S after applications of metam sodium showed levels reaching 76 ppb at 1-4 hours post application. The ACGIH TLV and the Cal OSHA PEL for H_2S are set at 10,000 ppb. The short term exposure limit (STEL) is 15,000 ppb. The ATSDR acute and intermediate minimum risk levels (MRLs) of 70 and 30 ppb, respectively, were derived from observations of respiratory effects in humans and mice. They incorporate uncertainty factors based on possible variations in human sensitivity, LOAEL-to-NOAEL extrapolation and species-to-species extrapolation. The chronic REL set by OEHHA is 7 ppb, based on the same mouse study. The OEHHA acute REL and the California Ambient Air Quality standard is 30 ppb for a 1-hour average based on a study of odor threshold in 16 human subjects.

Carbon disulfide (CS_2). Human exposure to carbon disulfide (CS_2) may follow metam applications. CS_2 is a degradation product of metam sodium, particularly under acidic conditions (pH<5). Acute human exposure to CS_2 *via* inhalation leads to local irritation, pharyngitis and CNS toxicity. Such exposure becomes life-threatening after 30 minutes at 3210-3850 ppm and fatal after 30 minutes at 4815 ppm. Oral exposure to 15 ml is also fatal. Dermal and ocular exposure causes severe burns. Oral LD_{50} values are available in rats (3188 mg/kg), mice (2780 mg/kg), rabbits (2550 mg/kg) and guinea pigs (2125 mg/kg). LC_{50} (2-hr) values are 25 g/m^3 in rats and 10 g/m^3 in mice. Central nervous system, cardiovascular, gastrointestinal and immune toxicity result from exposures in humans in the range of 3-320 ppm for periods of months to years. Subchronic and chronic exposures in animals impact the nervous system, cardiovascular system and kidneys. There is no definitive evidence for CS_2-mediated carcinogenicity in humans or animals, though some possibility remains from epidemiologic studies of exposed populations. Reproductive and developmental effects have been reported in humans, though the exposure times are not well-documented. Degenerative nervous system changes are also evident in animal studies. Genotoxicity data were not reported. Measurements of CS_2 after applications of metam sodium showed levels at or below the detection level of 4 ppb. The TLV (TWA) for CS_2 is 10 ppm. The Cal OSHA PEL is 4 ppm, with a STEL (short term exposure limit) of 12 ppm. No ambient air exposure values are available. OEHHA set an acute REL of 2 ppm based on developmental toxicity in the rat.

Methylamine. Like CS_2, methylamine is produced upon cleavage of metam sodium under acidic conditions. Acidic cleavage of MITC will also produce methylamine. This compound is known for its irritancy to eyes, nose and throat upon brief exposures to 20 - 100 ppm. Severe methylamine exposure may lead to pulmonary edema. The oral LD_{50} in rats is 100 - 200 mg/kg. The OSHA PEL for methylamine is 10 ppm. The ACGIH TLV (TWA) is 5 ppm, with a STEL of 15 ppm.

Carbonyl sulfide (COS). Like methylamine, carbonyl sulfide is produced upon cleavage of MITC in the gut. Acute inhalation exposure at levels >1000 ppm can result in fatality due to respiratory paralysis with little warning by way of local irritation or olfaction. Clinical signs following sublethal inhalation include giddiness, headache, vertigo, amnesia, confusion, unconsciousness, salivation, nausea, vomiting, diarrhea, cardiac arrhythmia, albuminuria,

weakness and cramps. Deaths occurred in 3/6 rats exposed to 1000 ppm for 90 minutes. COS administered by intraperitoneal injection as a gas to male rats resulted in an acute LD_{50} of 22.5 mg/kg. Pretreatment with the carbonic anhydrase inhibitor acetazolamide considerably reduced mortality, suggesting that conversion to hydrogen sulfide was an important mediating step in COS toxicity. No information on subchronic/chronic effects in humans was available. A 12-week inhalation study in rabbits exposed to 50 ppm COS did not result in clear adverse effects. No information is available on the carcinogenicity, genotoxicity or developmental / reproductive toxicity of COS. In addition, regulatory limits do not appear to be established.

Plausibility of additive or synergistic toxic effects. Simultaneous exposure of some workers to metam sodium and its primary breakdown products (MITC, MIC, H_2S, CS_2, COS, and methylamine) is plausible. However, because the route of exposure to the latter compounds is likely to be through the air, as opposed to the dermal route postulated for metam sodium, it seems unlikely that irritative synergistic effects involving metam sodium will occur. On the other hand, inhalation co-exposure to any combination of volatile degradation products could elicit additive or synergistic effects, either with each other or with metam sodium that was absorbed through the skin. These might particularly be expected in tissues such as the lung and eye, which are known to be sensitive to the irritative effects of these compounds in isolation. Unfortunately, as no clear experimental or epidemiologic data are available to suggest the presence of, or potential for, additive / synergistic interactions, it can only be said at this point that such effects are plausible.

II. INTRODUCTION

A. CHEMICAL IDENTIFICATION

Metam sodium (sodium N-methyldithiocarbamate) is a fumigant used primarily in agriculture as a preplant treatment to kill soil fungi, nematodes, weed seeds and soil insects (Tomlin, 1997). Application methods include injection, sprinkling and flood irrigation (Alexeeff *et al*, 1992). Metam sodium has also been used as wood preservative, slimicide, tree root killer and aquatic weed killer (US EPA, 1994a). The pesticidal and toxicologic mechanisms are not well-understood, though it is generally agreed that the primary degradation product, methylisothiocyanate (MITC), which evolves as a gas after metam application, provides most of the pesticidal activity. With reference to the dithiocarbamates in general, it is postulated that pesticidal action is dependent on their "being metabolized to the isothiocyanate radical (-N=C-S), which inactivates the -SH groups in amino acids contained within the individual pathogen cells" (Ware, 1983). However, the applicability of this mechanism to the specific case of metam / MITC is unknown.

Metam sodium gained prominence in the public arena following the spill of 19,500 gallons of aqueous 32.7% metam sodium from a ruptured train tank car into the Sacramento River at the Cantara Loop above Dunsmuir, California on July 14, 1991. Over the next 3 days the resultant green slick traversed the 45 miles of river between the rupture point and Lake Shasta to the south, causing enormous damage to the river ecosystem. In addition, area residents reported an array of acute health effects, including headache, eye, throat and nasal irritation, nausea, dizziness, shortness of breath, diarrhea and chest tightness. These were considered likely responses to MITC, a plume of which was released into the ambient air upon dilution of metam in the river water (Alexeeff *et al*, 1992). Other complaints (abdominal pain, diarrhea, rash and cough), lodged a week or more after the spill, were more difficult to attribute unambiguously to MITC since ambient levels were below the reference levels for toxic effects (Alexeeff *et al*, 1992). Effects directly attributable to metam sodium were not reported.

B. REGULATORY HISTORY

Metam sodium was originally registered for use in the United States in 1954 (US EPA, 1994a). In 1994, following an interim evaluation of human risk from agricultural use (DPR, 1994), DPR placed metam sodium and MITC on the restricted use pesticide list because they were considered to pose a danger either to public health or to farm workers, animals, crops or the environment. As a consequence, a use permit must be issued by the county agricultural commissioner after consideration of the proposed application site and use practices. Restrictions requiring buffer zones, reduced application rates and acreage limitations may be required based on the specific conditions under consideration.

On May 15, 1998, metam sodium was listed under Proposition 65 as known to the State of California to cause "reproductive toxicity (developmental toxicity)." In addition, on November 6, 1998, metam sodium was listed under Proposition 65 as known to the state to cause cancer. The US EPA has classified metam sodium as a B2 carcinogen (probable human carcinogen). Finally, on June 21, 2003, both metam sodium and MITC were listed by DPR as Toxic Air Contaminants under Assembly Bill 1807 (The Toxic Air Contaminants Act).

C. TECHNICAL / PRODUCT FORMULATIONS

There were 21 products containing metam sodium registered in California as of June 2004 (DPR, 2004). Metam concentrations in these products range between 15% and 44%. They are intended for use as antimicrobials, bactericides, fungicides, herbicides, insecticides and nematicides. Except for two products that contain dichlobenil at concentrations of 2.2% and 25%, respectively, all current formulations contain metam sodium as the only active ingredient.

D. USAGE

Agricultural use rates in California of metam sodium rose steadily from 5.9 million pounds in 1990 to 15.1 million pounds in 1995 and 17.3 million pounds in 1999. Use then declined to 12.3 million pounds in 2000 and 11.3 million pounds in 2001 (DPR Pesticide Use Report database). Carrots, tomatoes, potatoes, and leafy vegetables consistently registered the highest metam sodium use rates during the 1990s. For example, use rates in 1998 for these commodities were 5.8, 2.7, 1.3, and 1.1 million pounds, respectively (DPR, 2002c). The amount of metam sodium used in non-agricultural application scenarios is not known, though several such uses (*eg.*, wood structural protection, root control, and sewage system sterilization) are approved in California. Nonetheless, it is expected that these amount to a small fraction of the total poundage applied in California.

Metam sodium is converted on a mole-to-mole basis to MITC, which, based on the relative molecular weights of the 2 compounds, results in a conversion rate of approximately 60% by weight. It is thus estimated that an average of 9.3 million pounds per year of MITC was released into the air from agricultural applications of metam sodium in the 1995-1999 period. The health effects of MITC are summarized in this document (sections III.J.1 and IV.C.2). They are analyzed in detail in two risk assessments recently released by DPR (DPR, 2002b and 2003a).

E. ILLNESS REPORTS

In California, there was no separate classification of illnesses or injuries resulting from exposure to metam sodium or MITC. There were 790 illnesses / injuries attributed to exposure to metam sodium / MITC alone and 2 further illnesses / injuries attributed to exposure to metam sodium / MITC in combination with other pesticides (DPR, 2004). According to the 1990-2002 data shown in Table 1, the average annual illness / injury cases classified as definitely, probably or possibly related to metam sodium/MITC exposure totaled 5.5, 49.2 and 6.0, respectively, resulting in an annual average of 60.7 illness / injury cases. The majority of these cases involved residents / bystanders, and were classified as non-occupational exposure (Table 2).The large number of illness / injury drift incident reports in 1999 may be due to the Earlimart (Tulare County) incident, discussed in detail by O'Malley *et al.* (2004). Likewise, the spike in incident reports in 2002 were due to two separate drift incidents in Kern County.

Workers exposed during loading, applying, and field fumigation operations were also subject to illnesses and injury. A pronounced increase in illness / injury reports from non-occupational sources occurred in 1995 and 1996 compared to 1990 - 1994. This effect may be attributable to increased metam use rates over those years, though it is noted that non-occupational incidence rates declined to negligible levels in 1997 and 1998 when metam sodium use remained high

(DPR, 2004).

Illness/injury cases were also grouped according to symptoms experienced by affected persons (Table 3). These cases excluded illnesses / injuries as a result of the 1991 Sacramento River spill. It was assumed that the majority of illnesses / injuries were caused by exposure to MITC because it is the major degradation product of metam sodium after application to soil, though the contribution of other degradation products such as H_2S and MIC to this illness picture is unknown. As noted in previous drafts of the Exposure Assessment covering years up to 1996, a majority of cases referred to as “systemic” include not only systemic symptoms, but also irritative symptoms to the respiratory tract, eyes, or skin (these “systemic plus” reports were discontinued at that time). This is very likely also to be the case after 1996. For example, in 1999, when most of the reports stemmed from the Earlimart incident, irritative symptoms were a very prominent component of the total reports.

Table 1. Case reports received by the CA Pesticide Illness Surveillance Program (PISP) in which health effects were attributed to exposure to metam sodium / MITC (1990-2001)[a]

Year	Illnesses / injuries attributable to metam / MITC			
	Definite[b]	Probable[c]	Possible[d]	Total
1990	6	6	8	**20**
1991	2	2	9	**13**
1992	1	9	8	**18**
1993	14	4	0	**18**
1994	4	5	1	**10**
1995	27	20	1	**48**
1996	9	43	4	**56**
1997	5	12	3	**20**
1998	0	2	2	**4**
1999	1	149	33	**183**
2000	2	6	2	**10**
2001	0	5	2	**7**
2002[e]	1	377	5	**383**
Total	**72**	**640**	**78**	**790**
Average	**5.5**	**49.2**	**6.0**	**60.8**

[a] There were two illnesses / injuries in 1993 attributed to metam / MITC exposure in combination with other pesticides. Thus there were 792 total cases during the 1990-2002 period. These figures did not include illnesses / injuries from the Sacramento River spill of 1991.
[b] "Definite" indicates that the signs and symptoms observed were consistent with the exposure described.
[c] "Probable" indicates a close correspondence between exposure and the signs and symptoms reported.
[d] "Possible" indicates some correspondence between exposure and the signs and symptoms reported.
[e] The following cases were not included for 2002: 15 fieldworkers that could not be classified, 21 residents that remained asymptomatic, and 2 residents that could not be evaluated.

Table 2. Case reports received by the CA PISP in which health effects were attributed to exposure to metam sodium / MITC (1990-2001): Classified according to activities

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

[a] There were two illnesses / injuries in 1993 attributed to metam / MITC exposure in combination with other pesticides. Thus there were 792 total cases during the 1990-2002 period. These figures did not include illnesses / injuries from the Sacramento River spill of 1991.

[b] The following cases were not included for 2002: 15 fieldworkers that could not be classified, 21 residents that remained asymptomatic and 2 residents that could not be evaluated.

Table 3. Case reports received by the CA PISP in which health effects were attributed to exposure to metam sodium / MITC (1990-2001): Classified according to symptoms[a, b]

Year	Systemic	Skin	Eye & eye/skin	Respiratory & resp./eye	Total
1990	8	11	1	0	**20**
1991	4	6	1	2	**13**
1992	8	4	5	1	**18**
1993	10	6	2	0	**18**
1994	3	6	1	0	**10**
1995	40	2	6	0	**48**
1996	22	6	28	0	**56**
1997	10	9	1	0	**20**
1998	2	1	1	0	**4**
1999	161	18	4	0	**183**
2000	7	1	2	0	**10**
2001	4	3	0	0	**7**
2002[c]	1	2	2	378	**383**
Total	**280**	**75**	**54**	**381**	**790**
Average	**21.5**	**5.8**	**4.2**	**29.3**	**60.8**

[a] There were two illnesses / injuries in 1993 attributed to metam / MITC exposure in combination with other pesticides. Thus there were 792 total cases during the 1990-2002 period. These figures did not include illnesses / injuries from the Sacramento River spill of 1991.

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

[c] The following cases were not included for 2002: 15 fieldworkers that could not be classified, 21 residents that remained asymptomatic and 2 residents that could not be evaluated.

F. PHYSICAL / CHEMICAL PROPERTIES - (Technical Grade Active Ingredient (TGAI) [metam sodium dihydrate; solid] and end-use product [32-44% aqueous metam sodium; liquid])

1. Chemical name	Sodium N-methyldithiocarbamate Methyldithiocarbamic acid sodium salt Methylcarbamodithioic acid sodium salt
2. Common name	Metam sodium
3. Trade names	Amvac Metam, Busan 1016, Busan 1020, Busan 1236, Busan 1236W, Clean Crop Metam Sodium, Foam-Coat Vaporooter, ISK-Fume, Metam, Metam 426, Metam CLR 42%, Metam Sodium, Metam Sodium Manufacturer's Concentrate, Nemasol 426, Pole Life, Sanafoam Vaporooter II, Sectagon 42, Sewerout, Sewerout II, Soil Prep IV, Soil-Prep, UCB Metam 32.7% (Soil Fumigant), UCB Metam 42% (Soil Fumigant), VAPAM, VAPAM HL Soil Fumigant, VAPAM Manufacturing Concentrate, Woodfume, Woodfume Plus
4. CAS Registry Number	137-42-8
5. Structural formula	
6. Empirical formula	$C_2H_4NNaS_2$
7. Molecular weight	129.18
8. Physical state	TGAI: solid, colorless crystalline dihydrate (Tomlin, 1997) End-use: liquid, colorless to faint yellow-green (Myers & Johnson, 1985)
9. Density	End-use: 1.1648 g/cm^3 @ 20°C (Myers & Johnson, 1985)
10. Odor	TGAI: acrid garlic-like End-use: "rotten egg," mercaptan-like (Myers & Johnson, 1985)
11. Boiling point	End-use: 111°C @ 783 mmg Hg (Myers & Johnson, 1985)
12. Melting point	TGAI: decomposes without melting (Tomlin, 1994) End-use: n/a
13. pH	TGAI: n/a End-use: 9.0 - 10.5 (OR-CAL, 1987)
14. Specific gravity	End-use: 1.16-1.18 at 68/68°F (20/20°C) (OR-CAL, 1987)

15. Stability	End-use: Stable at pH range above 8.8. Below pH7 conversion to carbon disulfide and amine salts may begin. If acidified, may form hydrogen sulfide gas. Stable at ambient temperatures and atmospheric pressure. Heating will cause decomposition to MITC and CS_2. Prolonged exposure to air will result in gradual decomposition to MITC (OR-CAL, 1987).
16. Flash point	End-use: Did not produce a flash point at the highest temperature obtainable with the apparatus (110°C) (Myers & Johnson, 1985).
17. Solubility	722 g/L H_20 @ 20°C. In acetone, ethanol, kerosene, xylene: <5 g/L. Practically insoluble in most other organic solvents (Tomlin, 1997).
18. Vapor pressure	TGAI: non-volatile (Tomlin, 1997) End-use: 21 mm Hg @ 77°F/25°C (OR-CAL, 1987; Myers & Johnson, 1985)[a]
19. Octanol / water partition coefficient	TGAI: <10 (Tomlin, 1997) End-use: tests done at 2 concentrations (525 and 46 ppm), K_{ow}<0.036 (Myers & Johnson, 1985)
20. Henry's Law constant	End-use: 4.3 x 10^{-6} atm-m^3/g-mol @ 25°C (Myers,1987) 8 x 10^{-6} atm-m^3/g-mol @ 25°C (Tseng, 1986)
21. Corrosion characteristics	End-use: corrosive to brass, copper, zinc and aluminum. May soften or discolor iron (OR-CAL, 1987).

[a] The high vapor pressure of the aqueous end-use product is likely due to properties of the volatile degradation products (*eg.*, MITC, MIC, CS_2 and H_2S).

G. ENVIRONMENTAL FATE

1. Hydrolysis

Hydrolysis rates of aqueous metam sodium were examined at pH 5, 7 & 9 in two separate studies (Myers and Johnson, 1985; Ericson, 1990). In the former study, half-lives ($t_{1/2}$) were 23.8, 180 and 45.6 hours at 25°C and 7.8, 27.4 and 19.4 hours at 40°C. In the latter study, which only examined hydrolysis rates at 25°C, $t_{1/2}$s of 2, 2 and 4.5 days were obtained. Despite the somewhat discrepant data from these two studies, it is clear that aqueous metam is unstable. The more recent Ericson study suggests that the degree of instability is similar at acidic and neutral pHs. A third study examined metam degradation as a function of concentration in aqueous solution (Macpherson and Jones, 1992). At concentrations of 20 and 200 mg/ml, greater than 98% of the parent compound was still present after 20 hours in the dark. At 2 mg/ml, only about 68% was present after 20 hours. At 0.2 mg/ml, 32.3% of the parent compound was present. The pH was not defined in this study.

At pH 5 and 7, methylamine (co-eluting with dimethylurea and dithiomethylurea) and MITC were the major decomposition products of metam sodium (Ericson, 1990). At pH 9, MCDT (methylcarbamo[dithioperoxo]thioate) was noted in addition to the other two compounds. It is unclear why this study does not list carbon disulfide as a product under acidic conditions as it is formed along with methylamine upon scission of the carbon-nitrogen bond. In fact, Chang *et al* (1985), report that the major products of metam sodium hydrolysis at pH 5 were methylamine, MITC (39%) and carbon disulfide (51.2%).

Metam decomposition in soil is highly condition-dependent. MITC generation is favored under conditions of low soil moisture, warm temperature, high clay or organic matter and smaller soil particle size (see review by DPR, 2002c). Reported transformation times have ranged between less than an hour to a full day. Breakdown is almost completely inhibited in moist soil at low temperatures.

2. Photolysis

Myers and Johnson (1985) reported that the $t_{1/2}$ for photolysis under the most hydrolytically stable conditions (pH7, 25°C) was 1.6 hours. The light source was a UV "black light" lamp, which was stated to produce UV radiation and intensity similar to sunlight (Myers and Lee, 1984). Under those same conditions, Chang *et al* (1985) identified the major photolysis products as MITC, N-methylthioformamide, methylamine and elemental sulfur. Minor products included N-methylformamide, carbonyl sulfide, carbon disulfide and hydrogen sulfide. Using a xenon arc lamp to simulate natural sunlight, Spurgeon (1990) determined the photolytic $t_{1/2}$ to be 11.9 minutes (equivalent to 27.8 minutes of natural sunlight). It is not clear why the degradation rate appears to be so much faster in the latter study, though it is possible that there were differences in the nature and delivery of the light. The major photolytic degradates in the Spurgeon study were N-methylformamide, methylamine, MITC and MCDT.

Photolysis does not appear to affect the decomposition of metam sodium in a photoreactor in the presence of thin films of Columbia River Basin loamy sand. Under those conditions, metam sodium had a $t_{1/2}$ of 70 minutes in the light and 63 minutes in the dark, with 69% and 68%, respectively, going to MITC (Haag *et al*, 1989). This indicates as well that photolysis was not depleting MITC. A similar study in which Columbia River Basin sand was treated with ^{14}C-metam sodium and exposed to natural sunlight showed a moderate acceleration of metam breakdown in the presence of light (Burnett and Tambling, 1985). The $t_{1/2}$ was 21.5 minutes and 35.1 minutes for the illuminated and dark controls, respectively. The reason for this apparent discrepancy is not clear, though it is plausible that it may be related to the use of natural sunlight in the latter study.

In contrast to soil, metam decomposition in water was profoundly affected by light (Draper and Wakeham, 1993). Photodegradation half-lives measured in the laboratory ranged from 2.9-8.4 minutes depending on light intensity, whereas in the dark the $t_{1/2}$ was 35 hours.

3. Microbial degradation (aerobic, anaerobic)

The fate of metam sodium under aerobic and anaerobic soil conditions was examined in two studies (Burnett, 1987a and 1987b). In both cases sandy soil obtained from the Columbia River Basin was used. Under aerobic conditions, more than 80% of the radiolabel was recovered as a volatile component, identified as MITC, in an activated charcoal trap. Bound soil residues declined from 6.8% to 1.6% between days 1 and 127, while aqueous residues declined from

3.4% to 0.3%. These decreases were accounted for by the 8.7% of the radiolabel appearing as CO_2 on day 127. The soil half-life of metam sodium was determined to be 23 minutes. Under anaerobic conditions, ~65% of the radiolabel was recovered as MITC. Bound soil residues declined from 13% to 5.9% between days 1 and 60. Aqueous residues decreased from 20.6% to 0.69% over the same period. CO_2 accounted for 16.5% of the radiolabel at 60 days. N,N-dimethylurea was also identified in both studies.

Both of these studies were found unacceptable by DPR under SB 2021 due to flawed methodologies and experimental design.

4. Mobility

The disposition of metam sodium and MITC in the environment has been reviewed in detail by DPR, 2002c. The following represents a summary of the findings in that document (and in other studies), and the appropriate references can be found there.

The fate of metam sodium in soils is highly dependent on the prevailing conditions. An increase in temperature or a decrease in moisture results in an increased rate of decomposition to MITC. MITC production also increased with increased clay content. Gerstl *et al* (1977) characterized the kinetics of metam breakdown in various soil types, concluding that the process was generally very rapid and followed 1st order kinetics. No difference was detected when MITC recovery was compared between soils that had MITC applied *vs.* those that had metam sodium applied. This was interpreted as evidence that the time required for metam breakdown was negligible. In any case, half-lives of 30 minutes or less were observed in soils with low moisture content and high clay or organic matter content.

Like its parent compound metam sodium, the fate of MITC in environmental media was shown to be condition-dependent. Volatilization and hydrolysis were the primary means of transformation in soil. Volatilization rates increased at higher temperatures, in clay and sandy-loam soils, at higher pHs and under drier conditions. MITC distribution in soil was uneven under wet conditions when it was not readily volatilized. This may have been due to breakdown occurring before volatilization. Decomposition times ranged between 0.5 and 50 days depending on soil type, temperature, moisture content and microbial content. The stability of MITC in water decreased with increasing temperature and with the presence of sediment. Hydrolysis was slower at pH 7 than at pH 4 or 10. Photolysis was the primary means of MITC transformation in air where it occurs at a rate over twenty fold greater than the equivalent process in water. The products of gas phase MITC photolysis are methyl isocyanate, methyl isocyanide, methylamine, N-methyl formamide, sulfur dioxide, hydrogen sulfide and carbonyl sulfide. Under simulated sunlight, the photolytic $t_{1/2}$ was 10.5 hours, while under natural sunlight the $t_{1/2}$ was 29 hours.

5. Plant residues / metabolites

Studies have been submitted to DPR investigating the magnitude of metam residues in over 25 crops. Many of these data were summarized in a DPR memorandum (Cheng, 1990). The following paragraphs are quoted from that document:

> "Metam sodium (Vapam) was applied preplant to soils at the maximum label rate of 318 pound a.i. per acre, using either shank-injection, watering can or sprinkler-injection methods for treatment of preplant soils. Seeds or plants were planted 21

to 32 days after soil treatment. Samples were collected during the normal harvest times, which varied from 80 to 279 days, depending on the individual crops. The sites were chosen from those states which lead in producing each crop under study...

"... The analyses of all the samples [of snap beans, cantaloupes, sweet corn, cucumbers, garlic, head lettuce, leaf lettuce, peppermint, potatoes, spinach, strawberries, tomato fruit, and tobacco] showed that the residue levels were found to be below the detection limit of 0.05 ppm for the parent compound, and 0.02 ppm for the major metabolite, methyl isothiocyanate (MITC), in all samples.

"... The results of analyses of all [samples of broccoli, cabbage, mustard greens, green onions, bulb onions, radishes, and turnips] showed that MITC residue levels were less than 0.02 ppm; however, metam sodium residues were detected in all these samples, and ranged from 0.051 ppm in cabbage to 3.50 ppm for mustard greens.... The applicant contends that the detection of these high levels of residues was due to method failures, and offered reasons why metam sodium residues should not be present in the crops: 1) for 11 out of 13 other crop groupings, no residues of metam sodium were detected; 2) the new plant metabolism study "Investigations of the Residues of Metam sodium in Chinese Cabbage Grown on Pretreated Soil" indicate that total radioactivity incorporated is well below 0.001 ppm; 3) the half-life of metam sodium in soil has been measured in terms of hours. Therefore, crops harvested 80 to 120 days after planting are unlikely to have residues on metam sodium.

"... CONCLUSION: ... While realizing it may be true that the residue method gives false positive results for metam sodium residues for 3 crop groupings, 1) brassica leafy vegetables (broccoli, cabbage and mustard greens), 2) bulb vegetable (onions) and 3) some tuber vegetables (Turnips and radishes), up to 3.50 ppm of parent compound residue were detected in the samples, which can hardly be ignored. It is suggested a new, effective method should be developed or the current method adequately modified to confirm that residues are not present."

The conclusion of a later study that examined the fate in turnips of a preplanting soil treatment with metam sodium (Davis and Campbell, 1995; see also the corresponding DPR memorandum, by Leffingwell, 1995) was that no measurable residue of the parent compound could be identified in the resultant plants. The radioactive residue found in the plants was determined to be in natural products such as sugars, starch, cellulose / hemicellulose, pectin, proteins and lignin, interpreted as evidence that the metam had broken down in the soil and the radioactive label entered the general soil carbon pool before uptake. This conclusion is tempered, however, by the knowledge that unusually cold weather caused a virtual stop in turnip growth, necessitating the transfer of the plants into greenhouses. As stated in the DPR memo: "As a consequence of the substantial shift in planting season, the rate of development of the turnips and the aging of the metam sodium-related soil residues inevitably were put out of sync, not only likely affecting the amount of radioactive residue which the crop took up, but possibly changing the nature of the residues to which it was exposed, as well."

In the absence of tolerances, and until further refinements of the analytical techniques are achieved, it is considered likely that, based on the bulk of crop measurements and on the

physico-chemical properties of metam sodium, residues of this compound would exist, if at all, only at low levels. Consequently, a dietary assessment was not performed for this risk evaluation.

III. TOXICOLOGY PROFILE

A. PHARMACOKINETICS

1. Introduction

While no FIFRA (Federal Insecticide, Fungicide and Rodenticide Act) guideline standard metabolism studies were submitted by the registrants, an oral-dose metabolism study in rats (Hawkins *et al*, 1987; reviewed in sections B-E below) and an intraperitoneal-dose metabolism study in rats and mice (Lam *et al*, 1993; reviewed in section G below) were available. In addition, a single-dose dermal absorption study in rats using metam was also examined (Stewart, 1992; reviewed in section F below). In the environment, and after oral administration to animals, the major metam sodium degradate is methyl isothiocyanate (MITC). For this reason, the pharmacokinetic fate of MITC and metam sodium were examined together in the Hawkins and Lam studies. The fate of orally administered dazomet was also examined in the Hawkins study (see section 8 below).

2. Absorption (Oral exposure)

The oral-exposure metabolism study compared the absorption, tissue distribution, and excretion of metam sodium and MITC (Hawkins, *et al*, 1987). Rats were given radiolabeled metam sodium (>99%, labeled at the thiocarbonyl carbon) at 10 or 100 mg/kg, or MITC (labeled at the thiocyanate carbon) at 4.4 or 33 mg/kg, by gastric gavage. Feces were collected at 24-hour intervals up to 7 days. Expired air was collected at 24-hour intervals for up to 3 days, passing through a series of 3 traps capable of selectively capturing MITC, CO_2 and carbonyl sulfide + CS_2, respectively. Tissue levels were also determined at the end of the study. Recoveries of excreted metam and its metabolites (% of dose) are summarized in Table 4.

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

3. Distribution (Oral exposure)

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

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

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

4. Biotransformation (Oral exposure)
The same urinary metabolites were identified for both compounds, although there were some differences in the relative proportions. Neither parent compound was present in the urine. A single major metabolite (M5) represented 16-25% of the dose for metam sodium and 56-66% of the dose for MITC. There was only one other metabolite (M4) formed in appreciable amounts from both compounds, representing 5-10% of the dose. There was no evidence for the presence of glucuronides or sulfate conjugates. M5 was identified as N-acetyl-S-(N-methylthiocarbamoyl)-L-cysteine. M4 was shown to chromatographically match the corresponding cysteine conjugate. It was suggested that the metam sodium underwent acid hydrolysis in the stomach to form MITC and CS_2, but that a portion of the metam sodium may have been absorbed intact. This would explain the slower excretion and the dose-dependent excretion compared with MITC (Wagner, 1989).

No toxicity data were available for these cysteine conjugates.

5. Excretion (Oral exposure)
Following oral exposure to MITC the radioactivity was principally eliminated in the urine (see below) and in the expired air (as CO_2). With metam sodium, 52-58% of the low dose and 37-42% of the high dose was recovered in the urine. Expired air accounted for 33-38% of the low dose and 47-53% of the high dose. Much of the increase at the high dose was accounted for by a marked increase in the excretion of MITC. Other expired metabolites included CO_2, carbonyl sulfide and carbon disulfide (see Figure 1) (Jowa, 1992).

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

As indicated above, the Hawkins study did not completely satisfy FIFRA guidelines because no multiple dosing regime was conducted. However, the study did provide useful information on the pharmacokinetics of metam / MITC in rats.

6. Dermal absorption
The extent of absorption of metam sodium after dermal exposure was examined in the rat in a separate study (Stewart, 1992). A detailed analysis of this study is provided in DPR's Exposure Assessment document (DPR, 2003c). In summary, rats were treated dermally with ^{14}C-metam sodium and sacrificed at a series of times up to 72 hours post dose. Absorption, assessed by determining the radioactivity in urine, feces, blood, carcass and bound to skin, was essentially complete by 1 hour. The corrected dermal absorption value of 2.5% for the lowest dose (8.6 μg/cm^2) was considered appropriate for use. Nonetheless, the precise chemical nature of the absorbed compound(s) was not clear. Such a determination may be important, as oral studies indicate that metam sodium and MITC vary in their oncogenic effects (see sections III.D., III.J.2., IV A. 6., and V.B.3.).

7. Intraperitoneal exposure

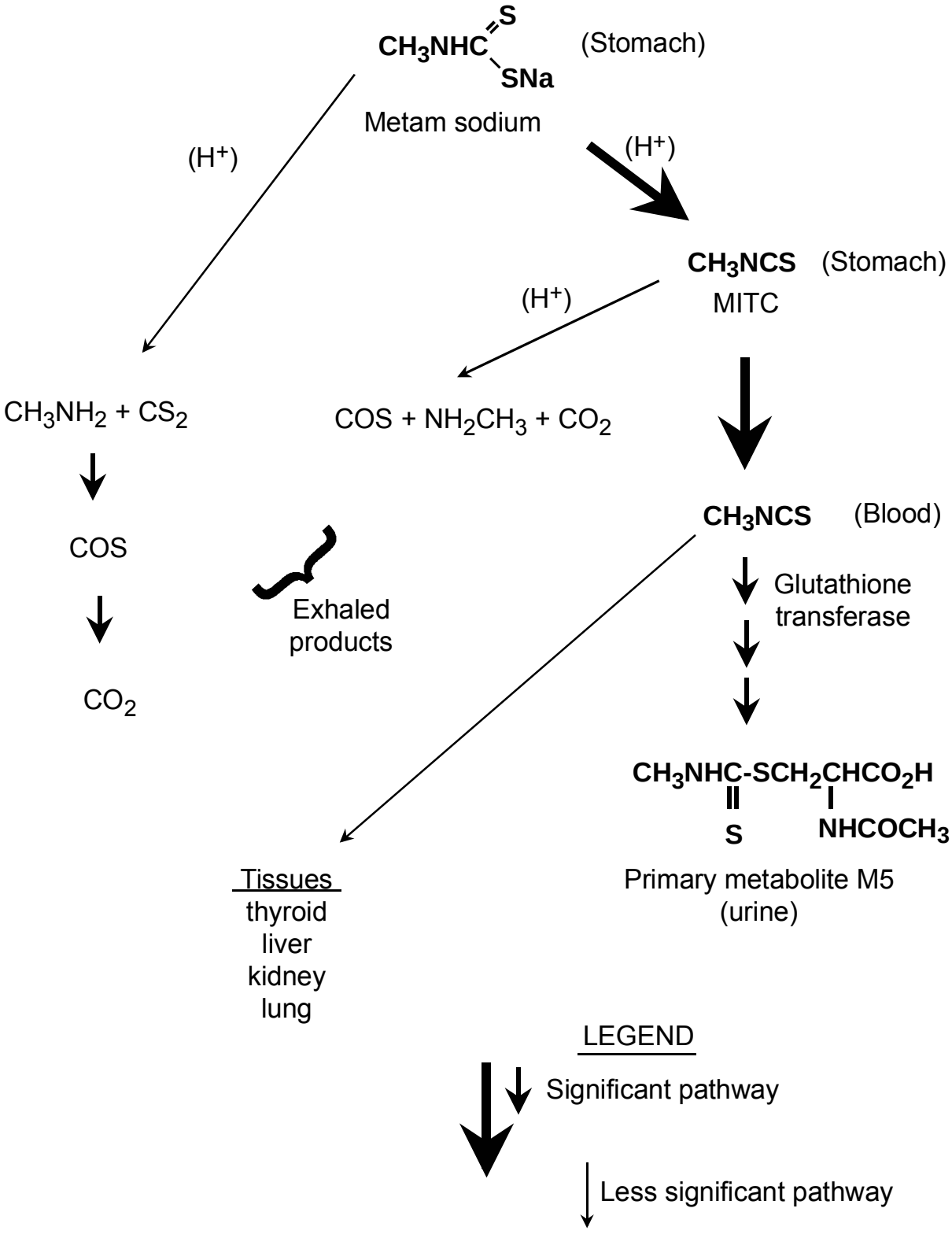
A study from the open literature (Lam *et al*, 1993) determined the fate of radiolabeled metam sodium and MITC following intraperitoneal injection of mice (Swiss-Webster, male) and rats (Sprague-Dawley, male). A mean value of 58% of the metam and 80% of the MITC was excreted in mouse urine by 48 hours. Feces, expired CO_2 and carcass accounted for 6, 5 and 7.5% of the total metam dose, respectively, and 5, 4 and 6% of the total MITC dose in mice. While widely distributed among tissues, liver, kidney and, interestingly, hair, accounted for the largest proportions of the tissue fraction for both metam and MITC. Metabolite studies identified the conversion to the GSH conjugate as common to both compounds, resulting in mercapturates in the urine. Methylamine and other unidentified metabolites were also detected in urine. Quantitative differences in the relative proportions of mercapturate, methylamine, unidentified polar metabolites and other unidentified metabolites were observed between mice and rats.

Table 4. Mean absorption, excretion and retention of radioactivity (% of dose) following gavage exposure to metam sodium or MITC (n=5) (Hawkins *et al*, 1987)

	Metam sodium				MITC			
	10 mg/kg		100 mg/kg		4.4 mg/kg		33 mg/kg	
	M	F	M	F	M	F	M	F
Urine								
0 - 8 hr	24.19	26.04	17.83	19.17	71.43	73.65	58.76	54.62
0 - 24 hr	46.49	53.34	33.83	38.34	80.68	82.45	81.69	80.13
0 - 168 hr	52.02	58.09	37.34	42.42	84.43	86.36	87.09	85.57
Expired air (Trap 1: MITC)								
0 - 24 hr	0.37	1.12	23.91	23.39	0.69	1.24	0.49	1.20
0 - 72 hr	0.45	1.26	24.53	24.04	0.95	1.51	0.72	1.67
Expired air (Trap 2: CO_2)								
0 - 24 hr	18.44	17.03	6.68	5.00	15.24	14.09	6.78	6.53
0 - 72 hr	19.56	18.13	7.20	5.53	16.08	14.88	7.32	7.23
Expired air (Trap 3: COS + CS_2)								
0 - 24 hr	17.99	13.55	20.41	17.00	0.04	0.04	0.29	0.33
0 - 72 hr	18.35	13.80	21.34	17.63	0.05	0.04	0.43	0.48
Amount absorbed (minimal estimate*)								
0 - 24 hr	83.29	85.04	84.83	83.73	96.65	97.82	89.25	88.19
0 - 168 hr	90.38	91.28	90.41	89.62	101.5	102.8	95.56	94.95
Feces								
0 - 24 hr	2.98	0.83	0.96	0.66	1.99	0.66	1.13	0.93
0 - 168 hr	4.48	2.88	1.87	1.57	2.74	1.45	1.93	1.83
Cage washings (total)	0.10	0.05	0.06	0.04	0.15	0.07	0.18	0.15
Tissues (168 hr)	2.01	1.75	1.17	1.32	2.20	1.86	1.71	2.29
Total recovery	96.96	95.95	93.50	92.55	106.6	106.2	99.37	99.22

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

Figure 1. Proposed degradation / metabolic pathways for metam sodium and MITC (redrawn from Jowa, 1992).



B. ACUTE TOXICITY

1. Technical / End-product Formulations

"Technical" metam sodium exists only in aqueous formulations ranging in concentration between 32% and 44%. A series of acute systemic toxicity and primary eye and dermal irritation studies on seven such aqueous formulations form the basis for the analysis below. Formulations registered in California containing less than 32-44% metam also contain either 14.5% cyanodithioimido carbonate (one product) or 2.2-25% dichlobenil (2 products) (DPR, 2002a). These will not be discussed further.

2. Acute oral toxicity

The lowest oral LD_{50} value in male rats was 781 mg/kg using Metam Sodium Technical (42.0%) (Kuhn, 1989). The lowest female rat LD_{50} value was 790 mg/kg using Sectagon 42 (42.2% metam sodium) (Noonan, 1993). An acute NOEL value could not be established from these studies because evidence of toxicity was nearly always present at the lowest dose tested (LDT). A LOEL of 500 mg/kg was established in 2 separate studies based largely on what appeared to be cholinergic signs: depression, activity decrease, ptosis, salivation, piloerection, lacrimation, miosis, upward spinal curvature, and decreased breathing rate. Necropsies revealed discoloration, adhesion and thickening of internal organs, lung and kidney cysts, inappropriate fluid in the bladder and thoracic cavity, and lung congestion. Acute oral studies are summarized in Table 5a.

3. Acute dermal toxicity

Metam sodium exhibits clear acute dermal toxicity to the rabbit, with 3 separate studies showing LD_{50} values less than 2000 mg/kg. One rabbit study identified depression and ataxia occurring at the LDT of 794 mg/kg (Morgan, 1985), thus comprising a LOEL for that study. This was corroborated in another rabbit study in which death occurred in 1/10 animals within 24 hr of dosing at an LDT of 1000 mg/kg (Noonan, 1983). Two rat studies both showed LD_{50}s > 2000 mg/kg. Local irritation was observed in both species, though again, a NOEL could not be determined because the effects were seen at the LDT. Lesions noted upon necropsy were both systemic and local, and included mottled liver and thymus, rough-textured, abscessed or necrotic liver, pale/red lungs, stomach spots or hemorrhage, congested heart, red or gas-filled intestines, oral and nasal staining, oral abscess, white material in stomach and cecum, red material in trachea, subcutaneous hemorrhage, scabs and ulcerations, and fascia fibrinous and adhered to muscle. Acute dermal studies are summarized in Table 5b.

4. Acute inhalation toxicity

LC_{50} values in rats as low as 2.20 mg/L (male; Metam Sodium, 43.8% a.i.) and 2.24 mg/L (female; Metam Sodium Technical, 42.0% a.i.), placing these compounds into the Toxicity Category II category, attest to the toxicity of metam sodium by this route of exposure. Again, only LOELs were established due to effects noted at the LDT. The lowest LOEL was 1.23 mg/L in the Metam Sodium study of Jackson and Hardy (1992), based on piloerection, exaggerated or noisy respiration, gasping, lethargy, eye discharge, swollen forepaws, and reduced weight and food/water consumption. Necropsies were occasionally negative (see Coate, 1983 and Parr-Dobrzanski, 1994), but also revealed congested, swollen, discolored, edematous and/or mottled lungs, gas and discoloration in the gastrointestinal tract, and liver edema. Histopathology carried out in one study (Jackson, G.C. and Hardy, C.J., 1992)

revealed alveolar congestion/edema, bronchial epithelial necrosis, and foci of alveolar macrophages, and eosinophilic crystals, centrilobular or periportal hepatocyte vacuolation and degeneration or necrosis in the liver. Acute inhalation studies are summarized in Table 5c.

5. Local irritation

Primary eye irritation. Three of the 7 studies show these metam formulations to be Toxicity Category III eye irritants (corneal involvement or irritation for 1-7 days using 0.1 ml/eye), while the remainder show a Toxicity Category IV irritation potential (no corneal involvement, minor effects clear within 24 hr).

Primary dermal irritation. Primary dermal studies show an inexplicable range of toxicity categories, with 4 Category I (corrosive, tissue damage or scarring), 1 Category II (severe irritation at 72 hr) and 2 Category IV (mild irritation at 72 hr). Because there are no apparent differences in inert ingredients, these inconsistencies may be due to differing concentrations of impurities, to uncontrolled lability of metam sodium at the test site, or to unknown variabilities in laboratory practice. However, without further clarification of these contradictory findings, metam formulations should continue to be regarded as corrosive (Toxicity Category I).

Primary eye and dermal irritation studies are summarized in Table 5d.

6. Dermal sensitization

Four of the 5 dermal sensitization studies in guinea pigs gave positive responses. Metam sodium is therefore considered to be a sensitizer. Schubert (1978) reports a similar result in humans, considering MITC to be the probable main, and metam sodium the secondary, effector. Dermal sensitization studies are summarized in Table 5e.

Table 5a. Summary of acute oral toxicity studies with metam sodium formulations

Test article	[Metam]	Species	LD_{50}	NOEL/LOEL (determining signs)	Ref.
Busan 1020	33% (aqueous formulation)	Rat	M: 1.26 g/kg F: 1.17 g/kg	LOEL = 0.62 g/kg (hypoactivity, ataxia, miosis, dyspnea, lacrimation	Hazleton Labs., 1983a
Metam Sodium 42% SL	42.16% (aqueous formulation)	Rat	M: 1231 mg/kg F: 1414 mg/kg	LOEL = 500 mg/kg (miosis, lacrimation, ptosis, piloerection, salivation, upward spinal curvature, decreased breathing rate)	Robinson, 1994a
Metam Sodium	533 g/L (43.8% w/w) (aqueous formulation)	Rat	M: 870 mg/kg F: 924 mg/kg	LOEL = 640 mg/kg (piloerection, hunched posture, waddling, lethargy, decreased respiratory rate, ptosis, pallor of extremities, salivation)	Baldrick & Healing, 1991a
Vapam Technical	32.3% (aqueous formulation)	Rat	M: 1294 mg/kg F: 1428 mg/kg	LOEL = 891 mg/kg (depression, hypersensitivity, ptosis, salivation, piloerection, lacrimation, snuffles)	Morgan, 1985
Metam Sodium Technical	42.0% (aqueous formulation)	Rat	M: 781 mg/kg F: 845 mg/kg	LOEL = 500 mg/kg (piloerection, activity decrease, salivation, diarrhea, nasal discharge, ptosis, lacrimation, miosis)	Kuhn, 1983a
Metam Sodium	32.7% (aqueous formulation)	Rat	M: 1415 mg/kg F: 1350 mg/kg	NOEL = 1200 mg/kg (lung mottling, gas/fluid-filled stomach) *Note: can't find clinical signs*	Deenihan, 1987a
Sectagon 42	42.2% (aqueous formulation)	Rat	M: 970 mg/kg F: 790 mg/kg	LOEL = 700 mg/kg (rough coat, crusted eye discharge, lethargy)	Noonan, 1993a

Table 5b. Summary of acute dermal toxicity studies with metam sodium formulations

Test article	[Metam]	Species	LD_{50}	NOEL/LOEL (determining signs)	Ref.
Busan 1020	33% (aqueous formulation)	Rabbit	M; 1.47 g/kg F: 1.53 g/kg	systemic NOEL = 1.02 g/kg (death) local LOEL = 1.02 g/kg (irritation)	Hazleton Labs., 1983b
Metam Sodium 42% SL	42.16% (aqueous formulation)	Rat	M/F > 2000 mg/kg	systemic NOEL > 2000 mg/kg local LOEL = 2000 m/kg (irritation)	Robinson, 1994b
Metam Sodium	533 g/L (43.8% w/w) (aqueous formulation)	Rat	M/F > 2 g/kg	systemic LOEL = 2 g/kg (death, hypothermia) local LOEL = 2 g/kg (irritation)	Baldrick & Healing, 1991b
Vapam Technical	32.3% (aqueous formulation)	Rabbit	M: 1163 mg/kg F: 1270 mg/kg	systemic LOEL = 794 mg/kg (depression, ataxia) local LOEL = 794 mg/kg (irritation)	Morgan, 1985
Metam Sodium Technical	42.0% (aqueous formulation)	Rabbit	M/F > 2020 mg/kg	systemic NOEL > 2020 mg/kg	Kuhn, 1989b
Metam Sodium	32.7% (aqueous formulation)	Rabbit	M: 3500 mg/kg F: 2100 mg/kg	concentration dependence of signs not provided	Deenihan, 1987b
Sectagon 42	42.2% (aqueous formulation)	Rabbit	M; 1050 mg/kg F: 1100-1250 mg/kg	systemic LOEL = 1000 mg/kg (death) local LOEL = 1000 mg/kg (irritation)	Noonan, 1993a

Table 5c. Summary of acute inhalation toxicity studies with metam sodium formulations

Test article	[Metam]	Species	LC_{50}	NOEL/LOEL (determining signs)	Ref.
Busan 1020	33% (aqueous formulation)	Rat	M/F > 7.94 mg/L (> ~1.27 g/kg/4-hr exposure[a])	LOEL = 7.94 mg/L (~1.27 g/kg/4-hr exposure[a]) (languidity, salivation, dyspnea during exposure)	Coate *et al*, 1983
Metam Sodium 42% SL	42.16% (aqueous formulation)	Rat	M/F > 6.29 mg/L (> ~1.03 g/kg/4-hr exposure[a])	LOEL = 6.29 mg/L (~1.03 g/kg/4-hr exposure[a]) (decreased activity, lacrimation, salivation, respiratory noise, erythema, hunched posture, piloerection, ungroomed)	Parr-Dobrzanski 1994
Metam Sodium	533 g/L (43.8% w/w) (aqueous formulation)	Rat	M: 2.20 mg/L (~0.36 g/kg/4-hr exposure[a]) F: 2.95 mg/L (~0.48 g/kg/4-hr exposure[a])	LOEL = 1.23 mg/L (~0.20 g/kg/4-hr exposure[a]) (piloerection, exaggerated or noisy respiration, gasping, lethargy, eye discharge, swollen forepaws, reduced weight and food/water consumption)	Jackson & Hardy, 1992
Vapam Technical	32.3% (aqueous formulation)	Rat	M/F > 4.7 mg/L (> ~0.77 g/kg/4-hr exposure[a])	LOEL = 4.7 mg/L (~0.77 g/kg/4-hr exposure[a]) (depression, blood-like facial stains, dyspnea, prostration, weight decrement, lung foci)	Miller, 1979
Metam Sodium Technical	42.0% (aqueous formulation)	Rat	M: 2.36 mg/L (~0.39 g/kg/4-hr exposure[a]) F: 2.24 mg/L (~0.37 g/kg/4-hr exposure[a])	LOEL = 1.90 mg/L (~0.31 g/kg/4-hr exposure[a]) (piloerection, ptosis, activity decrease, salivation, gasping, lacrimation, polyuria, gurgle, GI distention, lung discoloration)	Holbert, 1989

Metam Sodium	32.7% (aqueous formulation)	Rat	M/F > 5.43 mg/L (> ~0.89 g/kg/4-hr exposure[a]) (*study not acceptable; no particle size data*)	LOEL = 5.43 mg/L (~0.89 g/kg/4-hr exposure[a]) (respiratory signs, mottled lungs, head swelling)	Rothstein, 1987
Sectagon 42	42.2% (aqueous formulation)	Rat	M/F > 4.92 mg/L (> ~0.80 g/kg/4-hr exposure[a])	LOEL = 4.92 mg/L (~0.80 g/kg/4-hr exposure[a]) (decreased activity, irregular respiration, anogenital staining, lethargy, hunched posture, lung/liver discoloration and edema, intestinal blood vessel injection)	Wnorowski 1993

[a] Conversion assumes the breathing volume of a 0.25 kg rat to be 960 L/kg/day. Thus for Busan 1020 the actual test article intake is estimated as: (960 L/kg/day) (.00794 g/L) (0.17 *[this factor converts a 24-hr exposure to a 4-hr exposure*]) = 1.27 g/kg/4-hr exposure.

Table 5d. Summary of primary eye and dermal irritation studies with metam sodium formulations

Test article	[Metam]	Species	Tox. Category (eye irritation)	Tox. Category (dermal irritation)	Ref.
Busan 1020	33% (aqueous formulation)	Rabbit	III	I	Hazleton Labs., 1993c (eye); Hazleton Labs., 1993d (dermal)
Metam Sodium 42% SL	42.16% (aqueous formulation)	Rabbit	III	IV	Robinson & Leigh, 1994a (eye); Robinson & Leigh, 1994b (dermal)
Metam Sodium	533 g/L (43.8% w/w) (aqueous formulation)	Rabbit	III	I	Liggett & McRae, 1991a (eye); Liggett & McRae, 1991b (dermal)
Vapam Technical	32.3% (aqueous formulation)	Rabbit	IV	I	Morgan, 1985 (eye & dermal)
Metam Sodium Technical	42.0% (aqueous formulation)	Rabbit	IV	II	Kuhn, 1989c (eye); Kuhn, 1991 (dermal)
Metam Sodium	32.7% (aqueous formulation)	Rabbit	IV	I	Deenihan, 1987c (eye); Deenihan, 1987d (dermal)
Sectagon 42	42.2% (aqueous formulation)	Rabbit	IV	IV	Noonan, 1993a (eye & dermal)

Table 5e. Summary of dermal sensitization studies with metam sodium formulations

Test article	[Metam]	Species	Response	Ref.
Busan 1020	33% (aqueous formulation)	—[a]	---	---
Metam Sodium 42% SL	42.16% (aqueous formulation)	guinea pig	positive	Robinson & Leigh, 1994c
Metam Sodium	533 g/L (43.8% w/w) (aqueous formulation)	guinea pig	positive	Parcell & Denton, 1991
Vapam Technical	32.95% (aqueous formulation)	guinea pig	positive	Mutter, 1987
Metam Sodium Technical	42.0% (aqueous formulation)	guinea pig	negative	Kuhn, 1989d
Metam Sodium	32.7% (aqueous formulation)	---	---	---
Sectagon 42	42.2% (aqueous formulation)	guinea pig	positive	Noonan, 1993b

[a] Dermal sensitization data not available.

C. SUBCHRONIC TOXICITY

1. Rat - Gavage (11-day)

In an 11-day range-finding gavage study (Cave, 1991a), 4 rats/sex/group were administered 32.8% metam sodium at 20, 50, or 200 mg/kg/day (no controls). Salivation was noted, particularly after dosing at 50 and 200 mg/kg/day. Food consumption and body weights were reduced at 200 mg/kg/day. Relative spleen, kidney and liver weights were increased at the high dose. Ulceration of the non-glandular stomach was present at 50 and 200 mg/kg/day, while ulceration of the glandular stomach was seen only in high dose females. Based on post-dosing salivation and stomach ulceration, the NOEL was set at 20 mg/kg/day. This study was deemed supplemental due to a lack of guidelines for a study of this nature.

2. Rat - Drinking water (21-day)

In a 21-day range-finding study (Cave, 1991b), metam sodium (32.8%) was initially administered to 5 rat/sex/group in pH 9 drinking water at 0, 1, 3, or 6 mg/ml for 2 days. The doses were changed to 0, 0.1, 0.3, or 0.7 mg/ml after a 5-day rest period, since the rats would not drink the water containing metam sodium at the original dosages. After the change in dosage, the 0.1 and 0.3 mg/ml doses were accepted by the animals in a dose-dependent manner during the next 21 days. The 0.7 mg/ml level was still not accepted, so after 72 hours at 0.7 mg/ml the animals were returned to untreated water and sacrificed at study termination. The average dose received per rat over the whole duration of the study was 10.5 and 26.7 mg/kg/day for the 0.1 and 0.3 mg/ml dose groups, respectively. Decreased body weight gain and water consumption were noted at 0.1 and 0.3 mg/ml Decreased food consumption was noted at 0.3 mg/ml. Organ weights did not appear to be affected at 0.1 and 0.3 mg/ml. Based on the decreased body weight and water consumption the LOEL was 10.5 mg/kg/day. This study was deemed supplemental due to a lack of guidelines for a study of this nature.

3. Rat drinking water (90-day)

In a 90-day range-finding study (Allen, 1991), metam sodium (concentration 525.54 g/l) was administered to 12 rats/sex/group in pH 9 drinking water at 0, 0.018, 0.089, or 0.443 mg/ml. The mean doses were stated to be 0, 1.7, 8.1, or 26.9 mg/kg/day for males and 0, 2.5, 9.6, and 30.6 mg/kg/day for females. However, due to the instability of metam sodium in drinking water, the nominal doses of metam sodium received could only be considered approximations of the actual internal dose. Analysis of metam sodium stability in drinking water bottles indicated that, depending on the concentration, 15.0-70.9% of the chemical was lost by 24 hours. The mean dose of metam sodium actually received would then have been lower and could have been as low as 0, 0.49, 3.10 and 18.51 mg/kg/day for males and 0, 0.73, 3.68 and 21.05 mg/kg/day for females (these values were calculated from the 24-hr decay data measured on a single occasion)[1].

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[1]These values were calculated for both the rat and the mouse 90-day drinking water studies from the nominal concentrations using measurements of the maximum 24-hour degradation rates in water bottles. The degradation rates, which were determined in an assay performed in parallel with both studies, were highly dependent on the initial metam sodium concentration in the water bottle. If that concentration was less than 0.1 mg/ml, approximately 60-70% of the metam was shown to disappear after 24 hours. If the concentration was more than 0.1 mg/ml, degradations of 32% or less occurred within that time period. While it was stated in the study that the drinking water containing the test article was changed daily, the *time* of the change was not provided, nor was there any indication as to how long after each change the water was consumed by the mice. When combined with the lack of sub-24-hour degradation curves, there was no way to accurately gauge the quantity of metam that the animals

Clinical signs (subdued behavior, nasal staining and thinness) occurred in both sexes at the high dose. Mean high dose body weights were significantly less than controls by week 2 in both sexes. By week 14, high dose males weighed 78% of controls ($p<0.05$) and high dose females weighed 79% of controls ($p<0.05$). Mid-dose females also showed a statistically significant weight deficit during the second half of the study, though by week 14 the deficit was less than 4% ($p<0.01$). Food consumption was statistically suppressed in both sexes at the high dose (16-46%), with greater inhibition occurring toward the beginning of the study. Water consumption was reduced by 50-70% in both sexes at 0.443 mg/ml, by 30% in females at 0.089 mg/ml, and may have been marginally reduced in females at 0.018 mg/ml, though the latter values never achieved statistical significance.

Statistically significant reductions in the following serum parameters were measured in males at 0.443 mg/ml: alkaline phosphatase (16%), alanine aminotransferase (12%), aspartate aminotransferase (15%), and glucose (13%). A statistically significant reduction (9%) in cholesterol occurred in high dose females, along with significant increases in urea (55%) and triglycerides (33%). Slight, though statistically significant, decreases in red blood cell counts were present at all dose levels for females (4%, 4% and 5% at ascending doses) and at 0.089 (5%) and 0.443 mg/ml (6%) for males, and hematocrits were decreased at all dose levels in both sexes (up to 3%). The degree of the anemia at the higher dose levels may actually have been more pronounced than would be indicated from the data, as dehydration secondary to decreased food and water intake may have precluded an accurate determination of RBC numbers. According to the study authors, “the very minor changes [in RBCs and hematocrit] at the low doses are too small to be of haematological significance and, in view of the small magnitude and minimal dose relationship, none of the effects [at the low dose] can be directly attributed to compound.” Urinalysis revealed the following statistically significant changes at 13 weeks: (a) decreases in urine volume in high dose males and mid and high dose females (up to 50%), (b) decreases in urine pH in high dose males (6.46 in controls to 6.06 at the high dose), and (c) increases in urine specific gravity in high dose males and mid and high dose females (up to 13%). These changes were likely secondary to the reduction in water intake and of unclear toxicologic significance, though it is also possible that there may be some relation to the purported renal effects discussed in the next paragraph.

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consumed. For example, at the mouse NOEL and LOEL doses of 0.018 and 0.088 mg/ml, the only assurance was that the animals were drinking water containing between 29.1% and 100% of the initial concentration. In the interest of establishing a health-conservative NOEL, it was therefore assumed that *maximum* degradation had occurred by the time the mice drank the water. Thus, at the nominal concentration of 0.018 mg/ml, the initial analyzed concentration was 0.022 mg/ml. After 24 hours the metam concentration had declined to 0.0063 mg/ml, or 29.1% of the initial concentration. Using mean data provided in the study, it was stated that the metam sodium consumption at that dose was 2.7 mg/kg/day. This value was derived by the study authors using only the initial metam concentration, the body weights appropriate to that point in the study, and the measured water consumption rates. Assuming maximum degradation, the “actual” metam consumption was calculated to be 0.291 x 2.7 = 0.79 mg/kg/day. At 0.088 mg/ml, the initial analyzed concentration was 0.081 mg/ml. After 24 hours the concentration was 0.031 mg/ml, or 38.3% of the initial concentration. The stated consumption at that dose was 11.71 mg/kg/day, making the “actual” consumption 0.383 x 11.71 = 4.48 mg/kg/day. It is fully recognized that these NOEL and LOEL values may underestimate the actual values.

An increase in renal epithelial cells in the urinary sediment in both sexes at the high dose and possibly at the mid dose (male incidence: 1/12, 0/12, 2/12, 10/12; female incidence: 0/12, 0/12, 2/12, 8/12) was plausibly a function of renal toxicity. A small statistically significant increase (17%) in kidney weight adjusted for body weight occurred in females at 0.443 mg/ml. Histologically, an increase in the incidence of minimal renal tubular basophilia was noted (males: 1/12, 2/12 in controls and high dose animals; females: 0/12, 3/11). Combined with the presence of epithelial cells in the urine, these data indicate that the kidney is a possible target organ for metam. However, the major target site appears to be the nasal cavity; lesions consisting of disorganization of the olfactory epithelium and prominent or vacuolated Bowman's glands, were present in up to 5/12 males and 11/11 females at 0.443 mg/ml (and absent among controls). The investigators concluded that the nasal cavity changes suggested a systemic, rather than a direct local effect because the posterior nasal cavity was reported to be more severely affected than the anterior. Another possible explanation for the lesions, also based on their location, is induction by exposure to the metam metabolite methyl isothiocyanate during exhalation.

Body weight, water consumption, and urinary effects at 0.089 mg/ml place the nominal NOEL for this study at 0.018 mg/ml (estimated to be as low as 0.49 mg/kg/day due to compound instability). This study was considered acceptable under FIFRA guidelines.

4. Mouse - Drinking water (90-day)

In a 90-day range-finding study with a 28-day interim sacrifice (Whiles, 1991), metam sodium (concentration 525.54 g/l) was administered to 15 mice/sex/group in pH 9 drinking water at 0, 0.018, 0.088, 0.35, or 0.62 mg/ml. 5/sex/group were scheduled for the 28-day interim sacrifice. The mean doses were stated to be 0, 2.7, 11.7, 52.5, or 78.7 mg/kg/day for males and 0, 3.6, 15.2, 55.4, or 83.8 mg/kg/day for females. However, due to the chemical instability of metam sodium in drinking water, the nominal doses of metam sodium received could only be considered approximations. Analysis of the stability of metam sodium in drinking water bottles indicated that, depending on the concentration, 15-70.9% of the chemical was lost by 24 hours. The mean dose of metam sodium actually received would then have been lower and could have been as low as 0, 0.79, 4.48, 36.05 and 60.36 mg/kg/day for males and 0, 1.05, 5.82, 38.12 and 64.27 mg/kg/day for females (these values were calculated from the 24-hr decay data measured on a single occasion)[1].

Mean body weights were reduced by up to 13% and 11% (males and females) at 0.62 mg/ml and up to 9% and 8% at 0.35 mg/ml, achieving statistical significance in both sexes and both doses. Statistically significant suppression of food consumption was registered in high dose males at weeks 1, 3 and 13, and in high dose females at weeks 1, 3 and 9. Overall mean food consumption at 0.35 and 0.62 mg/ml was 99% and 95% of controls in males and 91% and 86% of controls in females. Total water consumption at the top 3 doses was suppressed by 10%, 4% and 21% in males and by 21%, 28% and 40% in females. Except for the high dose females, where the suppressive effect was expressed throughout the 13-week study, a statistically significant suppression occurred only during the first 7 weeks.

Dose-related reductions in mean hemoglobin, hematocrit, and RBC numbers of up to 6% were present at terminal sacrifice in males at 0.35 and 0.62 mg/ml, and in females of up to 10% at the top 3 doses. The degree of the anemia at the higher dose levels may have been more pronounced than was indicated from the data, as dehydration secondary to decreased water and food intake may have precluded an accurate determination of hematologic parameters. Adjusted terminal liver weights were significantly increased in both sexes at the top 3 doses (up to 29% in males, 27% in females). Adjusted kidney weights were significantly increased at the top 2 doses (up to 11% in both sexes). Interim liver and kidney weights

showed a similar tendency. Necropsy of interim sacrifices revealed up to a 60% incidence of livers with pale or accentuated lobular patterns in animals at 0.35 and 0.62 mg/ml. Similar characteristics were seen at terminal sacrifice.

Histologic analysis at termination revealed bladder cystitis (incidence of 30-100%) and bladder mucosal hyperplasia (70-100%) at the top 2 doses in both sexes. Eosinophilic granules of the transitional bladder epithelium were noted at the top 3 doses in both sexes (incidence: 70-100%). The urinary bladders of animals from the interim sacrifice were not retained for histologic examination.

Based on reductions in hemoglobin, hematocrit, and RBC numbers, increased liver weights, and eosinophilic granules in transitional epithelial cells of the urinary bladder, the NOEL was 0.018 mg/ml (estimated to be as low as 0.79 mg/kg/day due to compound instability). This study was considered acceptable under FIFRA guidelines.

5. Dog - Oral capsule (9-week and 90-day)

Preliminary 9-week range-finding study (Brammer, 1992a). This study was conducted for up to 9 weeks to determine an appropriate dose range for a 90-day subchronic study (see below). Attempts were made to expose beagles (1/sex/dose) via gelatin capsules to metam sodium at 0, 2.5, 10, 15 or 25 mg/kg/day, with secondary changes in dosing after week 6 generating exposures as high as 50 mg/kg/day in some animals. Because regurgitation occurred following administration at 15 & 25 mg/kg, attempts were made to lessen the immediate response by using milk as an emollient, by administering test article by gavage using water as a diluent, or by offering food at specified times in relation to exposure; however, the results were mixed. Severe toxicity and death occurred in animals first dosed at 15 and 25 mg/kg. Clinical and pathologic data were of little practical use given the on/off nature of the dosing regimen. Assignment of a NOEL was, consequently, not possible. Nonetheless, significant clinical effects were not seen at or below 10 mg/kg/day. Only males showed effects on body and organ weights, clinical chemistry, pathology and histopathology at 15 mg/kg, suggesting the possibility of a gender difference in sensitivity to metam in dogs.

90-day definitive study (Brammer, 1992b). In a 90-day study in beagle dogs, groups of 4 dogs/sex/group were administered 0, 1, 5, or 10 mg/kg/day metam (43.15% purity) via gelatin capsule. Two high dose dogs (one female at week 11 and one male at week 12) were sacrificed due to poor clinical condition. Clinical signs included post-dosing emesis at 5 and 10 mg/kg/day, and salivation, thinness and jaundice at 10 mg/kg/day. Mean body weights declined in high dose males after week 9, resulting in statistically significant differences from controls for the last 4 weeks of the study, and a 14% decrement by week 14. High dose females also sustained mean weight losses after week 9, but began gaining again after week 11. Lowered food consumption was evident by week 8 at 10 mg/kg, appearing in 3 males and 2 females and contributing ultimately to the early termination of 2 animals. Lowered food consumption was also noted in one 5 mg/kg male.

Slight decreases in mean cell hemoglobin concentration were balanced by increases in mean cell volume and mean cell hemoglobin at 10 mg/kg. Increases in plasma levels of alanine transaminase (up to 37-fold), aspartate transaminase (up to 6-fold), alkaline phosphatase (up to 8-fold), bilirubin (up to 26-fold), creatine kinase (up to 2-fold), and gamma-glutamyl transferase (up to 6-fold) were also noted. These changes, detailed in Table 6, were indicative of liver damage and increased in severity with dose, in one case (alanine transaminase in females) occurring at the low dose. The latter case was based on a precipitous rise in activity in a single animal at week 13 (from 44 IU/L at week 12 to 454 IU/L at week 13). Urine parameters showed alterations at 5 and 10 mg/kg. Kaolin-cephalin time, a

measure of blood clotting ability, showed statistically significant increases at the high dose, rising as high as 19% compared to controls as early as 4 weeks.

The primary effects observed at necropsy were related to the liver. These included an accentuated lobular pattern, pale coloration, red depressed areas (indicative of collapsed hepatic cords with an influx of blood) at 10 mg/kg, with the latter sign noted also at 5 mg/kg. Animals killed intercurrently showed thinness and yellow discoloration of the tissues. Histologically, a severe hepatitis composed of hepatocyte degeneration and necrosis, inflammation, and increased pigmentation and biliary proliferation was present in all animals at 10 mg/kg/day. Less severe changes were present at 5 mg/kg/day, and one female at 1 mg/kg day showed bile duct proliferation and inflammatory cell infiltration (Table 7). As this was considered a possible precursor to the liver histopathology at the higher doses, it was sufficient to determine the LOEL (one male and one female at 5 mg/kg and one male at 10 mg/kg also showed these characters). The same low dose female also displayed the precipitously increased alanine aminotransferase activity described above, suggesting liver dysfunction.

Other treatment-related changes noted in the study included a minimal to slight increase in the number of mitoses of urinary bladder epithelial cells in several animals at 5 and 10 mg/kg/day. A single occurrence of thymic atrophy, and of immature testis and prostate that occurred in the 10 mg/kg/day male group may have been a non-specific response to toxicity.

Based on the evidence for liver damage and the associated rise in plasma ALT activity in one female at 1 mg/kg/day, a LOEL was established at that dose. Benchmark dose methodology using the quantal linear algorithm, which generated the best fit to the data points of 16 algorithms tested, was employed to establish an LED_{10}. The benchmark response level of 10% was considered appropriate because the bile duct proliferation / inflammatory cell infiltration noted at the low dose was “minimal” (even less severe than “slight”) and occurred in only a single animal. The incidence curve was 0/4, 1/4, 3/4 and 4/4 for liver / bile duct damage at increasing doses (Figure 2). The resultant LED_{10} was 0.163 mg/kg/day (ED_{10} = 0.326 mg/kg/day), which will be rounded to 0.2 mg/kg/day for calculations of margins of exposure (see section IV.C.1.b and Appendix III).

Table 6. Selected mean plasma enzymes and bilirubin in dogs after 13 weeks oral exposure to metam sodium (Brammer [1992b])

	Metam sodium, mg/kg/day			
	0	**1**	**5**	**10**
ALT[a], males[b]	28.5[c]	29.0	429.3**	711.3**
females[b]	29.8	134.5*[e]	207.5**	266.7**
AST[a], males[b]	20.8[c]	19.5	50.3*	115.3**
females[b]	21.0	28.3	30.3	43.7**
ALP[a], males[b]	155[c]	160	524*	1177**
females[b]	141	157	377	588**
BR[a], males[b]	0.20[d]	0.20	0.27	5.20**
females[b]	0.20	0.20	0.27	0.73
CK[a], males[b]	79[c]	84	93	154**
females[b]	74	76	71	81
GGT[a], males[b]	0.8[c]	0.5	1.5	4.7**
females[b]	0.8	0.8	1.3	4.0**

[a] ALT, alanine transaminase; ASP, aspartate transaminase; ALP, alkaline phosphatase; CK, creatine kinase; GGT, gamma-glutamyl transferase; BR, bilirubin.
[b] n=4 for each dose except the high dose where n=3.
[c] Enzyme activities in IU/L.
[d] Bilirubin activity in mg/100 ml.
[e] The apparent rise in ALT activity in low dose females was based on a precipitous rise recorded in a single female at the week 13 determination.
* $p<0.05$ (Student's t-test, 2-sided)
** $p<0.01$ (Student's t-test, 2-sided)

Table 7. Liver histopathology in dogs after 13 weeks oral exposure to metam sodium (Brammer [1992b])

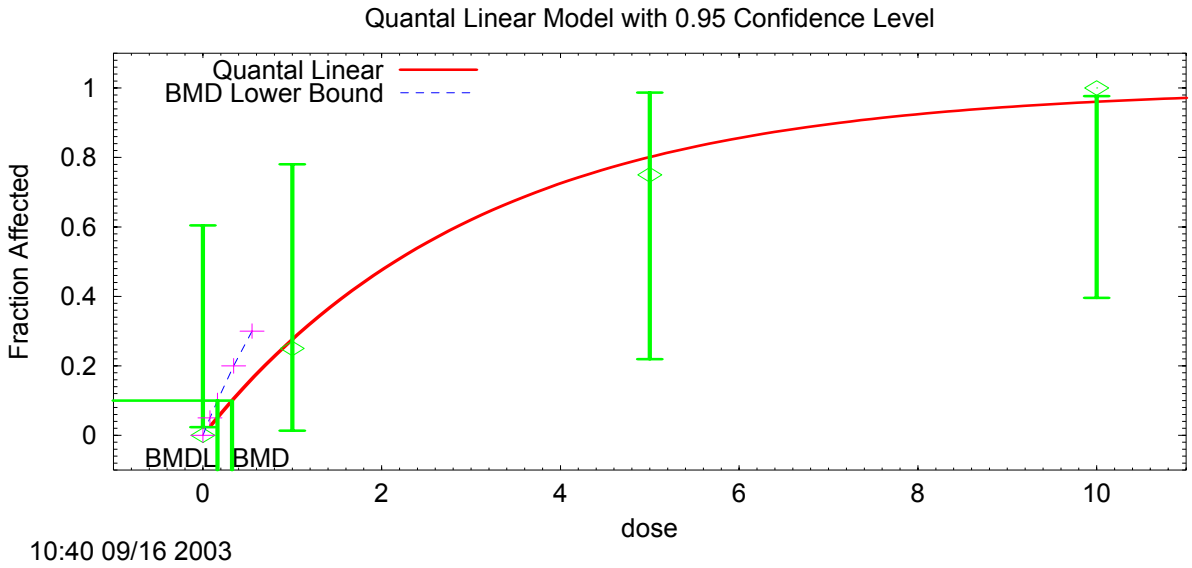
	Metam sodium, mg/kg/day			
	0	**1**	**5**	**10**
Hepatitis (total)				
males	0/4	0/4	3/4	4/4*[a]
females	0/4	0/4	2/4	4/4*
Hepatitis (slight)				
males	0/4	0/4	1/4	0/4
females	0/4	0/4	1/4	0/4
Hepatitis (moderate)				
males	0/4	0/4	2/4	0/4
females	0/4	0/4	1/4	2/4
Hepatitis (marked)				
males	0/4	0/4	0/4	4/4*
females	0/4	0/4	0/4	2/4
Bile duct / inflammatory cell proliferation (minimal)				
males	0/4	0/4	0/4	0/3[b]
females	0/4	1/4	1/4	0/3
Bile duct / inflammatory cell proliferation (slight)				
males	0/4	0/4	1/4	0/3
females	0/4	0/4	0/4	0/3

* p<0.05, Fisher exact test

[a] The incidence of hepatitis at the high dose includes the single male and single female that were killed intercurrently in weeks 12 and 11, respectively. Histopathologic examination of both animals revealed marked hepatitis, characterized by hepatocyte necrosis and degeneration, inflammatory cell infiltration, increased pigmentation in hepatocytes and Kupffer cells, and biliary proliferation.

[b] The incidence of bile duct / inflammatory cell proliferation at the high dose does *not* include the animals that were killed intercurrently, despite the reported "biliary proliferation" in those animals (see footnote 1). This is because there was no indication of the severity of the biliary sign, leaving the assessor with no idea as to whether it should be classified as "minimal", "slight", or something more severe. This leaves open the question of why no bile duct / inflammatory cell proliferation is noted at the high dose. The report is not clear on this issue, though it may be that the marked hepatitis at that dose includes biliary effects.

Figure 2. Benchmark dose modeling of liver / bile damage in beagle dogs (benchmark response = 10%) (Brammer [1992])



6. Rat - inhalation (90-day)

In a 90-day inhalation study (Knapp, 1983 and Duffell, 1992), 18 Sprague-Dawley rats/sex/group were exposed to aerosolized metam sodium in whole-body chambers for 6 hr/day, 5 days/week. The cumulative mean chamber metam concentrations for the four dose groups were 0, 6.5, 45 or 160 mg/m^3. These values, which were determined using measurements of sodium ion levels, were calculated by DPR to be equivalent to internal doses of 1.11, 7.71 or 27.43 mg/kg/day. Mean MITC concentrations, measured by infrared adsorption, were 0.7, 2.2 or 5.7 mg/m^3 (0, 0.23, 0.74, and 1.90 ppm), equivalent to internal doses of 0.12, 0.38 or 0.98 mg/kg/day (calculated by DPR). Weight gain was suppressed at the high dose for 3-4 weeks such that the final weights were 94% and 92% of controls in males and females, respectively. Cumulative mean food consumption was suppressed by 8% and 10% at 7.71 and 27.43 mg/kg.

The following clinical signs were detected at the high dose: salivation (13/36 *vs.* 3/36 among controls), dullness (11/36 *vs.* 0/36), chromodacryorrhea (30/36 *vs.* 9/36), dehydration (3/36 *vs.* 0/36), rough coat (20/36 *vs.* 0/36), and wet coat (30/36 *vs.* 0/36). An increase in seminal plugs in the waste pan, considered evidence of stress, occurred at 7.71 and 27.43 mg/kg, achieving statistical significance at the high dose.

Interim plasma lactate dehydrogenase levels were suppressed by 50% and 62% ($p<0.05$) at the top two doses in females, and by 18% ($p<0.05$) at the top dose in males. Reductions in total serum protein (up to 18%) and globulin (up to 14%) were present at all doses in females, though a lack of clear dose responsiveness made test article involvement at the low dose questionable in both cases. A reduction in albumin (up to 22%) and an increase in alkaline phosphatase (up to 2.15-fold) were observed at the two top doses at termination. These blood chemical changes were possibly indicative of liver damage.

Gross necropsies identified focal discolorations of the stomach lining (high dose, both sexes). Significant increases in relative lung (13% and 21% in males and females) and kidney (7% and 14%) weights occurred at the high dose in both sexes. All organ systems showed increases in relative weight among females. The biologic significance of these increases was unclear. Histopathology revealed signs of irritative stress in the nasal passages (lymphocytic rhinitis and mucigenic epithelial hyperplasia), achieving statistical significance at the top two doses (Table 8). At no dose did the severity of these lesions rise above “very slight.” Erosive gastritis and pulmonary histiocytosis were present at the high dose. It should be noted that the air concentrations of MITC at these irritative doses were similar to those causing nasal epithelial irritation when MITC itself was used as a test article (see DPR, 2002b).

Based on serum chemical changes, some of which may indicate liver damage, and nasal stress revealed by histopathology, the NOEL was set at 1.11 mg/kg/day (6.5 mg/m^3). (Some of the effects noted in this study were likely due to MITC (see the MITC 1807 health assessment, DPR, 2002b). This study was considered to be acceptable by FIFRA standards.

Table 8. Selected irritative histopathology from the 90-day rat inhalation study with aerosolized metam sodium (Knapp, 1983)

	Metam sodium, mg/m^3			
	0	6.5	45	160
Nasal passages				
mucigenic hyperplasia				
males	5/18+++	1/18	9/18	13/17**
females	1/17++	6/18	10/18**	11/18**
lymphocytic rhinitis				
males	1/18+	4/18	6/18*	7/17*
females	1/17	3/18	4/18	5/18
mucigenic cyst				
males	0/18	0/18	0/18	0/17
females	0/17	1/18	1/18	2/18
Stomach				
erosive gastritis				
males	1/18+++	0/18	0/18	9/17**
females	0/17+++	0/18	0/18	13/18***
ulcerative gastritis				
males	0/18	0/18	0/18	0/17
females	0/17+	0/18	0/18	2/18
Lungs				
histiocytosis				
males	0/18++	0/18	1/18	3/17
females	0/17+	0/18	0/18	2/18

Explanatory note: Metam sodium concentrations are expressed as air concentrations in this table because the effects are considered to be irritative in nature, making absorbed doses less relevant. It should be recalled that an unknown, but perhaps major, contributor to these effects may be the metam degradation product, MITC. Equivalent MITC concentrations in this study were, at ascending doses, 0, 0.7, 2.2, and 5.7 mg/m^3 (0, 0.23, 0.74, and 1.90 ppm).
+, ++, +++ -Positive in Peto's trend test at $p < 0.05$, 0.01 and 0.001, respectively.
*, **, *** -Significantly different from control at $p < 0.05$, 0.01 and 0.001 (Fisher's Exact Test).

7. Rabbit - dermal (21-day)

In a dermal toxicity study (Leuschner, 1979), 10 White Russian rabbits/sex/dose were treated with metam sodium (42.4% active ingredient in 0.8% aqueous hydroxypropylmethylcellulose gel; controls received the gel alone) at 0, 31.25, 62.5, or 125.0 mg/kg/day (local concentrations were 0, 360, 720, or 1440 μg/cm^2; for calculation, see section IV.A.2.). The application was made to a clipped 15x16 cm patch of skin (~10% of body surface area, non-occluded). The dose groups were subdivided such that the test sites on 5 rabbits/sex/dose were intact, while those on the remaining 5 rabbits/sex/dose were abraded. During the exposure period the animals were confined to cages that permitted some movement, but in

which turning of the whole body was not possible. This presumably constrained the licking off or rubbing off of the test article. The test article was applied daily for 21 consecutive days, 8 hours/day. Two animals/sex/group were observed for an additional 21 days. Systemic toxicity was gauged by recording the general appearance, rate of weight gain, behavior, food and water consumption, hematology, clinical chemistry, urinalysis, ophthalmology, necropsy, and histology.

No systemic toxicity was observed. Local dermal effects were delineated as follows: At 0 and 360 μg/cm^2 no effects were observed. At 720 μg/cm^2 slight erythema was observed from day 4-13 (depending on the individual) until termination. This occasionally developed to stage 2 with slight rhagades (fissures or cracks in the skin) in parallel for 10/20 animals. By 21 days only stage 1 effects were observed in 7 of the 10 animals that had initially developed stage 2 erythema. Stage 1 edema was apparent in 11/20 animals, with earliest appearance at day 7. All effects disappeared by recovery day 9 in those animals that were continued into the following 21-day post-dose period. At 1440 μg/cm^2 local erythema was observed from day 1, progressing from stage 1 to stage 2 or 3 (with slight or moderate rhagades) by the end of the test period in all animals. Edema, developing to stage 2 in most animals, was noted in all animals. All effects had disappeared by recovery day 12 in those animals observed during the 21-day post-dose period. Dermal abrasion had no influence on the incidence or severity of the irritation at any dose. Autopsy and histopathology results for the animals terminated at day 21 (*i.e.*, those sacrificed at the end of exposure, before the recovery period) were reflective of the observations listed above. The macroscopic autopsy results for the skin appear in Table 9.

Based on local erythema, edema and dermatitis at the LOEL dose of 720 μg/cm^2 (62.5 mg/kg/day), the acute local NOEL was 360 μg/cm^2 (31.25 mg/kg/day). As there were no systemic effects, the systemic NOEL was $\geq$125.0 mg/kg/day. This study was considered supplemental due to the absence of an analysis of the dosing material.

Table 9. Macroscopic autopsy findings after 3 weeks of metam sodium application to intact and abraded rabbit skin (Leuschner, 1979)

	Metam sodium, μg/cm^2							
	Males				Females			
	0	360	720	1440	0	360	720	1440
Slight erythema								
Unabraded skin	0/3	0/3	2/3	0/3	0/3	0/3	1/3	0/3
Abraded skin	0/3	0/3	2/3	0/3	0/3	0/3	2/3	0/3
Mod./marked eryth.								
Unabraded skin	0/3	0/3	0/3	3/3	0/3	0/3	0/3	3/3
Abraded skin	0/3	0/3	0/3	3/3	0/3	0/3	0/3	3/3
Slight/mod. edema								
Unabraded skin	0/3	0/3	0/3	3/3	0/3	0/3	0/3	3/3
Abraded skin	0/3	0/3	0/3	2/3	0/3	0/3	0/3	3/3
Slight/mod rhagades								
Unabraded skin	0/3	0/3	0/3	3/3	0/3	0/3	0/3	3/3
Abraded skin	0/3	0/3	0/3	3/3	0/3	0/3	0/3	3/3
Epidermo-dermatitis								
Unabraded skin	0/3	0/3	2/3[a]	3/3[b]	0/3	0/3	1/3[a]	3/3[c]
Abraded skin	0/3	0/3	3/3[a]	3/3[c]	0/3	0/3	2/3[a]	3/3[c]

Note: Only 3 of the 5 animals in each group were subjected to autopsy at the end of the dosing period. The remaining 2 animals were allowed to recover during a 21-day post-dose period.

[a] Slight epidermo-dermatitis.

[b] Moderate epidermo-dermatitis.

[c] Of the animals in each of these groups, 2 showed moderate and 1 showed marked epidermo-dermatitis.

Table 10. Summary of NOELs and LOELs for the subchronic toxicity of metam sodium

Species / Sex	Exposure regimen	Effects at LOEL	NOEL (or LED)	LOEL	Reference
Rat (M/F)	11-day gavage	Stomach ulceration & salivation	20 mg/kg/day	50 mg/kg/day	Cave, 1991a
Rat (M/F)	21-day drinking water[a]	Decreased body weight & water consumption	---	10.5 mg/kg/day[b]	Cave, 1991b
Rat (M/F)	90-day drinking water	Decreased body weight & water consumption, hematologic & urinary effects	0.49 mg/kg/day	3.10 mg/kg/day	Allen, 1991
Mouse (M/F)	90-day drinking water	Decreased Hct/Hb/RBCs, increased liver weights, eosinophilic bladder granules	0.79 mg/kg/day	4.48 mg/kg/day	Whiles, 1991
Dog (M/F)	90-day gavage	Liver damage	0.2 mg/kg/day (LED_{10})[c]	1 mg/kg/day	Brammer, 1992b
Rat (M/F)	90-day inhalation (5 days/wk, 6 hr/day)	Nasal mucigenic hyperplasia (females) & lymphocytic rhinitis	1.11 mg/kg/day	7.71 mg/kg/day	Knapp, 1983
Rabbit (M/F)	21-day dermal	Local: erythema, edema, dermatitis Systemic: none	Local: 360 $\mu g/cm^2$ Systemic: >125 mg/kg/day	Local: 62.5 mg/kg/day	Leuschner, 1979

[a] Doses were lowered ~10-fold after 2 days due to non-acceptance.
[b] Lowest dose tested.
[c] Estimated from the LOEL dose of 1 mg/kg/day using the quantal linear algorithm.

D. CHRONIC TOXICITY / ONCOGENICITY

1. Rat - Combined chronic toxicity/oncogenicity (2-yr)

Metam sodium (43.15%) was administered in the drinking water to 64 Hsd/01a:Wistar-Tox rats/sex/dose at doses of 0, 0.019, 0.056 or 0.19 mg/ml for up to 104 weeks (Rattray, 1994). An interim kill of 12/sex/dose was conducted at 1 year. Mean internal doses were 1.5, 4.3 and 12.5 mg/kg/day in males and 2.7, 6.8 and 16.8 mg/kg/day in females. Body weight decrements (~12% at termination) were observed at 0.19 mg/ml (female body weight was also reduced by ~5% at 0.056 mg/ml). Statistically significant reductions in food consumption were noted in males at 0.19 mg/ml (mean reduction, ~8%), and in females at 0.056 and 0.19 mg/ml (mean reduction, ~6% and 12%). Water consumption was inhibited at all doses in a dose-dependent manner, with a maximum reduction of 45% and 58% occurring in males and females at 3 weeks. Statistically significant reductions in hemoglobin of as much as 17%, accompanied by parallel reductions in hematocrit and red blood cell counts, were noted at $\geq$0.056 mg/ml. This observation takes on greater significance in light of the decreased water consumption observed at these doses.

Reduced hindlimb function was detected in males at the high dose. This correlated with an increase in voluntary muscle myopathy, particularly in high dose intercurrent males (incidence rate at ascending doses: 7%, 5%, 3%, 58%). Adverse pathologic changes in the nasal cavity (rhinitis, hypertrophy of Bowman's gland, hyperplasia / degeneration of the olfactory epithelium, atrophy and adenitis of Steno's gland and respiratory epithelial hyperplasia) also occurred in a majority of animals at 0.19 mg/ml. The Steno's gland abnormalities were similarly detected in mid-dose females.

Interpretation of the data on tumor incidence was ambiguous with respect to hemangiosarcoma induction (Table 11). Although there was a statistically significant increase in hemangiosarcoma incidence at the mid dose relative to controls, and all treated groups showed a greater incidence than the control group, a clear dose-response relationship was not observed. Furthermore, historical control data were not available, complicating interpretations of the mid dose increase. It is possible that decreased caloric intake at the high dose was responsible for the lowered hemangiosarcoma incidence rate at that dose. Partial caloric restriction suppresses the development of many kinds of tumors in laboratory animals (Tannenbaum, 1959). Were this the case, however, one might expect a similar dose profile for hemangioma incidence, which was not observed. When incidences of hemangiomas and hemagiosarcomas were combined as suggested by the NTP (McConnell *et al*., 1986), no increase with dose was evident (Table 11). The incidence of another vascular tumor type, benign meningiomas, did, on the other hand, exhibit biphasic behavior, though the low absolute rates (0/50, 1/50, 3/51, 1/51 at increasing doses) precluded a determination that they were treatment related. Without historical controls, the absence of hemangiosarcomas and meningiomas in the concurrent controls must be accepted as representative of non-treated animals. Females showed even less of a tendency toward tumorigenic response than males in the categories discussed (meningioma, hemangioma or hemangiosarcoma) (data not shown). A final point: the observation in the mouse oncogenicity study (see below) of a metam-induced increase in angiosarcomas (equivalent to hemangiosarcomas) tends to support a metam etiology for such tumors in the rat.

The chronic NOEL was set at 0.019 mg/ml (~1.5 mg/kg/day in males) based on decreased food consumption and RBC values in both sexes and decreased water consumption and Steno's gland abnormalities in females at 0.056 mg/ml. This study was considered acceptable under FIFRA guidelines.

Table 11. Hemangioma, hemangiosarcoma and menigioma incidence in male rats given metam in drinking water for 2 years (Rattray, 1994)

	Metam sodium, mg/ml			
	0	**0.019**	**0.056**	**0.19**
Meningioma	0/50 (0%)	1/50 (2%)	3/51 (6%)	1/51 (2%)
Hemangioma	9/50 (18%)	3/50 (6%)	4/51 (8%)	8/51 (16%)
Hemangiosarcoma	0/50 (0%)	3/50 (6%)	8/51** (16%)	3/51 (6%)
Hemangioma + hemangiosarcoma	9/50 (18%)	6/50 (12%)	12/51 (24%)	11/51 (22%)

Note: Only animals considered to be "at risk" were considered in this tabulation. "At risk" was defined as those animals surviving beyond one year of exposure. This was done because no animals bearing meningiomas died before 586 days, no animals bearing hemangiomas died before 518 days, and no animals bearing hemangiosarcomas died before 457 days. In addition, no 1-year interim sacrifices bore these lesions.

** $p<0.01$ (Fisher Exact Test, two sided)

2. Mouse - Oncogenicity (2-yr)

Metam sodium (43.15%) was administered in the drinking water to 55 C57BL/10JfCD:1/Alpk mice/sex/dose at doses of 0, 0.019, 0.074 or 0.23 mg/ml for up the 2 years (Horner, 1994). Mean internal doses were 1.9, 7.2 and 28.9 mg/kg/day in males and 2.6, 9.6 and 31.2 mg/kg/day in females. Among high dose males, a 16% decrement in weight gain resulted in final body weights that were 93% of controls ($p<0.05$). Among high dose females, a 6% decrement in weight gain resulted in final body weights that were 98% of controls (statistical significance was maintained through week 87). Water consumption was reduced in females at $\geq$0.074 mg/ml, as was food consumption in males at 0.23 mg/ml.

Significantly increased absolute liver weights (up to 36%) were observed in both sexes at the 2 top doses. Epididymides showed significant weight decreases (up to 19%) at those same doses.

Males showed a statistically significant increase in angiosarcomas at 0.23 mg/ml, with positive trend tests present in both sexes (Table 12). Angiosarcoma was a factor contributory to death at 0.23 mg/ml, and pairwise comparison of the decedent animals showed a statistically significant increased incidence in males at the top two doses. The increase in angiosarcomas was reflected in several organ systems, including liver, spleen and subcutaneous tissue. Interestingly, both sexes showed an increase in subcutaneous masses at the high dose (males: 2/55 in controls, 5/55 at the high dose; females: 1/55 in controls, 5/55 at the high dose) that correlated with an increase in subcutaneous angiosarcomas. It was difficult, however, to distinguish primary tumors from metastases; consequently the total number of mice with angiosarcoma (first four lines, Table 12) is probably the most reliable indicator of incidence. Cancer potency calculations were performed using the "at risk" males, *i.e.*, those that survived at least one year of exposure (see section IV.A.5.).

Histopathology revealed an increase in eosinophilic/hyaline cytoplasmic epithelial inclusions in the bladders of both sexes at 0.019 mg/ml and bladder epithelial hyperplasia at

0.074 mg/ml. In both cases, the incidence in females was higher than in males (Table 13). The toxicologic significance of these changes, along with others occurring in the bladders of high dose animals (mononuclear cell infiltration, increased submucosal connective tissue and inflammatory cell infiltration), was unclear. However, it should be noted that a transitional cell papilloma of the urinary bladder of 1 male and a transitional cell carcinoma of the urinary bladder in 1 female, both considered extremely rare tumor types by the examining pathologist, were seen at 0.23 mg/ml. The existence of a correlation between the bladder tumors and the more frequent bladder anomalies is unknown in this case, though it is plausible that a compensatory response to tissue damage involving hyperplasia and immune infiltration is part of an adaptive response leading to neoplasia. Such a process has been extensively documented in the rat liver and the possibility of similar development in the bladder has been discussed (Farber, 1996). Other non-neoplastic histopathology included increases at the high dose of hepatocytic fat vacuolization (males: 20/55 *vs.* 4/55 in controls; females: 6/55 *vs.* 0/55 in controls) and splenic hemosiderosis (females: 3/55 *vs.* 0/55 in controls).

The chronic NOEL was set at 0.019 mg/ml (1.9 mg/kg/day) based on organ weight changes in both sexes and bladder epithelial hyperplasia in females at 0.074 mg/ml. (The presence of eosinophilic/hyaline cytoplasmic epithelial inclusions at all doses was considered to be of unclear toxicologic significance.) A statistically significant increase in angiosarcomas was observed at 0.23 mg/ml. This study was considered acceptable by FIFRA standards.

Table 12. Incidence of tumors in mice given metam in drinking water for 2 years (Horner, 1994)

	Metam sodium, mg/ml			
	0	0.019	0.074	0.23
Angiosarcoma				
total, males[a]	7/55+++ (12.7%)	12/55 (21.8%)	12/55 (21.8%)	27/55*** (49.1%)
females	4/55++ (7.3%)	2/55 (3.6%)	6/55 (10.9%)	10/55 (18.2%)
decedents, males	4/34+++ (11.8%)	5/35 (14.3%)	9/28* (32.1%)	17/35*** (48.6%)
females	2/27 (7.4%)	2/30 (6.7%)	4/36 (11.1%)	6/33 (18.2%)
terminal, males	3/21+ (14.3%)	7/20 (35.0%)	3/27 (11.1%)	10/20* (50%)
females	2/28+ (7.1%)	0/25 (0%)	2/19 (10.5%)	4/22 (18.2%)
"at risk", males[a]	7/53+++ (13.2%)	12/53 (22.6%)	12/55 (21.8%)	27/53*** (50.9%)
females[a]	4/55++ (7.3%)	2/55 (3.6%)	6/46 (13.0%)	10/52 (19.2%)
Liver angiosarcoma				
males	0/55+ (0%)	6/55* (10.9%)	3/55 (5.5%)	7/55** (12.7%)
females	0/55++ (0%)	0/55 (0%)	1/55 (1.8%)	3/55 (5.5%)
Spleen angiosarcoma				
males	5/55+++ (9.1%)	2/55 (3.6%)	8/55 (14.5%)	15/55* (27.3%)
females	0/55+ (0%)	1/55 (1.8%)	3/55 (5.5%)	4/55 (7.3%)
Subcutan. angiosarcoma				
males	1/6 (16.7%)	1/5 (20%)	1/4 (25%)	3/7 (42.9%)
females	0/4+ (0%)	1/4 (25%)	1/2 (50%)	3/5 (60%)
Hepatocellular adenoma				
males	0/55+ (0%)	0/55 (0%)	1/55 (1.8%)	2/55 (3.6%)
females	0/55++ (0%)	0/55 (0%)	0/55 (0%)	2/55 (3.6%)

*, **, *** p<0.05, 0.01, 0.001 (Fisher Exact Test); +,++,+++ p<0.05, 0.01, 0.001 (Cochran-Armitage Trend test)

[a] "At risk" animals were those surviving beyond one year of exposure. Quantitative analysis of oncogenicity was done using these figures, which is the convention when the first animal presenting the tumor in question (angiosarcoma) is not detected before one year (the first animal bearing angiosarcomas died at 68 weeks).

Table 13. Incidence of histopathologic bladder anomalies in mice given metam sodium in drinking water for 2 years (Horner, 1994)

	Metam sodium, mg/ml			
	0	0.019	0.074	0.23
Epithelial hyperplasia				
males	0/54+++ (0%)	0/55 (0%)	2/55 (3.6%)	45/55*** (81.8%)
females	0/54+++ (0%)	0/52 (0%)	10/53*** (18.9%)	44/55*** (80.0%)
Mononuclear cell infiltration				
males	8/54+++ (14.8%)	7/55 (12.7%)	5/55 (9.1%)	32/55*** (58.2%)
females	34/54 (63.0%)	25/52 (48.1%)	21/53 (39.6%)	29/55 (52.7%)
Eosinophilic/hyaline cytoplasmic epithelial inclusions				
males	0/54+++ (0%)	5/55* (9.1%)	50/55*** (90.9%)	33/55*** (60%)
females	5/54+++ (9.3%)	42/52*** (80.8%)	51/53*** (96.2%)	47/55*** (85.5%)
Increased submucosal connective tissue				
males	1/54+++ (1.9%)	0/55 (0%)	0/55 (0%)	11/55** (20%)
females	0/54+++ (0%)	0/54 (0%)	2/53 (3.8%)	19/55*** (34.5%)
Submucosal inflammatory cell infiltration				
males	0/54+++ (0%)	0/55 (0%)	0/55 (0%)	4/55 (7.3%)
females	0/54+++ (0%)	0/54 (0%)	0/53 (0%)	9/55** (16.4%)

*, **, *** p<0.05, 0.01, 0.001 (Fisher Exact Test); +,++,+++ p<0.05, 0.01, 0.001 (Cochran-Armitage Trend test)

3. Dog - Chronic toxicity (1-year)

Metam sodium (43.15%) was administered as a daily oral dose in gelatin capsules to beagle dogs (4/sex/group) at 0, 0.05, 0.1 or 1 mg/kg/day (Brammer, 1994). There was no overt toxicity, nor were there toxicologically significant effects on food consumption. Female body weights at the top 2 doses appeared suppressed during the second half of the study, progressing to about 8% by termination for both groups, though these were not generally statistically significant. Similarly, all of the male treatment groups exhibited slightly lower mean body weights than controls. A treatment-related etiology for these weight effects was not clear.

One high dose female exhibited an ~8-fold rise in alanine aminotransferase at weeks 26, 32, 39, 45 and 52 (compared to weeks 4, 8, 13 and 19). The same individual exhibited signs of hepatotoxicity (a slight increase in hepatocyte and macrophage/Kupffer cell pigmentation, slight mononuclear cell infiltration, slight telangiectasis) that, in view of similar results in the dog 90-day study (Brammer, 1992b), was probably test article-related. Other observations, such as an increase in mean alkaline phosphatase activities (up to 47%, both sexes, mostly high dose) and a reduction in mean plasma triglycerides (up to 34%, females, high dose) may also indicate a more generalized liver dysfunction. An increase in kaolin-cephalin time (also known as activated partial thromboplastin time) of up to 15% in both sexes at the high dose indicates some interference with blood clotting.

Based on these effects, a chronic NOEL of 0.1 mg/kg/day was established. This study was considered acceptable by FIFRA standards.

Table 14. No-Observed-Effect-Level (NOEL) / Lowest-Observed-Effect-Level (LOEL) for the Chronic Toxicity of Metam Sodium

Species / Sex	Exposure regimen	Effects at LOEL	NOEL	LOEL	Reference
Rat (M/F)	2-year drinking water	Decreased hct/hb/RBCs & food consumption in both sexes, decreased water consumption in females	1.5 mg/kg/day	4.3 mg/kg/day	Rattray, 1994
Mouse (M/F)	2-year drinking water	Organ weight changes (both sexes) and epithelial hyperplasia (females)	1.9 mg/kg/day	7.2 mg/kg/day	Horner, 1994
Dog (M/F)	1-year gavage	Hepatotoxicity (1 female), increased mean ALP & kaolin-cephalin time, and decreased mean triglycerides	0.1 mg/kg/day	1 mg/kg/day	Brammer, 1994

E. GENOTOXICITY

A summary of the results of the genotoxicity studies is provided in Table 15. The results both of *in vivo* and *in vitro* tests indicate that metam sodium is clastogenic; one *in vivo* hamster study also suggested that polyploidy may occur (see "Chromosome effects" below). There was only equivocal evidence for gene mutation or other genotoxic effects, however.

1. Gene mutation

Salmonella typhimurium strains TA 1535, TA 1537, TA 1538, TA 92, TA 98 and TA 100 were exposed to metam sodium (42.2%) in a range of concentrations between 5 and 500 μg/plate for 48 hours, with and without metabolic activation, in duplicate standard plate tests and duplicate preincubation tests using triplicate plates (Engelhardt, 1987a). There was no evidence for mutagenicity, which would have been detectable by a rise in histidine independent colonies.

Chinese Hamster ovary cells (CHO-K1) were exposed to metam sodium (42.2%) at a range of concentrations between 0.0000464 and 0.01 mg/ml for 4 hours in the absence and presence of a metabolic activation system (Engelhardt, 1987b). Occasional small increases in mutagenicity, detected by increases in 6-thioguanine-resistant clones resulting from mutations at the HGPRT locus, were noted, though there was neither predictability (i.e., there was a lack of dose dependence) nor consistency to this observation. In addition, none of the negative controls registered above a mutation rate of 0, a situation that makes one suspect that occurrence at other doses is random. Nonetheless, equivocal mutagenicity in the absence and presence of a metabolic activation system cannot be discounted. This is particularly true at the high dose of 0.01 mg/ml in the presence of an S9 activating system.

2. Chromosome effects

SH (chin) Ki, SPF Chinese Hamsters (5/sex/group) were dosed orally with aqueous metam sodium (42.2%) at 0, 150 and 300 mg/kg (sacrificed at 24 hours post dose) and at 600 mg/kg (sacrificed at 6, 24 and 48 hours) (Gelbke and Engelhardt, 1987a). 1000 metaphase cells (100/hamster) from bone marrow preparations were scored at each dose level. An increased frequency of chromosome aberrations was observed at the high dose (24-hour sacrifice), and increased frequencies of polyploidy were present in all groups. The possibility of direct bone marrow toxicity is supported by the observation that, in preliminary exposures at as low as 900 mg/kg, slides from surviving hamsters could not be prepared due to poor chromosomal quality or low cell number. The interpretation of positivity in this *in vivo* study is supported by the results of the parallel *in vitro* study in human lymphocytes (see next paragraph).

Metam sodium was applied to duplicate cultures of human lymphocytes at 0, 1, 5, 10 and 20 μg/ml without activation (24-hour exposure) and 0, 10, 20 and 40 μg/ml with activation (2-hour exposure) (Gelbke and Engelhardt, 1987b). 200 metaphase cells (100/culture) were scored at each dose level. A dose-dependent increase in aberration frequency both in the absence and presence of metabolic activation was observed.

Metam sodium (32.3%) was applied to duplicate cultures of human lymphocytes at a dose range of 0-30 μg/ml (-S9) or 0-40 μg/ml (+S9) for 72 hours (Mackay, 1996). Exposure at or above 20 μg/ml +S9 resulted in small increases in clastogenesis (mean % aberrant cells excluding gaps at 0, 5, 20 and 40 μg/ml was 0.25, 0.50, 1.75**, 2.75**; ** indicates statistical

significance at the 0.01 level). The report points out that the apparent rise may be a function of low solvent control values rather than clastogenic potential of metam. However, the consistency of these data with the similar study discussed just previous to this study supports a role for metam in this increase. Cytotoxicity was seen at $\geq$30 μg/ml (-S9) and at $\geq$20 μg/ml (+S9).

CD-1 mice, 5/sex/dose, were exposed to a single gavage dose of metam sodium (32.3%) at an MTD dose of 500 mg/kg (Barber and Mackay, 1996). Bone marrow samples were processed 24 and 48 hours after dosing. No increase in micronuclei was noted, nor was there a statistically or biologically significant change in the percentage of polychromatic erythrocytes.

3. DNA damage

A matched pair of *Bacillus subtilis* strains (H17 [rec+] and M45 [rec-]) was treated with metam sodium (42.2%) in three assays, each with and without activation (Hoorn, 1987). The dose ranges for two assays was 0.1-150 μl/plate and for the third was 0.1-15 μl/plate (triplicate plates; 24-48 hours exposure). The test results appeared equivocal, even though a repeat test was performed. The study was not acceptable to DPR because positive control agents were only marginally effective, and it was difficult to determine from the test results whether or not there was an increase in the zone of inhibition due to the test article. The positive control agent used with activation (sterigmatocystin), is not normally used in a rec-assay with *B. subtilis*.

Primary hepatocytes from an adult male Fischer 344 rat were treated in triplicate cultures with Metam sodium (42.2%) at a range of concentrations between 0.5 and 500 nl/ml for 18 hours (Cifone, 1987). Fifty cells/culture were scored for unscheduled DNA synthesis. Considerable cytotoxicity was present at concentrations above 5 nl/ml. There was no evidence for DNA damage.

Table 15. Summary of the genotoxicity studies conducted with metam sodium

Test type / system	Strain	Dose	S9	Result	Comments / Ref.
Gene Mutation					
Salmonella typhimurium / Reversion to histidine independence	TA 1535, 1537, 1538, 92, 98	≤500 μg/plate	-/+	Negative	(Engelhardt, 1987a)
Chinese hamster ovary cells / HGPRT locus mutations	CHO-K1	≤0.01 mg/ml	-/+	Equivocal	(Engelhardt, 1987b)
Structural Chromosome Aberrations					
In vivo cytogenetic chromosome aberration	SPF Chinese hamsters	0, 150, 300, 600 mg/kg	n/a	Positive	Increased aberration at 600 mg/ml, increased polyploidy at all doses / (Gelbke & Engelhardt, 1987a)
In vitro cytogenetic chromosome aberration	Human lymphocytes	-S9: 0, 1, 5, 10, 20 μg/ml +S9: 0, 10, 20, 40 μg/ml	-/+	Positive	Dose-dependent increase in aberration frequency -/+ S9 / (Gelbke & Engelhardt, 1987b)
In vitro cytogenetic chromosome aberration	Human lymphocytes	-S9: 0-40 μg/ml +S9: 0-30 μg/ml	-/+	Positive	Dose-dependent increase in aberration frequency +S9 (Mackay, 1996)
In vivo micronucleus	CD-1 mouse	500 mg/kg	n/a	Negative	(Barber & Mackay, 1996)
Other Genotoxic Effects					
Unscheduled DNA synthesis	Fischer 344 rat hepatocytes	0.5-500 nl/ml	n/a	Negative	(Cifone, 1987)
Bacillus subtilis rec	M45, H17	0.1-150 μl/plate (2 assays) 0.1-15 μl/plate (1 assay)	-/+	Equivocal	Test invalid due to marginal effectiveness of positive controls

F. REPRODUCTIVE TOXICITY

1. Rat - Drinking water (2-generation)

Metam sodium (43.15%) was administered as an additive in drinking water over 2 generations to Alpk:APfSD rats (30/sex/dose) at 0, 0.01, 0.03 or 0.10 mg/ml (Milburn, 1993). Stability analyses indicated that after 24 hr, metam concentrations in 3 of 13 samples at 0.01 mg/ml, 6 of 13 samples at 0.03 mg/ml and 1 of 13 samples at 0.1 mg/ml had dipped below 85% of nominal (the lowest was 42.3% of nominal). Dosing was, however, considered best represented by the nominal levels (this would assume that most water consumption occurred at night soon after daily resupply of the water bottles containing freshly-added metam). The actual doses received varied greatly depending on sex, time and pregnancy status.

There were marginal decrements in body weight at 0.1 mg/ml in pre-mating adults both of the F0 and F1 generations. These differences were maintained during pregnancy and lactation, though they did not increase during those periods. While mean pre-mating food consumption at the high dose was within 6% of control, statistically significant decrements were registered during many individual weeks. Statistically significant reductions in water consumption occurred at the top 2 doses in both sexes among parental animals (low dose F1 females also showed small, but significant, reductions during 4 premating weeks and during pregnancy and lactation), likely reflecting a palatability problem. At the high dose these reductions approached 50%. Thus a parental systemic NOEL was set at 0.01 mg/ml (the lowest measured intake at this dose level at any time during the study was 1.0 mg/kg/day) based on decreased water consumption.

Bowman's gland duct hypertrophy with loss of alveolar cells and disorganization / degeneration / atrophy of the olfactory epithelium were noted in $\geq$87% of all F0 and F1 females at the high dose. Dilatation of Bowman's gland ducts occurred in $\geq$33% of the high dose adult females. Hyperplasia of the olfactory epithelium occurred in one F0 female and in three F1 females. The absence of nasal abnormalities in males was considered by the investigators to be a function of the increased metam dosage received by pregnant females during lactation.

The parental reproductive NOEL was >0.1 mg/ml (intake ranged from 8.3-53.5 mg/kg/day) based on no significant reproductive effects. The pup NOEL was set at 0.03 mg/ml (the gestational mean dose was 6.9 mg/kg/day [F0 parents] and 5.7 mg/kg/day [F1 parents]) based on a tendency toward low pup weights at the high dose (6% less than control among F1 pups, 10-11% among F2 pups on day 22). This study was considered acceptable by FIFRA standards.

G. DEVELOPMENTAL TOXICITY

1. Rat - Gavage (BASF study)

Metam sodium (42.2%) was administered in a water vehicle by oral gavage at 0, 4.2, 16.9, or 50.6 mg/kg/day to pregnant Wistar rats on days 6-15 of gestation (24/dose except the high dose which had 22) (Hellwig and Hildebrandt, 1987). Feed consumption was immediately impacted at the top two doses (84% and 81% of controls on gestation days 7-8), a decrement largely maintained at the top dose throughout gestation. Body weight loss occurred in a statistically significant, dose-dependent fashion during gestation days 6-8, with weight gain decrements still present at both doses through gestation day 13. High dose body weights were 94% of controls at the end of treatment on day 15. Decreases were also noted at 4.2 mg/kg, but these were not clearly test article related.

The percentage of resorptions was significantly greater than controls at the low and high doses, and similar to controls at the mid dose (Table 16). This effect, which was also present when the data were expressed on a litter basis, was due in largest part to an increase in early postimplantation loss. For example, at 4.2 mg/kg/day, 35 of the 47 total resorptions were considered "early" losses. (Early resorptions were defined in the study as "dead embryos visible to the naked eye in the form of yellowish-brown spots [on the uterine inner surface]" (p. 10). They would have occurred within 2 days of the advent of dosing on gestation day 6, qualifying them as potentially acute effects.) At 50.6 mg/kg/day, 39 of 46 resorptions were early losses. This indicates that the effect, if test article-mediated, occurred soon after the commencement of dosing. However, the increase in post-implantation loss at the low and high doses was not considered by the investigators to be substance-related due to the lack of dose responsiveness. DPR reviewers considered the effects at those two doses as possibly substance-related, citing evidence from a preliminary dosing study showing a "marked increase in intermediate resorptions at 120 and 240 mg/kg (*Note*: These doses were uncorrected for test article purity. It is likely that the actual doses were on the order of 50 - 100 mg/kg.) (DPR, 1988).

Fetal and placental weights were suppressed at the top 2 doses. A neural tube closure defect (meningocele) was reported in two fetuses at 50.6 mg/kg/day, and 12 fetuses with meningocele were recorded at 240 mg/kg/day (which was possibly 100 mg/kg/day; see previous paragraph) in a range finding study which preceded the main study (DPR, 1988). A review of the historical control data from the laboratory did not reveal any cases of meningocele. Fetal "retardations" in the form of delayed ossifications were increased at the top 2 doses (% fetuses/litter at ascending doses: 75.82%, 77.13%, 90.64%, 91.84%). These were considered signs of fetal immaturity as reflected in the reduced fetal body weights.

Based on reduced food consumption, body weight, and body weight gain the maternal NOEL was 4.2 mg/kg/day (LOEL=16.9 mg/kg/day). Based on increased dead implantations, the developmental LOEL was 4.2 mg/kg/day, though there was question about the validity of the data at this dose (see above and section IV.A.1). This study was considered acceptable by FIFRA standards.

Table 16. Incidence of resorptions in Wistar rats after gavage with metam during gestation days 6-15, caesarean data (Hellwig and Hildebrandt, 1987)

	Metam sodium, mg/kg/day			
	0	**4.2**	**16.9**	**50.6**
Total # resorptions	27	47	22	46
# early resorptions	25	35	19	39
Total # implantations	330	329	299	307
Mean % dead implants / pregnant dam[a]	7.28	17.89[+b]	6.66	14.79[+]
# litters with dead implants / total # litters (% litters with resorptions)	10/24 (40.0)	18/24* (75.0)	13/24 (54.2)	17/22* (77.3)

[a] Mean of the percent dead implants for each litter.
[b] Includes one dam in which the only fetus underwent early resorption, giving it a 100% resorption rate. If this value is excised from the calculations, the mean % dead implants per pregnant dam goes from 17.89% to 14.32%.
[+] $p<0.05$, Krauth test.
* $p<0.05$, Fisher's Exact test.

2. Rat - Gavage (Zeneca study)

Metam sodium (43.15%) was administered daily by gavage to mated Wistar-derived Alpk:APfSD female rats at 0, 5, 20 or 60 mg/kg/day (24/dose) on gestation days 7-16 inclusive (Tinston, 1993). Maternal toxicity was evident at 20 and 60 mg/kg in an increased incidence of salivation, vaginal bleeding, and oral staining, and at 60 mg/kg in an increased incidence of piloerection, eye discharge, subdued behavior, and urinary incontinence (Table 17). These signs did not occur among control dams. Many of these signs were acute responses, occurring within one day of the onset of dosing. Statistically significant body weight losses were noted at 20 and 60 mg/kg within 1 day of treatment, with weight gain decrements (or losses) occurring at all three doses within 3 days of treatment. By the end of treatment on gestation day 16, absolute weight decrements of 3%, 5% and 10% (low to high dose groups) were noted. Dose-dependent, statistically significant decrements in food consumption were also noted during the treatment period (6-7%, 13-16% and 23-34% at increasing doses). Pelvic dilatation of the kidney was noted at 60 mg/kg (4/24). No effect was observed on resorption incidence, either at the fetal or litter level (Table 18).

At 60 mg/kg there was an increase in the following major malformations: meningocele (1 fetus), microphthalmia (2 fetuses), anophthalmia (1 fetus), gross skull malformation (1 fetus), hydrocephaly (3 fetuses) and abnormal zygomatic arch (1 fetus). These were spread over several litters. Some major defects were observed at 5 and 20 mg/kg, as well, but these did not exhibit a coherent dose-response pattern. The investigators thus considered it unlikely that these defects were treatement-related.

A suppression of fetal body weights along with the presence of numerous skeletal developmental delays were observed at $\geq$20 mg/kg (Table 19). Statistically significant increases in incidence of non-ossified 2nd centrum and calcaneum were also noted at 5 mg/kg. These rates, however, were at or below the historical mean incidence rates and were within the historical range (see footnotes "a" and "b," Table 19). A similar point could be made

about the incidence rates at 20 mg/kg, except that the means were above the historical control means (though within the range). In contrast to the situation at the low dose, the decreased ossification at these two sites at 20 mg/kg was associated with a statistically significant decline in fetal weights. This makes it more convincing that the ossification declines at 20 mg/kg were due to test article exposure. In any case, the ossification effects at 5 mg/kg were not considered of sufficient toxicologic significance to designate a regulatory LOEL (see discussion in section V.B.1). Manus and pes scores indicated there was delayed ossification in fetal hand and foot bones at 60 mg/kg, suggesting developmental immaturity.

Based on the appearance of clinical signs and on decrements in maternal weight and food consumption at the mid dose of 20 mg/kg/day (decrements at the low dose were considered too small to be of toxicologic significance), the maternal NOEL was set at 5 mg/kg/day. Based on the suppression of fetal weights and the appearance of skeletal developmental delays at 20 mg/kg, the developmental NOEL was set at 5 mg/kg/day. This study was considered acceptable by FIFRA standards.

Table 17. Incidence of clinical signs and effects on body weight and food consumption in Wistar rats after gavage with metam during gestation days 7-16 (Tinston, 1993)

	Metam sodium, mg/kg/day				
	0	5	20	60	Days observed
Salivation	0/24	0/24	10/24***	24/24***	7-16
Vaginal bleeding	0/24	1/24[a]	3/24	3/24	14-16
Oral staining	0/24	0/24	5/24*	23/24***	8-16
Piloerection	0/24	0/24	0/24	10/24***	7-22
Eye discharge	0/24	0/24	0/24	3/24	7-13
Subdued behavior	0/24	0/24	0/24	6/24	7-9
Urinary incontinence	0/24	0/24	1/24	10/24***	7-22
Mean body wt. gain; days 7-8 (g)	+3.9	+1.2	-0.6**	-6.5**	n/a
Mean body wt. gain; days 7-10 (g)	+13.2	+9.5*	+4.9**	-6.7**	n/a
Mean food consumption; days 7-10 (g/day)	29.1	27.0**	25.2**	19.2**	n/a

[a] Because vaginal bleeding was evident prior to dosing in this animal, the sign was not considered dose-related.

*, **, *** p<0.05, 0.01, 0.001, respectively. Fischer exact tests were conducted for the incidence data, Dunnett's parametric t test for the body weight gain data, and analysis of variance for the food consumption data.

Table 18. Incidence of resorptions in Wistar rats after gavage with metam during gestation days 7-16, caesarean data (Tinston, 1993)

	Metam sodium, mg/kg/day			
	0	5	20	60
Total # resorptions	17	20	16	23
# early resorptions	13	17	14	18
Total # implantations	278	293	292	284
Mean % dead implants / pregnant dam[a]	6.8	7.6	5.9	8.7
# litters with dead implants / total # litters (% litters with resorptions)	10/24 (40.0)	13/24 (54.2)	10/23 (43.5)	12/21 (57.1)

[a] Mean of the percent dead implants for each litter.

Table 19. Fetal body weight suppression and fetus / litter incidence of unossified or partially ossified bones after gavage with metam during gestation days 7-16 (Tinston, 1993)

	Metam sodium, mg/kg/day			
	0	**5**	**20**	**60**
Mean fetal body weights at birth (grams)	5.07	5.03	4.80**	4.33**
Number of fetuses examined	261	273	276	261
Number of litters examined	24	24	23	21
Cervical vertebrae				
2nd Centrum, not ossified	44[a]	68*[a]	109**[a]	185**[a]
	(17)	(19)	(20)	(21*)
3rd Centrum, not ossified	10	12	18	60**
	(6)	(6)	(13)	(18**)
4th Centrum, not ossified	4	5	8	27**
	(3)	(3)	(7)	(13**)
5th Centrum, not ossified	2	3	3	14**
	(2)	(2)	(2)	(8*)
6th Centrum, not ossified	1	0	2	9*
	(1)	(0)	(2)	(5)
Ventricle tubercle**,** not ossified	10	12	26*	22*
	(6)	(9)	(9)	(13*)
Sternebrae				
5th, Not ossified	2	2	8	10*
	(2)	(2)	(5)	(9*)
5th, Partially ossified	76	70	80	106*
	(20)	(21)	(22)	(20)
Calcaneum, not ossified	113[b]	155**[b]	186**[b]	245**[b]
	(22)	(21)	(22)	(21)

Ossification data are expressed as number of fetuses (first row) and number of litters (second row, in parentheses).

* p<0.05, Fisher Exact test.

** p<0.01, Fisher Exact test for incidence data, analysis of variance for body weight data.

[a] Incidence of non-ossified 2nd centrum at 0 mg/kg/day = 44/261 (16.9%), 5 mg/kg/day = 68/273 (24.9%), 20 mg/kg/day = 109/276 (39.5%), 60 mg/kg/day = 185/261 (70.9%). Historical control mean incidence rate (10 studies, June 1990 - Feb. 1993) = 30.94%. Historical control range = 17.1% - 46.1%.

[b] Mean incidence of non-ossified calcaneum at 0 mg/kg/day = 113/261 (43.3%), 5 mg/kg/day = 155/273 (56.8%), 20 mg/kg = 186/276 (67.4%), 60 mg/kg/day = 245/261 (93.9%). Historical control mean incidence rate (10 studies, June 1990 - Feb. 1993) = 59.37%. Historical control range = 39.4% - 82.6%.

3. Rabbit - Gavage (BASF study)

Metam sodium (42.2%) was administered in a water vehicle by oral gavage to 15 artificially inseminated female Himalayan rabbits/dose at 0 (vehicle), 4.2, 12.7, or 42.2 mg/kg/day on days 6-18 post insemination (Hellwig, 1987). Maternal toxicity was evident at the high dose in the slightly decreased food consumption during the treatment period (~93% of controls).

Mean placental weight was increased by 14% at 42.2 mg/kg. This was considered to be a function of the decreased number of live fetuses at the high dose (48 *vs.* 81 in controls). Two fetuses with a neural tube closure defect (meningocele + spina bifida) were recorded at 42.2 mg/kg/day. This was considered likely to be was a response to metam sodium.

Resorptions were increased over controls by statistically significant margins at 12.7 and 42.2 mg/kg/day when expressed on a fetal basis (*i.e.*, total # resorptions / total # implantations) (Table 20). When expressed on a litter basis (*i.e.*, # litters with dead implants / total # litters), statistical significance was achieved at the high dose only, though the mid dose incidence approached significance ($p = 0.08$). The great majority of resorptions in treated animals were described as "early", defined in the study report as "dead embryos visible to the naked eye in the form of yellowish-brown spots". This was interpreted as evidence that fetal development had not yet occurred to a noticeable degree. Incidence of early resorptions increased from 1/85 to 6/92 between controls and low dose animals (Fisher exact "p" value = 0.08), further increasing to 7/84* and 40/107*** at the mid and high doses ($p \leq 0.05$, 0.0001, respectively). At the litter level, statistical significance occurred at the high dose ($p \leq 0.0001$), with the mid dose and low dose approaching significance ($p = 0.07$ and 0.06, respectively). This analysis suggests a high likelihood that early resorptions were induced at the low dose. Consequently the developmental LOEL was set at 4.2 mg/kg/day, based on the increase in early resorptions at that dose.

Benchmark dose analysis was used to calculate a developmental / acute LED_{01} based on the early resorption incidence data. A benchmark response level of 1% was considered appropriate in light of the seriousness of the endpoint, which was representative of fetal death. Of the 16 algorithms tested, both the quantal linear and the log probit models generated equivalently low AIC numbers. They were thus judged as the best approximations to the data points. The quantal linear model was ultimately chosen to represent the data because the resultant LED_{01} and ED_{01} values were lower than those generated by the log probit model, making them more health protective. The quantal linear LED_{01} was 0.79 mg/kg (Figure 3). It was rounded to 1 mg/kg for calculation of acute margins of exposure (see sections IV.A.1, IV.C.1.a and Appendix II). The corresponding ED_{01} was 1.01 mg/kg. Examination of the litter data shows that the effect at the low dose was spread among 5 litters, thus was not confined to just one or two pregnant rabbits.

Based on the decreased food consumption at 42.2 mg/kg, the maternal NOEL was set at 12.7 mg/kg/day. The LED_{01} for developmental / acute toxicity was less than the NOEL for maternal toxicity, suggesting that the embryo / fetus may be more sensitive to the toxic effects of metam sodium.

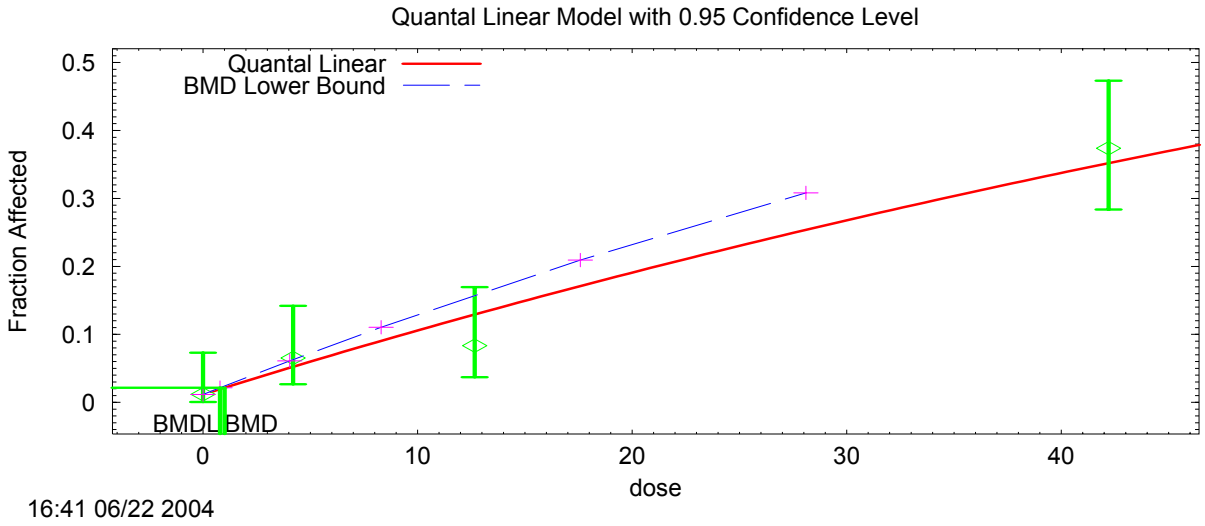
This study was deemed acceptable under FIFRA guidelines.

Table 20. Incidence of resorptions in Himalayan rabbits after gavage with metam sodium during gestation days 6-18, caesarean data (Hellwig, 1987)

	Metam sodium, mg/kg/day			
	0	**4.2**	**12.7**	**42.2**
Total # resorptions	4	7	11*	59***
# early resorptions	1	6[b]	7*	40***
Total # implantations	85	92	84	107
Mean % dead implants / pregnant dam[a]	3.6	8.1	12.4[+]	54.9[++]
# litters with dead early implants / total # litters (% litters with early resorptions)	1/14 (7.1)	5/13[c] (38.5)	5/14[d] (35.7)	13/15*** (86.7)
# litters with dead implants / total # litters (% litters with resorptions)	3/14 (21.4)	5/13 (38.5)	8/14[b] (57.1)	15/15*** (100)

[a] Mean of the percent dead implants for each litter.
[b] p = 0.08, Fisher Exact test.
[c] p = 0.06, Fisher Exact test.
[d] p = 0.07, Fisher Exact test.
*, *** p ≤ 0.05, 0.0001, Fisher Exact test.
[+], [++] p ≤ 0.05, 0.01, Krauth test.

Figure 3. Benchmark dose modeling of early resorptions / total implants in Himalayan rabbits (benchmark response = 1%); data from Hellwig (1987)



4. Rabbit - Gavage (Zeneca study)

Metam sodium (43.14%) was administered by gavage at 0, 5, 20 or 60 mg/kg/day to 20 time-mated female New Zealand White rabbits/dose on gestation days 8-20 inclusive (Hodge, 1993). Food consumption during gestation days 8-11 was suppressed to 81% and 30% of control values at 20 and 60 mg/kg. These suppressions were maintained, though to a lesser degree, through the remainder of gestation. Gestation days 8-11 were also marked by dose-dependent maternal weight losses in each of the top 2 doses. Body weight of high dose animals was 92-93% of controls on days 11-13 (98% at 20 mg/kg), when the maximum differences were expressed. Neither dose group re-attained control body weights by the end of gestation.

Some clinical signs (blood on tray, few feces on tray, genital staining, orange/red stain on tray) were evident at 60 mg/kg. Resorptions were also markedly increased at 60 mg/kg/day (Table 21). Nine out of 18 mothers at that dose sustained total litter loss. Even when the total litter loss data were excluded, resorptions were clearly increased at the high dose: 9/9 remaining high dose mothers had resorptions compared to 10/20 controls. Expressed as a proportion of fetuses, 41.3% high dose fetuses were resorbed *vs.* 10.4% among controls. No increase in resorptions was noted at the mid dose.

Among fetuses, the high dose was also associated with decreases in mean live litter size (5.78 *vs.* 8.40 in controls) and mean litter and fetal weights (40.1 g *vs.* 44.8 g in controls, $p<0.01$). Cleft palate was observed in one out of 148 live fetuses at 5 mg/kg and two out of 52 live fetuses at 60 mg/kg. Since this character was only rarely observed among historical controls (while these data were not provided, it is stated that “This defect was seen most recently in a control rabbit fetus [a runt, *i.e.*, <25 g] in a study conducted in January 1990.”), metam involvement could not be excluded. However, as there was no occurrence at 20 mg/kg, the single low dose fetus may have been anomalous. There was a statistically significant increase in skeletal variants at the two top doses (incidence at ascending doses: 82.2%, 89.7%, 93.2%*, 98.6%*; $p<0.05$). Individual skeletal variants exhibiting statistically significant increases included partially ossified odontoid (44.6% in controls, 80.8% at the high dose), 27 pre-sacral vertebrae (20.2% in controls, 33.8% at the mid dose, 71.2% at the high dose), partially ossified 5th vertebrae (38.1% in controls, 13.5% at the high dose [*i.e.*, a decrease]), extra 13th ribs (35.7% in controls, 86.5% at the high dose).

Based on reductions in food consumption and body weight at 20 mg/kg, the maternal NOEL was set at 5 mg/kg/day. Based on the increase in skeletal variants at 20 mg/kg, the developmental NOEL was set at 5 mg/kg/day. This study was acceptable under FIFRA guidelines.

Table 21. Incidence of resorptions in New Zealand White rabbits after gavage with metam sodium during gestation days 6-18, caesarean data (Hodge, 1993)

	Metam sodium, mg/kg/day			
	0	**5**	**20**	**60[b]**
Total # resorptions	21	17	11	35** 104**
# early resorptions	17	11	8	32** 100**
Total # implantations	189	165	159	87 156
Mean % dead implants / pregnant dam[a]	10.4	12.6	6.8	41.3** 70.7**
# litters with dead implants / total # litters (% litters with resorptions)	10/20 (50.0)	9/16 (56.3)	6/17 (35.3)	9/9* 18/18** (100)

[a] Mean of the percent dead implants for each litter.
[b] At 60 mg/kg/day, nine of the 18 litters sustained total resorption (*i.e.*, all of the fetuses were resorbed). The top figure in each row of this column represents the data when the total litter resorptions were excluded from the tally. The bottom figure represents the data when the total litter resorptions were included in the tally.
*/** $p \leq 0.05$ and 0.01, respectively, Fisher Exact test.

5. Rat - Oral gavage (2 Soviet-era studies)

An English abstract accompanying a short paper in Russian by Chegrinets *et al* (1990) reported a "substantial increase in the total and postimplantation fetal death in rats" following daily administration of metam sodium at 90 mg/kg to an unspecified number of pregnant dams throughout gestation. It was presumed, though again not specified, that dosing was by oral gavage. Furthermore, "though no external deformities were noted in 20-day old fetuses, body weight and body length changes were noted at this dose. Fetal skeletons showed slowed ossification." OEHHA (1992), apparently in possession of the full paper, noted further that "there was a significant increase in edema found in various organs and tissues and one case of hydrocephalus," also at 90 mg/kg. Finally, "nine cases of umbilical hernia were also observed." Because no effects were noted at the next lower dose of 4.5 mg/kg, this was designated by OEHHA as the NOAEL dose.

Nesterova (1969) treated an unspecified number of rats by gavage with 22.5 mg/kg carbathion (metam sodium) from before pregnancy until 1 month after parturition. No account was provided of the effect of this treatment on the dams. It was reported, however, that "in their number, weight and length, the progeny born to treated rats did not differ significantly from the progeny of control animals. The young rats displayed no pathological deviations."

Table 22. No-observed-effect-level (NOEL) / lowest-observed-effect-level (LOEL) for reproductive and developmental toxicity of metam sodium

Species / Sex	Exposure regimen	Effects at LOEL	NOEL	LOEL	Reference
Rat (M/F)	2-generation reproduction; drinking water	1. repro. effects: none 2. pup effects: lower day 22 pup weights (F1 & F2)	1. repro. NOEL > 0.1 mg/ml/day (8.7-53.5 mg/kg/day) 2. pup NOEL = 0.03 mg/ml/day (mean gestational dose & range, F0 parents = 6.9 (5.2-8.1) mg/kg/day; F1 parents = 5.7 (4.6-6.5) mg/kg/day)	1. n/a 2. pup LOEL = 0.1 mg/ml/day (mean gestational dose and range, F0 parents = 17.6 (14.2-19.6) mg/kg/day; F1 parents = 14.4 (12.1-15.3) mg/kg/day)	Milburn, 1993
Rat (F)	Teratology; gavage	1. dvpmtl. effects: increased post-implantation loss 2. maternal effects: reduced food consumption, body weight & weight gain	1. dvpmtl. NOEL< 4.2 mg/kg/day[a] 2. maternal NOEL = 4.2 mg/kg/day	1. dvpmtl. LOEL = 4.2 mg/kg/day[a] 2. maternal LOEL = 16.9 mg/kg/day	Hellwig & Hilde-brandt, 1987

Table 22 (continued)

Species / Sex	Exposure regimen	Effects at LOEL	NOEL (or LED)	LOEL	Reference
Rat (F)	Teratology; gavage	1. dvpmtl. effects: decreased fetal weights, skeletal developmental delays 2. maternal effects: clinical signs and reduced food consumption / body weight	1. dvpmtl. NOEL = 5 mg/kg/day 2. maternal NOEL = 5 mg/kg/day	1. dvpmtl. LOEL = 20 mg/kg/day 2. maternal LOEL = 20 mg/kg/day	Tinston, 1993
Rat (F)	Teratology; route and dosing regimen unknown, but assumed to be oral gavage	1. dvpmtl. effects: ⇑ total & postimplantation fetal death, ⇓fetal body wt./length, slowed ossification, edema in various organs / tissues 2. maternal effects: not reported	1. dvpmtl. NOEL = 4.5 mg/kg/day 2. ---	1. dvpmtl. LOEL = 90 mg/kg 2. ---	Chegrinets *et al*, 1990; OEHHA, 1992
Rat (F)	Teratology; gavage	1. dvpmtl effects: none 2. maternal effects: not reported	1. dvpmtl. NOEL > 22.5 mg/kg/day 2. ---	1. --- 2. ---	Nesterova, 1969
Rabbit (F)	Teratology; gavage	1. dvpmtl. effects: increased incidence of early resorptions 2. maternal effects: decreased food consumption	1. dvpmtl. LED_{01} = 1 mg/kg/day[b] 2. maternal NOEL = 12.7 mg/kg/day	1. dvpmtl LOEL = 4.2 mg/kg/day 2. maternal LOEL = 42.2 mg/kg/day	Hellwig, 1987

Table 22 (continued)

Species / Sex	Exposure regimen	Effects at LOEL	NOEL	LOEL	Reference
Rabbit (F)	Teratology; gavage	1. dvpmtl. effects: increased incidence of skeletal variants 2. maternal effects: decreased food consumption & body weight	1. dvpmtl. NOEL = 5 mg/kg/day 2. maternal NOEL = 5 mg/kg/day	1. dvpmtl. LOEL = 20 mg/kg/day 2. maternal LOEL = 20 mg/kg/day	Hodge, 1993

[a] Lowest dose tested.

[b] This value was a result of rounding up from the LED_{01} of 0.79 mg/kg. This value was calculated using the benchmark dose - quantal linear algorithm.

H. NEUROTOXICITY

1. Rat - Acute neurotoxicity

Rangefinding study. Metam sodium (43.15%) dissolved in water was delivered one time only by gavage to non-fasted Sprague-Dawley Crl:CDBR rats at 22, 43, 65, 129, 259, 539, 647, 755, or 863 mg/kg (2-6 rats/sex/dose) (Lamb, 1993a). Deaths occurred at 755 (1/6 males, 2/6 females) and 863 (0/4 males, 3/4 females) mg/kg on days 0-2. Major clinical signs in survivors included salivation (≥43 mg/kg; time of peak effect [TPE]=30 min), lacrimation (≥65 mg/kg: TPE=30-45 min), rocking / swaying (≥259 mg/kg: TPE=1 hr), high carriage (≥539 mg/kg: TPE=45 min; 259 & 345 mg/kg: TPE=4 hr), hypoactivity (≥259 mg/kg: TPE=1.5-3 hr) and ptosis (≥539 mg/kg: TPE=1.5-2 hr). Incidence of these signs was dose-dependent, reaching 100% in most cases by 600 mg/kg. Signs persisted in some animals through the last observation point (480 min). Decrements in body weight were noted at ≥259 mg/kg. Detection of body weight effects at the low doses was impossible due to the lack of control data. The NOEL was set at 22 mg/kg based on clinical signs appearing at 43 and 65 mg/kg. This study was considered supplemental by FIFRA standards.

Definitive study. Metam sodium (43.15%) dissolved in water was administered as a single gavage dose to Sprague-Dawley Crl:CDBR rats (12-16/dose) at 22, 324 or 647 mg/kg (Lamb, 1993b). 31% of the males and 19% of the females died at the high dose, all but one of these by day 2. A large number of behavioral observations included in the functional observational battery (home cage, handling, open field, sensory, neuromuscular and physiological observations) were altered at the top two doses, with incidence rates ranging from 16%-100% at those doses. Ambulatory and total motor activity were decreased at all doses on day 0. Suppression of mean ambulatory counts was noted at the low dose on day 0 in 34.8% of the males ($p<0.05$) and 27.4% of the females. Similarly, total activity counts were suppressed 31.9% in low dose males and 31.6% in low dose females ($p<0.05$ for both sexes) on day 0. An acute systemic NOEL was set at 22 mg/kg based on hypothermia, weight gain decrements and small fecal size at ≥324 mg/kg. An acute neurotoxicity LOEL was set at 22 mg/kg based on effects on ambulatory and total motor activity at that dose.

In a companion study designed to gauge the potential for inhibition of plasma, RBC, or brain cholinesterase, metam sodium was gavaged in a single dose at concentrations of 0 (deionized water at pH 9) and 647 mg/kg to 10 Sprague-Dawley rats/sex/dose (Lamb, 1993c). Blood samples were collected from 5 animals on day 0 at the time to peak effect (45 minutes post dose) and from the other 5/sex/group at 24 hours post dose. One male and two females died on the day following dosing at 647 mg/kg. These animals exhibited reddened adrenals, reddened mucosa or dark red areas in the glandular stomach, and pale or mottled lungs. The male had reddened kidneys and cervical lymph nodes, while one female had reddened kidneys. Prominent signs in survivors included gait alterations, lacrimation, salivation, and clear and/or tan staining on the forelimbs and/or around the mouth. Clear inhibition of plasma, RBC, or brain cholinesterase was not demonstrated. However, these results may be inconclusive as it appears that precautions were not taken to minimize dilution-mediated dissociation of the inhibitor from the enzyme (*Note*: this is particularly important with respect to carbamates. For further discussion, see Ecobichon, 2001).

2. Rat - Subchronic neurotoxicity

Metam sodium (43.15%) was administered in the drinking water to 12 Alpk:APfSD rats/sex/dose for 13 weeks at 0, 0.02, 0.06 or 0.2 mg/ml (Allen, 1994). The mean received

doses were 2.0, 6.0 or 14.7 mg/kg/day in males and 3.3, 8.4 or 17.8 mg/kg/day in females. Weight gain decrements were noted at the high dose in both sexes, and at the mid and low doses in females, though these latter were less than 10% (8% at 0.06 mg/ml and 6% at 0.02 mg/ml). Food consumption was also depressed at the high dose (mean weekly reduction: 9.7% in males, 12.4% in females) and, to a lesser extent, at the lower doses, particularly in females. Water consumption was depressed at all doses, though this may have been a function of poor potability. Behavioral and motor activity tests did not show clear effects (though motor activity appeared to be generally higher at the top dose in males and at the top 2 doses in females as the study progressed). A subchronic NOEL was set at 0.02 mg/ml (~2.0 mg/kg) based on decreased food/water consumption. A neurotoxic NOEL was not established due to the high control levels of neuronal necrosis (3/6 control males and 3/6 high dose males; 1/6 control females and 1/6 high dose females), which rendered the study unacceptable by FIFRA standards. Nonetheless, clear behavioral neurotoxicity was not seen at any dose.

Table 23. No-observed-effect-level (NOEL) / lowest-observed-effect-level (LOEL) for neurotoxicity of metam sodium

Species / Sex	Exposure regimen	Effects at LOEL	NOEL	LOEL	Reference
Rat (M/F)	Acute; gavage (rangefinding)	Salivation	22 mg/kg	43 mg/kg	Lamb, 1993a[a]
Rat (M/F)	Acute; gavage	1. Acute systemic effects: hyperthermia, reduced weight gain, small fecal size 2. Acute ntx effects: decreased ambulatory & total activity counts on day 0	1. Acute systemic: 22 mg/kg 2. Acute ntx: <22 mg/kg[c]	1. Acute systemic: 324 mg/kg 2. Acute ntx: 22 mg/kg[3]	Lamb, 1993b[b]
Rat (M/F)	13 weeks; gavage	1. Subchronic systemic effects: decreased food/water consumption 2. Ntx effects: unclear	1.Subchronic systemic: 0.02 mg/ml (~2 mg/kg/day) 2. Subchr. ntx: not established	1. Subchronic systemic: 0.06 mg/ml (~6 mg/kg/day) 2. Subchr. ntx: not established	Allen, 1994

Note: Despite the fact that neurotoxic effects are undoubtedly systemic in nature (as opposed to irritative effects, which are local responses), a distinction was made in the analysis of the neurotoxicity studies included in section III.H and in Table 23 between effects that were clearly the result of neurotoxicity and other systemic effects. Accordingly, separate NOELs/LOELs were assigned for these categories.

[a] LD_{50} > 755 mg/kg

[b] LD_{50} > 647 mg/kg

[c] Lowest dose tested.

I. SPECIAL TOXICITY OR PHARMACOLOGY STUDIES

Several non-FIFRA guideline studies were reported for metam sodium.

1. Immunotoxicity

Female B6C3F1 mice treated with metam (referred to as SMD; purity, 90-95%, though it was administered as a dihydrate so that the actual concentration was 70-74%; the vehicle was water) by gavage at 300 mg/kg/day for 3, 5, 10 or 14 days produced the following signs: 1. decreased thymus weight at all time points, 2. increased spleen weight after 10 and 14 days, 3. increased bone marrow cellularity at 10 and 14 days, 4. decreased mature lymphocyte populations (with a greater effect in the thymus than in the spleen), 5. relatively selective depletion of $CD4^+CD8^+$ thymocytes, and 6. decreased body weight (Pruett *et al*., 1992). According to the study authors, "Overall patterns of changes were consistent with the conclusion that SMD rapidly depletes most $CD4^+CD8^+$ thymocytes, more slowly depletes a smaller number of more mature lymphocytes in the thymus and spleen, and induces compensatory and/or detoxication mechanisms after 10-14 days of exposure." Also, "SMD at 50-300 mg/kg/day for 7 days caused substantial, dose-dependent suppression of NK cell activity."

SMD was also administered by the dermal route to shaved upper dorsal skin after pretreatment of the site with 20 μl of acetone to disrupt surface tension. Doses were 100, 200 and 300 mg/kg/day. Animals were treated for 4 days, followed by analyses on day 5. Dose dependent, statistically significant, suppression of NK cell activity was observed at 200 and 300 mg/kg/day. Spleen weights were statistically increased by ~25% at 200 mg/kg/day, though statistical significance was not achieved at 300 mg/kg/day. Thymus weights were statistically decreased by ~30% at 300 mg/kg/day. Body weight gains were reduced in a dose-dependent manner, though statistical significance was achieved only at 300 mg/kg/day. At that dose the animals lost ~6% of their original body weight. All lymphocyte subpopulations in the thymus were statistically decreased at 300 mg/kg/day compared with controls, though the percentage of the total population was decreased only for the $CD4^+CD8^+$ cells (65.9% in controls, 46.3% in high dose animals). A dermal NOEL for SMD was set at 100 mg/kg/day, based on suppression of NK cell activity and spleen weights at 200 mg/kg/day.

A follow-up study from the same laboratory compared the ability of SMD to affect immunological parameters in female B6C3F1 mice with that of two other dithiocarbamates, sodium diethyldithiocarbamate (DEDTC) and disodium ethylene-bis(dithiocarbamate) (EBD) (Padgett *et al.*, 1992). Animals were treated daily for 7 days by gavage with SMD in a dose range of 150-300 mg/kg/day (the high dose was considered near the maximum tolerated dose). DEDTC and EBD were administered at up to 3.3-fold higher levels due to their lower oral toxicity.

SMD caused significant reductions in thymus weight at 200, 225, or 300 mg/kg/day (~50%) and splenic NK cell activity at 150, 225, or 300 mg/kg/day (~50%). These doses were markedly lower than the dose of 1000 mg/kg/day of DEDTC that was required to achieve a similar thymus weight reduction. 675 mg/kg/day EBD had a smaller, non-statistically significant effect on thymus weight. Neither DEDTC nor EBD suppressed splenic NK cell activity at any dose. Spleen weight was significantly increased by 1000 mg/kg/day DEDTC (~50%) and 675 mg/kg/day EBD (~15%). 200 mg/kg/day SMD elicited only a non-statistically significant increase in spleen weight. Despite the greater immunotoxic potency of SMD *in vivo*, DEDTC was almost two orders of magnitude more effective than either SMD or EBD in causing thymocyte and splenocyte death *in vitro*. This study confirmed the immunotoxic

effects of SMD, showing also that the *in vitro* cytotoxic effects of dithiocarbamates do not correlate with their *in vivo* immunotoxic effects.

In a study of the immunotoxicity of MITC, groups of five 8-10 week old female B6C3F1 mice/dose were given 0, 15, 30, or 45 mg/kg/day MITC (purity unstated) in water for 5 days by oral gavage (Kiel *et al*, 1996). Hematological determinations were evaluated on the day after the last dose. Thymus and spleen were removed for cellular and flow cytometric analysis of control and 45 mg/kg/day animals.

Body weight decreased by less than 10% in all MITC-treated groups. Significant changes in thymus weight (~50% of control) and thymus cell subpopulations were reported in mice given 45 mg/kg/day. There were no significant changes in spleen weight or natural killer (NK) activity. Total WBC numbers were increased to ~175% of control at 30 mg/kg/day. The percentage of blood neutrophils was increased approximately 2-fold, and the percentage of blood lymphocytes was decreased to 80-90% of control at 15 and 45 mg/kg/day. Flow cytometric analysis of thymus cells indicated a decrease to ~90% of control of $CD4^{+}CD8^{+}$ thymocytes, and an increase to ~140% of control in the percentage (but not absolute number) of $CD4^{-}CD8^{-}$ thymocytes at 45 mg/kg MITC. *Unlike* the parent compound, MITC did not significantly affect NK cell activity or increase spleen weight. This suggested that some effects of SMD are separable from those of MITC. It was also shown that SMD-induced thymic atrophy occurs in rats at a dose about 50% lower dose than in mice. Individual study data were not submitted to DPR; therefore, only summary information were available for evaluation.

2. Reproductive pharmacology

Like other dithiocarbamates, metam sodium blocks the conversion of dopamine to norepinephrine, probably by chelating the copper-containing portion of dopamine-β-hydroxylase, the enzyme responsible for this conversion. In a study by Goldman *et al.* (1994), "ovariectomized, steroid-primed Long-Evans rats showed a dose-related (25-100 mg/kg, IP) suppression of the [norepinephrine-dependent LH] surge and a drop in norepinephrine when SMD was given at 1100 hours, a few h prior to the expected LH rise." The percentage of ovulating (intact) rats was also shown to decline with IP doses of 50-300 mg/kg. A potential mechanism for a metam-mediated decline in reproductive fitness is thus presented by this study. However, no evidence for such a decline surfaced in the 2-generation reproduction study of Milburn (1993) (see discussion, section III.F.1.). Possible reasons for this apparent discrepancy include: (1) differences in route of exposure (intraperitoneal in Goldman, oral in Milburn), which may have resulted in higher systemic blood or pituitary concentrations in the Goldman study, (2) rat strain (Long-Evans in Goldman, Alpk:APfSD in Milburn), (3) use of ovariectomized, steroid-primed rats in Goldman *vs.* intact rats in Milburn, and (4) timing of the dose (just before the LH rise in Goldman, constant in Milburn).

J. TOXICITY OF THE BREAKDOWN PRODUCTS AND METABOLITES OF METAM SODIUM

1. Methyl isothiocyanate (MITC)

The primary degradation product of metam sodium is MITC (methylisothiocyanate). MITC evolves as a gas after metam application, providing most of the pesticidal activity. A complete Risk Characterization Document on MITC has been issued by DPR (DPR, 2004).

There are currently only 2 registered products, both wood preservatives, that list methyl isothiocyanate (MITC) as an active ingredient. In 1999, reported use of MITC totaled 620 pounds in California, representing a tiny fraction of the MITC released into the atmosphere. Agricultural use rates in California of metam sodium, the major parent compound of MITC, rose steadily from 5.9 million pounds in 1990 to 15.3 million pounds in 1995 to 17.3 million pounds in 1999. Metam sodium is converted on a mole-to-mole basis to MITC, which, based on the relative molecular weights of the 2 compounds, results in a conversion rate of approximately 60% by weight. It is thus estimated that an average of 9.2 million pounds per year of MITC were released into the air from agricultural applications of metam sodium in the 1995-1999 period. Another compound, dazomet, a thiadiazine used as an anti-microbial and soil sterilant, also produces MITC upon degradation. However, dazomet use rates under agricultural settings are minor compared to those of metam sodium, never rising above 23,000 pounds for any year between 1990 and 1999.

MITC entered the public consciousness following the accidental spill of 19,500 gallons of 32.7% metam sodium from a railroad tank car into the Sacramento River on July 14, 1991. This occurred at the Cantara Loop, 6 miles north of the town of Dunsmuir and 45 miles north of Shasta Lake. Exposure of the Dunsmuir area population to airborne MITC evolving from the river resulted in numerous visits to local healthcare facilities, largely due to complaints of eye and respiratory irritation, nausea, headache, dizziness, vomiting and shortness of breath. More persistent symptoms, including a chemically-induced asthma known as reactive airways dysfunction syndrome (RADS), may also have occurred. Reliable measurements of MITC air concentrations in the affected localities were not available during the first three days after the accident. Once they did become available, the highest of these measurements was 125 ppb, registered at Dunsmuir on Day 4 post spill. Attempts to estimate peak MITC air concentrations during the first 3 days were based on Gaussian plume modeling. There was substantial uncertainty associated with the parameters required to generate the estimates using the Gaussian approach, leading to substantial uncertainty in the estimates themselves. The parameters included the metam sodium-to-MITC conversion rate, the flux of MITC from the water surface, and the meteorologic conditions. The Office of Environmental Health Hazard Assessment estimated the peak 1-hour time weighted average concentration to be 1300 ppb for a distance of up to 100 meters from the river, dipping to 340 ppb at 500 meters. DPR's maximal 1-hour time weighted average estimates were 4500 ppb at 100 meters and 1240 ppb at 500 meters downwind from the river. The Metam Sodium Task Force, an industry support group, estimated maximum 1-hour time weighted average air concentrations of MITC at the river's edge to be between 3 ppm and 650 ppm.

Some residents of the town of Earlimart, California were exposed to airborne MITC following an apparently improper sprinkler application of metam sodium to an adjacent field on November 13, 1999. Symptoms included eye, respiratory tract, and skin irritation, as well as possible exacerbations of asthmatic conditions. The presence or absence of persistent

symptoms (*eg.*, RADS) is currently unknown. One hour average air concentration estimates based on Gaussian plume modeling fell between 0.5 and 1 ppm for the neighborhood closest to the field. These were likely to be lower bound estimates.

Pharmacokinetics. Because no inhalation pharmacokinetics studies have been published in the open literature or submitted to the State of California, the metabolic fate of MITC was assessed mainly by the same oral exposure study as was used to analyze metam sodium pharmacokinetics. Eighty eight to 96% of the orally administered MITC was absorbed within 24 hours. In that time period, 80-82% was excreted in the urine, <1-2% in the feces and 6-15% in the expired air (as CO_2). The rest was excreted in the expired air as unmetabolized MITC (<1-2%) or carbonyl sulfide + carbon disulfide (<1%), or remained bound to tissues (1-3% after 168 hours). Thyroid, liver, kidneys, whole blood and adrenals were sites of tissue distribution. The major metabolites in the urine were N-acetyl-cysteine and cysteine conjugates. No unmetabolized MITC was detected in the urine.

Acute toxicity. The most relevant acute toxicity endpoint identified was eye irritation, established in an experimental study conducted with human volunteers. The critical air concentration NOEL was 220 ppb for exposure to the isolated eye region using special goggles. It was based on the observation of eye irritation at 800 ppb. A NOEL for an absorbed dose was not calculated for the study because MITC was not inhaled by the subjects. The irritating effect of MITC on ocular and respiratory tissues was also evident in animal studies, and in humans exposed to MITC either after the 1991 Sacramento River spill or after agricultural use. The air concentration NOEL of 220 ppb was the critical NOEL used for evaluation of potential short-term risk to residents and bystanders (adults and children) from exposure to airborne MITC.

The acute toxicity of MITC has also been demonstrated in animal studies. Acute oral exposure of rats between 25 and 300 mg/kg in one study led to sedation, dyspnea, altered body positions, ruffled fur, crying, spasms and exophthalmos. The LD_{50} in that study was 55 mg/kg in females and 82 mg/kg in males. Similar clinical signs were noted upon dermal exposure of rats at a dose range of 60-600 mg/kg (LD_{50} = 181 [F] and 225 [M] mg/kg) and rabbits at a dose range of 50-300 mg/kg (LD_{50} = 202 [F] and 145 [M] mg/kg). Other studies have shown MITC to be a powerful irritant to both skin and eyes. Acute inhalation studies in animals have yielded conflicting results, but do identify a potentially very damaging route of exposure. The most reliable studies in Sprague-Dawley rats show a 1-hour LC_{50} of 633 ppm and a 4-hour LC_{50} of 180 ppm. Clinical signs in the former study included hyperactivity followed by hypoactivity, eye irritation, dyspnea and convulsions.

Subchronic toxicity. Subchronic toxicity was evident in the critical 4-week Wistar rat inhalation study, which was conducted according to a 6-hours/day, 5-days/week exposure regimen. This study established a LOEL at the low dose of 1.7 ppm based on evidence of nasal epithelial atrophy at that dose. Signs and symptoms at the intermediate dose of 6.8 ppm included nasal epithelial atrophy, a rise in polymorphonuclear granulocytes (considered evidence for sub-histopathologic lung damage), and clinical signs. The latter, which were of unclear toxicologic significance, included somnolence, eye closure, and ruffled fur. Signs of severe respiratory tree irritation and, possibly, damage, were observed at the high dose of 34 ppm. These included bronchopneumonia, emphysema, bronchial and tracheal epithelial proliferation, rhinitis, and focal metaplasia, in addition to increases in lung weight and decreases in body weight. Haber's Law, which assumes that the longer the exposure time, the less MITC is

required to elicit a particular response, was invoked to convert the 6-hours/day, 5-days/week exposure regimen to 24-hours/day, 7-days/week. This resulted in an estimated LOEL of 300 ppb. A default uncertainty factor of 3 was then used to calculate an estimated critical subchronic NOEL of 100 ppb. A LOEL of 2 mg/kg/day was reported in a 3-month oral gavage study in rats based on stomach lesions, liver inflammation, spermatogenic disturbance, and alteration in adrenal and ovary weights. These effects were considered slight at that dose, but increased in severity at 10 and 40 mg/kg/day. A NOEL of 0.7 mg/kg/day was established in a 3-month mouse oral gavage study based on reduced body weight gain and increased liver weight at 1 mg/kg/day. At higher doses, toxic effects included thickening of the forestomach lining, inflammation of the liver, testicular / spermatogenic disturbances and decreased ovary weights.

Chronic toxicity and oncogenicity. No chronic inhalation toxicity studies of MITC were identified in the published literature or in documents submitted to DPR. Chronic exposure of rats and mice through the drinking water resulted in decrements in body weight gain. These were likely secondary to decreased water consumption, which was, in turn, due to unpalatability. The chronic NOELs in rats and mice, 0.46 and 2.74 mg/kg/day, were based on signs largely, if not completely, dependent on the decreased water consumption.

In dogs exposed to MITC by gavage, an apparent NOEL for MITC of 0.4 mg/kg/day was based on a plethora of signs both irritative and systemic in nature. Severe pathology noted at the mid dose was most likely due to overexposure to the corn oil vehicle. Unfortunately, a precise evaluation of this study has not been possible because it is not currently available to DPR.

The 2-year rat drinking water study provided weak evidence that MITC may have induced mammary fibroadenomas and carcinomas in females. A small increase in subcutaneous fibromas was also noted at the high dose, though it was unclear if MITC was responsible for the rise. The 2-year mouse drinking water study provided evidence that MITC may have induced cutaneous fibrosarcomas in both sexes. However, neither long-term drinking water study provided data that were sufficiently strong with regard to oncogenesis to trigger a quantitative oncogenic risk evaluation. In mice, various serum chemical, hematologic and histologic alterations were also noted at the top 2 doses, with amyloid degeneration in the kidney possibly increased at all doses in males and ovarian cysts in high dose females. However, the significance of these histologic observations was obscured by the lack of a historical control data base.

Genotoxicity. The results from gene mutation assays using two different microorganisms (*Salmonella typhimurium*, *Escherichia coli*) were negative for MITC mutagenicity. However, none of the studies was acceptable to DPR due to various deviations from TSCA guidelines. In one acceptable mammalian cell assay, Chinese hamster V79 cells exposed to a range of MITC concentrations, ±S9 activating microsomes, showed no increase in mutation frequency in two trials. Cytogenetic investigations of possible chromosome effects provided no evidence for induction chromosomal aberrations in human lymphocytes. A weakly positive aberration response was registered in Chinese hamster V79 cells. Tests for DNA damage, and sister chromatid exchange were negative.

Reproductive toxicity. A 2-generation drinking-water study and a 3-generation oral gavage study were conducted to determine if MITC had effects on reproductive function in rats. While a decrease in pre-weaning viability was noted in the F_1 pups at all doses in the 2-generation study, lack of dose-responsiveness and statistical significance made it unlikely that MITC exposure was responsible. MITC was therefore not considered to be a reproductive toxicant.

Teratogenicity. Both maternal and fetal toxicity were evident in the teratogenicity studies. Maternal toxicity was expressed as decrements in body weight and food consumption at as low as 5 mg/kg in both species. Thickened maternal stomach lining was evident at 25 mg/kg in rats. Decreases in fetal size and weight were noted in rats at 25 mg/kg and in rabbits at 5 mg/kg, with a separate study showing embryo toxicity and reduction in 24-hour survival at 10 mg/kg. However, MITC was not considered a developmental toxicant because doses which affected fetal parameters were associated with maternal toxicity.

Immunotoxicity. Immune toxicity was noted in one 5-day mouse gavage study, though the MITC doses examined were generally higher than those determining the critical subchronic NOELs. Significant changes in thymus weight (~50% of control) and thymus cell subpopulations were reported in mice given 45 mg/kg/day. Total WBC numbers were increased (~175% of control) at 30 mg/kg/day. The percentage of blood neutrophils was increased (~200% of control), and the percentage of blood lymphocytes was decreased (~80-90% of control) at 15 and 45 mg/kg/day. Flow cytometric analysis of thymus cells at 45 mg/kg/day indicated a decrease (~90% of control) in $CD4^+CD8^+$ thymocytes and an increase (~140% of control) in the percentage (but not absolute number) of $CD4^-CD8^-$ thymocytes. These results raised the possibility that immunotoxicity could result from longer-term exposures to lower doses of MITC. Unfortunately, no studies were available to assess the extent of immunotoxicity when exposure occurs by inhalation.

For a summary of the results of the MITC risk characterization, see section IV.C.2. below.

2. Methyl isocyanate (MIC)

Human exposure to methyl isocyanate (MIC) may occur following metam sodium applications due to photolysis of the metam sodium breakdown product MITC. Methyl isocyanate is not a registered pesticide in California. Therefore, detailed reports of human and animal experimental toxicity studies were not submitted to DPR for review. Information was obtained from toxicity reviews of MIC supplied by the American Conference of Governmental Industrial Hygienists (ACGIH), the Hazardous Substance Data Bank (HSDB) of the National Library of Medicine, the University of California at Davis (UCD), and the US EPA, as well as from reports published in the open literature in the wake of the Bhopal MIC disaster of December, 1984, which killed 2500-5000 people and injured up to 200,000 (Mehta *et al.*, 1990).

Acute toxicity, including data from Bhopal. Methyl isocyanate is highly acutely toxic to humans and animals, causing tissue damage by reacting with sulfhydryl, carboxyl and hydroxyl groups (Bajaj *et al.*, 1993). The rate of MIC hydrolysis to methylamine and dimethylurea is thought to be much slower in moist air than in water (US EPA, 1986), making it likely in the case of an environmental release that human exposure will be to the parent compound. Symptoms following acute exposure to high air concentrations of MIC include pulmonary edema, dyspnea, respiratory failure, asthma, chest pain, skin and eye injuries, and death. The 6-hr LC_{50} is 6100 ppb (14 mg/m^3) in rats, 12,200 ppb (28 mg/m^3) in mice and 5400

ppb (12 mg/m^3) in guinea pigs (Dodd *et al*, 1986). There were no deaths in any species at 2400 ppb, indicating that the LC_{50} curve is steep. No direct evidence was found to indicate that MIC can cause pulmonary sensitization. However, a Mellon Institute report (1970) indicated that not only is MIC a strong dermal sensitizer in guinea pigs, but that inhalation exposure may elicit dermal sensitization upon subsequent dermal exposure (though the possibility remained that the inhalation protocol was not well-controlled for dermal exposure). Interestingly, conventional pulmonary sensitization in guinea pigs was not observed in the Mellon study. The report concluded that the data did not permit exclusion of MIC as a possible pulmonary sensitizer, particularly in view of the technical difficulties in measuring this response and the well-known ability of other isocyanates to induce pulmonary sensitization.

Three acute human studies were reviewed by the American Conference of Governmental Industrial Hygienists (ACGIH, 1986). The following is quoted from that source:

> In the first study, "acute experiments of one- to five- minute duration were performed on four human volunteers. At 0.4 ppm MIC the subjects could not perceive odor and experienced no irritation of the eye, nose, or throat. At 2 ppm no odor was detected, but the subjects experienced irritation and lachrymation. At 4 ppm the symptoms of irritation were more marked. Exposure was unbearable at 21 ppm. In another study, eight human volunteers in a ceramic lined chamber were exposed for one minute at 1.75 ppm MIC. None perceived an odor, all experienced eye irritation, seven had tearing, and three had nose and/or throat irritation. At the end of exposure all effects disappeared within 10 minutes, except that one woman reported of having something in her eye for 45 minutes. Six of the same persons were exposed for 10 minutes at 0.5 ppm. Eye irritation was evident earliest and was experienced by all. Tearing and nose / throat irritation were less evident. One person perceived an odor. In a third study, seven male volunteers were exposed to various concentrations of MIC, usually for one minute. Airborne concentrations studied were 0, 0.3, 1.0, 2.5, or 5.0 ppm. Only three of the seven subjects could detect 5 ppm MIC by its odor. There was no consistent relationship between odor detection and vapor concentration. All persons who perceived an odor reported olfactory fatigue. The only unanimous responses consisted of eye irritation and tear formation at 5 ppm in 50 seconds or less. All responses disappeared within 3 minutes after exposure."

There is no consensus with respect to the concentration of airborne MIC attained at Bhopal, though levels between 13 (Dave, 1985) and 100 ppm (Varma, 1986) have been estimated. Nonetheless, much insight on the toxicity of the compound after acute exposure has been gained by studying the survivors, as well as in investigations on laboratory animals in which the experimental design was informed by the clinical data from Bhopal. Much of the following discussion of this subject is distilled from a comprehensive review by Mehta *et al.* (1990).

The main symptom resulting from the acute exposure at Bhopal, and the main cause of death, was pulmonary distress, expressed in many facets of lung function and pathological examination. Adverse impacts were also noted on the circulatory, gastrointestinal and central nervous systems. Studies on survivors suggested that the pulmonary effects were due to the corrosivity of MIC. Clinical signs reported within the first 3 days of the accident included breathlessness, cough, throat irritation / choking, chest pain and hemoptysis (expectoration of

blood) (Misra *et al.*, 1987). Radiological signs included interstitial and alveolar edema and destructive lesions with cavitation, pneumomediastinum (presence of air in the mediastinum which may interfere with respiration and circulation) and emphysema (Sharma and Gaur, 1987). Lung function tests revealed chronic respiratory impairment indicative of restrictive lung disease with alveolitis (Patel *et al.*, 1987), as well as pulmonary hypertension in some victims. Biopsies performed 6-8 months post exposure revealed alveolar wall thickening, interstitial fibrosis and bronchiolar exudates (Kamat *et al.*, 1985). Fibrosing bronchiolitis obliterans appears to be a long term result of injury. Animal studies corroborate the field observations, with a 50% decrease in respiratory rate noted at 1.3 ppm in mice during a 90-minute exposure, suggesting that MIC is a potent respiratory irritant (Alarie *et al,* 1987*)*. Mice exposed to 30 ppm MIC for 2 hours exhibited extensive tracheal / bronchial necrosis followed by rapid epithelial regeneration, but with persistent bronchial fibrosis in some animals for at least the 3-month period of the experiment (Boorman *et al.*, 1987). Pulmonary hypertension was evident in rats 4-6 months after a 2-hour exposure to 10 ppm MIC (Tepper *et al.*, 1987).

A host of ophthalmic effects were noted at Bhopal. These included severe tearing, photophobia, profuse lid edema, corneal ulcerations, ocular pain, diminished vision, corneal opacity, cataracts and night blindness. Some of these symptoms were persistent, though permanent serious eye damage was not reported (Mehta *et al*., 1990).

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).

MIC is clastogenic and cytotoxic. Statistically higher frequencies of damaged peripheral lymphocytes and chromosomal aberrations per damaged lymphocyte were detected in MIC-exposed Bhopal females than in their non-exposed counterparts (Ghosh *et al.*, 1990). Shelby *et al.* (1987) demonstrated an increase in trifluorothymidine-resistant clones in response to MIC in cultured L5178Y mouse lymphoma cells. Increased frequencies of sister chromatid exchanges and chomosomal aberrations in Chinese hamster ovary cells (methylamine also showed positivity in the L5178Y assay, but at several hundred-fold higher concentrations) were also observed. Chromosomal aberrations in bone marrow cells, sister chromatid exchanges in lung cells and micronucleus formation in peripheral erythrocytes were noted in mice exposed to 1, 3 or 6 ppm MIC by inhalation on 4 succeeding days. A negative response in the *Salmonella* mutagenicity and *Drosophila* sex-linked recessive lethal tests prompted the authors to hypothesize that the positive L5178Y cell response, conventionally regarded as indicative of mutagenicity, may actually reflect loss of thymidine kinase activity in positive clones due to chromosomal rearrangements. This is supported by the evidence for chromosomal impacts

delineated in the same study (see above). However, some evidence for positivity in the *Salmonella* assay was noted in two base pair substitution strains when care is taken to stabilize the MIC by lowering the temperature and increasing the time during the preincubation step (Meshram *et al.*, 1988).

Immunologic effects were also detected in Bhopal survivors. Cell-mediated immunity was suppressed, as indicated by a suppression of phagocytosis and T-cell population, and an increase in chromosomal aberrations in peripheral lymphocytes were observed in exposed victims 2.5 months after the event (Saxena *et al.*, 1988). Some animal experiments suggest immunotoxicity. For example, Hong *et al.* (1987) reported myelotoxicity (hypocellularity, suppression of pluripotent stem cells, granulocyte-macrophage progenitors and erythrocyte precursors) in female mice exposed to 1 and 3 ppm MIC for 6 hours per day on 4 succeeding days.

Neurologic effects of MIC at Bhopal were indicated by the reports of loss of consciousness, muscle weakness, tremors, vertigo, ataxia and fatigue (Bharucha and Bharucha, 1987). Nonetheless, these authors were impressed by the apparently low incidence of neurologic dysfunction considering the magnitude of the exposure.

Subchronic / chronic toxicity. Little information on the toxic effects of longer-term low level exposure to MIC in humans or animals is available. Two studies examined the effects of an 8-day, 6 hours/day, inhalation exposure in rats to MIC at 0, 0.15, 0.6 and 3.1 ppm (Dodd *et al.*, 1987; Fowler and Dodd, 1987). Effects were observed only at the high dose. These included decreased body weights detected after the first day's exposure and maintained throughout the exposure period, decreased food consumption following days 3 and 8, and increased hemoglobin concentration and decreased blood oxygen saturation in males and increased lung weights in both sexes at the conclusion of the exposure period. In addition, there was histological evidence for pulmonary inflammation, epithelial degeneration, squamous metaplasia, regenerative hyperplasia, rhinitis, fibroplasia and bronchiolitis. Hypoactivity and increased respiratory rates were detected in the first 15 days post-exposure. Male mortality, likely due to respiratory impacts, was greatly increased over controls and over females during the recovery period. Some recovery from the cytotoxic effects of MIC was indicated in survivors. Interestingly, an epidemiological study of workers from a facility that produced and used MIC did not reveal functional pulmonary deficits, though the levels of exposure could not be specified (Avashia *et al.*, 1996).

Oncogenicity. The potential oncogenicity of MIC was examined in a special carcinogenicity bioassay designed to mimic the conditions of exposure at the Bhopal disaster. At the National Toxicology Program (NTP), groups of 50 or 100 six to eight-week-old F344 rats and B6C3F1 mice were exposed once to MIC by inhalation at 0, 3, or 10 ppm for 2 hours. After 2 years, animals were sacrificed and tissues and organs were examined microscopically. No differences in survival rates or body weight gains were found in MIC exposed animals versus controls. Male and female rats exposed to 10 ppm MIC had 42% and 36% incidence, respectively, of intraluminal fibrosis of lung secondary bronchi; no evidence of this lesion was seen in controls or animals exposed to lower concentrations. For male and female mice and female rats, no neoplastic lesions were significantly associated with MIC exposure. Male rats exposed to MIC had marginally increased rates of pheochromocytomas of the adrenal medulla, and adenoma of pancreatic acinar cell (HSDB, 1997). No information was available on the carcinogenic effects in humans. Nonetheless, MIC's clastogenic and cytotoxic properties may

have some bearing on this question. The US EPA has classified MIC as in Group D, “not classifiable as to human carcinogenicity” (US EPA, 1994a).

Conditional acute REL calculation. The lowest air concentration for which adverse effects were noted was 0.5 ppm, associated with eye irritation in humans exposed for 10 minutes in ceramic chambers (ACGIH, 1986; Mellon Institute, 1970). An eye irritation NOEL was not determined in that study. An estimated NOEL (ENOEL) for the 10-minute exposure was calculated by dividing the LOEL (500 ppb) by an uncertainty factor of 10, to yield 50 ppb. A one-hour ENOEL was then calculated from the 10-minute ENOEL using Haber’s Law:

$$C^n \times T = K$$

C = concentration, n = 1.1 [a chemical-specific value established in OEHHA (1999b)], T = time

To generate the acute REL, the 1-hour ENOEL value is divided by an uncertainty factor of 10 to account for intra-human variation. These calculations follow:

1-hr acute ENOEL

$$(50 \text{ ppb})^{1.1} \times 0.167 \text{ hr} = 12.35 \text{ ppb·hr}$$
$$(y)^{1.1} \times 1 \text{ hr} = 12.35 \text{ ppb·hr}$$
$$y = 9.8 \text{ ppb}$$

1-hr acute REL

$$9.8 \text{ ppb} \div 10 = 0.98 \text{ ppb}$$

Calculation of a subchronic or chronic REL for MIC was deferred until adequate toxicological data on repeated exposure become available.

MIC levels after metam applications; regulatory limits. The yield of MIC from MITC has been reported to be about 7% in laboratory experiments (Geddes et al., 1995). Inspection of the laboratory by the California Department of Toxic Substance Control confirmed the validity of the findings (DTSC, 1993; OEHHA, 1993). Preliminary measurement of MIC after agricultural use of metam sodium in Kern County revealed MIC levels between 0.09 and 2.5 ppb (ARB, 1995). The potential highest level of MIC to be found under conditions similar to those in this study, estimated by correcting for maximum metam application rate and recovery similarly to MITC (DPR, 2003a), would be 5.4 ppb. This exceeds by more than 5-fold the 1-hour acute REL calculated above. Additional field measurements will be necessary before quantitative estimation of potential human risk from MIC following agricultural use of metam sodium can be undertaken. In any case, this study would not have conformed to current Technical Information Bulletin requirements for the application of metam sodium.

On the basis of the high reactivity, marked corrosive, irritating properties to mucus membranes, and to prevent possible sensitizing doses to the pulmonary tract, an 8-hour Threshold Limit Value - Time Weighted Average (TLV-TWA) standard of 0.02 ppm (20 ppb) was recommended by the American Conference of Governmental Industrial Hygienists (ACGIH). The TLV-TWA is a time-weighted average concentration for a normal 8-hour workday and a 40-hour work week. The United States Occupational Safety and Health Administration (OSHA) 8-hour Permissible Exposure Limit (PEL), as well as the Cal OSHA PEL, is also 0.02 ppm. The US EPA has not established a Reference Dose (RfD), or Reference Concentration (RfC) for MIC, nor are ambient air standards available.

3. Hydrogen sulfide (H_2S)

H_2S is formed as part of the same monomolecular cleavage reaction that produces MITC from metam sodium under dilute aqueous conditions (Kreutzer *et al*, 1994). While it was not detected in official air monitoring studies after the Cantara Loop spill, its characteristic rotten egg smell was reported by individuals in the area; it was thus assumed to be present, at least for a short period. The low water solubility and high vapor pressure of H_2S would have favored rapid off-gassing from the river and subsequent rapid breakdown (Alexeeff *et al*, 1992). H_2S would presumably be produced upon application of metam sodium in agricultural and perhaps other settings as an adjunct to MITC evolution. Sulfur dioxide and sulfuric acid may be formed when atmospheric H_2S is oxidized.

Like cyanide, H_2S disrupts intracellular electron transport by inhibiting cytochrome oxidase. Metabolic acidosis results when the shift from aerobic to anaerobic metabolism occurs, provoking a build-up of lactate. H_2S is also a mucus membrane and respiratory irritant. Death results from respiratory arrest and hypoxia (Ellenhorn, 1997).

Acute toxicity. The geometric mean human odor threshold for H_2S is 0.008 ppm, with a range of 0.00007 to 1.4 ppm, based on a review of 26 studies (Amoore, 1985; cited in OEHHA, 1999a). H_2S levels between 2.5 and 5 ppm were associated with coughing and throat irritation after 15 minutes (Bhambani and Singh, 1985; cited in OEHHA, 1999). Exposure to 7 ppm H_2S during moderate physical exercise led to impaired oxygen and lactate uptake in the blood (Bhambani and Singh, 1991). Olfactory fatigue occurs at 50-100 ppm, with respiratory tract and eye irritation developing at 150-300 ppm (though some ocular effects may be present at 10 ppm), severe systemic toxicity at 500 ppm and cardiovascular arrest and death at 700 ppm and above (Ellenhorn, 1997). Symptoms commonly reported after accidental human exposures include dyspnea, sore throat, coughing, chest pain and signs of pulmonary obstruction. Less common symptoms include pulmonary edema, cyanosis and pneumonia. Severe neurologic and cardiovascular effects can be present in those recovering from high level exposures. Mortality resulting from severe acute exposure situations reportedly ranges between 2.8% and 6 % (Arnold *et al.*, 1985).

The mean 4-hour LC_{50} in rats was determined to be 440 ppm (Tansy *et al.*, 1981). The 1-hour lethal concentration in mice was 673 ppm (RTECS, 1994). Respiratory arrest and death occurred in dogs at 1000 ppm (Haggard and Henderson, 1922). A NOAEL of 10 ppm, based on depression of lung mitochondrial cytochrome c oxidase at 50 ppm was established in a study with Fischer 344 rats (Khan *et al.*, 1990).

Subchronic and chronic toxicity; other effects CIIT conducted companion studies of the effects on rats and mice of H_2S exposure 6 hours/day, 5 days/week, for 90 days at 0, 10.1, 30.5 or 80 ppm (cited in OEHHA, 2000). Weight decrements were observed at the high dose in both sexes. The only other effect was inflammation of the nasal mucosa of the anterior segment of the nose in mice, also at the high dose. The NOAEL was set at 30.5 ppm based on the latter effect.

Hulbert *et al.* (1989; cited in Alexeeff *et al.*, 1992) noted moderate to severe dose-related proliferation of ciliated and basal cells and decreased non-ciliated Clara cell numbers in Fischer 344 rats following exposure to 10 and 100 ppm H_2S for 8 hours/day, 5 days/week, 5 weeks. Other pulmonary effects, including lymphocytic infiltrates, pulmonary edema and tracheitis, were also observed. Mild acute suppurative tracheitis, laryngitis and mild chronic

nephritis were noted in guinea pigs exposed to 220 ppm H_2S for 7 days (Renne *et al*., 1980; cited in Alexeeff *et al*., 1992).

H_2S appeared weakly mutagenic in one *Salmonella* study. No long-term carcinogenicity studies have been conducted. Two reproduction studies in rats did not indicate adverse effects, though there was a dose-dependent increase in delivery time (cited in Alexeeff *et al.*, 1992).

H_2S exposure may be associated with a risk of spontaneous abortion. A retrospective epidemiologic study in China conducted in a large petrochemical complex identified 106 reproductive-aged married women exposed only to H_2S. The overall odds ratio for spontaneous abortion was 2.3 (95% confidence interval, 1.2-4.4) (Xu *et al*., 1998). H_2S levels were not identified.

H_2S levels after metam applications; regulatory limits. Measurements of H_2S after applications of metam sodium showed levels reaching 76 ppb at 1-4 hours post application, becoming non-detectable at 5-7 hours and rising again to 8 ppb at 21-24 hours. The ACGIH TLV (TWA) and the Cal OSHA PEL for H_2S is 10,000 ppb. The short term exposure limit (STEL) is15,000 ppb. The Agency for Toxic Substances and Disease Registry (ATSDR) lists an acute minimum risk level (MRL) of 70 ppb (ATSDR, 1999). It is based on a LOAEL of 2 ppm for respiratory effects (bronchial obstruction) in humans, incorporating uncertainty factors of 10 for the LOAEL to NOAEL extrapolation and 3 for intra-human variability. The California Ambient Air Quality Standard is 30 ppb for a 1-hour average (CCR, Title 17, Section 70200). This is based on an odor threshold study conducted by the California State Dept. of Public Health (1969; cited in OEHHA, 1999) which established a geometric mean threshold for 16 individuals of 0.029 ppm (rounded to 0.03 ppm [or 30 ppb]; range, 0.012-0.069 ppm). OEHHA (1999a), which also designated 30 ppb as the acute REL, argued that this concentration may be inappropriately high for 2 reasons: 1. there are reports of lower odor thresholds (see above) and 2. other symptoms, *eg.,* headaches, may occur in some people at 30 ppb.

An intermediate duration MRL of 30 ppb was established by ATSDR based on the NOAEL of 30.5 ppm in mice for respiratory effects (see above). Adjustments were made for intermittent exposure, species-to-species extrapolation and intrahuman variability. OEHHA (2000) based their determination of the chronic REL of 8 ppb on this study. A human equivalent exposure concentration was calculated, and uncertainty factors of 3 for subchronic-to-chronic extrapolation, 3 for interspecies extrapolation, and 10 for intraspecies extrapolation were used to calculate the REL.

4. Carbon disulfide (CS_2) (*Note: Except where noted, this section was extracted from US EPA, 1994c.)*

Human exposure to carbon disulfide (CS_2) may follow metam applications as CS_2 is a degradation product of metam sodium, particularly under acidic conditions (pH<5).

Pharmacokinetics. CS_2 is readily absorbed in humans after inhalation exposure. Human and animal studies also indicate absorption of the vapor through skin, and animal studies indicate absorption through the gastrointestinal tract. Following inhalation exposure in mice, CS_2 was found in body fat, blood, lungs, liver and kidneys, whereas in rats and rabbits the highest levels appeared in lipid-rich tissues, brain and liver. CS_2 crosses the mouse placenta and is found in the milk of occupationally exposed human mothers. The following metabolites have been

detected in the urine of exposed workers: thiocarbamide, 2-thio-5-thiazolidinone, 2-thioazolidine-4-carboxylic acid and thiourea. 70-90% of the absorbed dose is metabolized and excreted by the kidneys, with 10-30% excreted unchanged by the lungs (decreasing rapidly once exposure stops). Sulfur excretion in rat urine is complete by 12-14 hours after an 8-hr inhalation exposure.

Acute toxicity. Acute human exposure to CS_2 by inhalation leads to local irritation, pharyngitis and CNS toxicity. Such exposure becomes life-threatening after 30 minutes at 3210-3850 ppm and fatal after 30 minutes at 4815 ppm. Oral exposure to 15 ml is also fatal. Dermal and ocular exposure causes severe burns. Oral LD_{50} values: rat, 3188 mg/kg; mouse, 2780 mg/kg; rabbit, 2550 mg/kg; guinea pig, 2125 mg/kg. LC_{50} (2-hr) values: rat, 25 g/m^3; mouse, 10 g/m^3.

Subchronic / chronic toxicity. Central nervous system, cardiovascular, gastrointestinal and immune toxicity result from exposures in humans in the range of 3-320 ppm for periods of months to years. Subchronic and chronic exposures in animals impact the nervous system, cardiovascular system and kidneys. There is no definitive evidence for CS_2-mediated carcinogenicity in humans or animals, though some possibility remains from epidemiologic studies of exposed populations. Genotoxicity data were not reported.

Epidemiology. The following impacts have been noted in epidemiologic studies of potential reproductive / developmental effects (length of exposures not indicated): inhalation exposure at 13-77 ppm: changes in sperm morphology, decreased hormone levels, decreased male libido, menstrual irregularities; 12-18 ppm: menstrual disorders and higher incidence of toxemia in pregnancy; 9 ppm: increased spontaneous abortions; fetal malformations do not appear elevated. Animal studies: increased fetal resorption in rabbits at 25 mg/kg/day (oral) during gestation. CS_2 is listed as a developmental toxin and a male and female reproductive toxin under Proposition 65.

Adverse impacts on the nervous system follow inhalation exposure in both humans and animals. Acute effects in humans include dizziness, fatigue, headache, mood change, lethargy, blurred vision, agitation, delirium, hallucinations, convulsions and coma. Symptomology is evident at as low as 320-390 ppm for several hours. Chronic exposures in humans can result in polyneuritis, encephalopathy, tremors, vertigo, psychosis, myopathy and reductions in nerve fiber conduction velocity. The latter sign was evident after exposure to 1 - 7.6 ppm for an average of ~12 years. Degenerative nervous system changes are also evident in animal studies.

CS_2 levels after metam applications; regulatory limits. Measurements of CS_2 after applications of metam sodium showed levels at or below the detection level of 4 ppb (Wofford *et al*, 1994). The TLV (TWA) for CS_2 is 10 ppm. The Cal OSHA PEL is 4 ppm, with a STEL (short term exposure limit) of 12 ppm. No ambient air exposure values are available. OEHHA (1999a) set an acute REL of 2 ppm. This was based on a developmental toxicity study in which pregnant rats were exposed to 0, 100, 200, 400 or 800 ppm CS_2 for 6 hours/day on gestation days 6-20. Significant reductions in fetal body weight were observed at the LOAEL dose of 400 ppm, establishing the NOAEL at 200 ppm. Uncertainty factors of 10 each for inter- and intraspecies extrapolations were used to determine the acute REL. A chronic REL is not currently available.

5. Methylamine
Like CS_2, methylamine is produced upon cleavage of metam sodium under acidic conditions. Acidic cleavage of MITC will also produce methylamine. This compound is known for its irritant properties to eyes, nose and throat upon brief exposures to 20 - 100 ppm. Severe methylamine exposure may lead to pulmonary edema. The oral LD_{50} in rats is 100 - 200 mg/kg (Proctor *et al*, 1988). As noted above, Shelby *et al.* (1987) demonstrated positivity in the L5178Y mutagenicity assay, but at several hundred-fold higher concentrations than MIC. Gavage exposure to 122 mg/kg methylamine for 5 days in mice produced a statistically significant 27% drop in white blood cell counts (Keil *et al.*, 1996).

Regulatory limits. The OSHA PEL for methylamine is 10 ppm. The ACGIH TLV (TWA) is 5 ppm, with a STEL of 15 ppm.

6. Carbonyl sulfide (COS) (US EPA, 1994d *except where noted*)
Like methylamine, COS is produced upon cleavage of MITC in the gut. Acute inhalation exposure at levels >1000 ppm can result in fatality due to respiratory paralysis with little warning *via* local irritation or olfaction. Clinical signs following sublethal inhalation include giddiness, headache, vertigo, amnesia, confusion, unconsciousness, salivation, nausea, vomiting, diarrhea, cardiac arrhythmia, albuminuria, weakness and cramps. Rat studies showed deaths in 0/6 animals subjected to inhalation exposure at 1000 ppm for 75 minues, 3/6 at 3000 ppm for 9 minutes and 3/6 at 1000 ppm for 90 minutes. COS administered by intraperitoneal injection as a gas to male Sprague-Dawley rats resulted in an acute LD_{50} of 22.5 mg/kg. Pretreatment with the carbonic anhydrase inhibitor acetazolamide considerably reduced mortality, suggesting that conversion to hydrogen sulfide was an important mediating step in COS toxicity (Chengelis and Neal, 1980). No information on subchronic/chronic effects in humans was available. A 12-week inhalation study in rabbits exposed to 50 ppm COS did not result in clear adverse effects. No information is available on the carcinogenicity, genotoxicity or developmental / reproductive toxicity of COS. In addition, regulatory limits do not appear to be established.

7. Plausibility of additive or synergistic toxic effects
Simultaneous exposure of some workers to metam sodium and its primary breakdown products (MITC, MIC, H_2S, CS_2, COS, and methylamine) is plausible. However, as the route of exposure to the latter compounds is likely to be through the air, in contrast to the dermal route postulated for metam sodium, it seems unlikely that irritative synergistic effects involving metam sodium will occur. On the other hand, inhalation co-exposure to any combination of volatile degradation products could elicit additive or synergistic effects, either with each other or with metam sodium that was absorbed through the skin. However, as no clear experimental or epidemiologic data are available to suggest the presence of, or potential for, additive / synergistic interactions, it can only be stated at this point that such effects are plausible.

IV. RISK ASSESSMENT

A. HAZARD IDENTIFICATION

A human health risk assessment of metam sodium has been conducted to evaluate the significance of the toxicity demonstrated in various animal studies.

1. Acute Toxicity

Single dose acute toxicity tests are generally conducted to establish LD_{50} / LC_{50} values and to determine clinical / macropathologic signs. The high doses selected to produce lethality characteristically do not establish NOEL values that are useful as regulatory endpoints. In the case of metam sodium, it was necessary to turn to one of the rabbit developmental toxicity studies to establish the relevant regulatory value for acute effects.

The critical acute regulatory value was established in the Himalayan rabbit developmental toxicity study of Hellwig (1987) using benchmark dose (BMD) methodology (DPR, 2003b). The BMD approach was employed because an empirical NOEL was not established in the Hellwig study. A benchmark response level of 1% was chosen because the endpoint, early resorption, was representative of fetal death and thus considered to be severe. The critical acute LED_{01} was **1 mg/kg** (rounded from an actual value of 0.79 mg/kg). As noted, it was based on an increase in early resorptions at the low dose of 4.2 mg/kg. The acute nature of the response was inferred by the fact that these were *early* resorptions, having occurred soon after the commencement of dosing, without evidence of fetal development.

A parallel study in New Zealand White rabbits also reported an increase in early resorptions, though the LOEL was 60 mg/kg (Hodge, 1993). Nonetheless, the Hodge findings were considered to support the observations of Hellwig (1987). In addition, weaker evidence for resorptions was available in the Wistar rat study (Hellwig and Hildebrandt, 1987), though the precise dose level was not clear (see discussion in section III.G.1).

Further support was garnered from the study of Tinston (1993), which established an acute NOEL of 5 mg/kg in Wistar rats based on acute maternal and developmental effects noted at a LOEL dose of 20 mg/kg. The maternal effects included clinical signs (salivation, vaginal bleeding and oral staining) and decrements in body weight gain and food consumption. The acute nature of these signs was inferred by their rapid development after the commencement of dosing on gestation day 7. The developmental effects included suppression of fetal body weights and numerous skeletal developmental delays. As these growth effects were considered to be functions of the acute maternal growth effects, they were considered likely to be the result of acute (or perhaps short-term) exposures.

2. Dermal irritation

Dermal irritation complaints were prominent among those reported in the California Pesticide Illness Surveillance Program (section II.E. above). For this reason, an evaluation of the potential for dermal irritation under field conditions was appropriate. Only one dermal toxicity study, the 21-day study of Leuschner (1979) in White Russian rabbits, contained the appropriate information to generate credible risk estimates. It was necessary in this context to convert the NOEL and LOEL doses relevant to dermal irritation from systemic units (31.25 and 62.5 mg/kg/day, respectively) to local irritation units (mg/cm^2/day). According to the report, the

test article, suspended in 0.8% aqueous hydroxypropylmethylcellulose gel, was spread over a 15x16 cm patch, comprising a surface area of 240 cm^2. The mean body weights in the present study ranged between 2.6 and 2.9 kg, or approximately 2.75 kg. Thus the local NOEL and LOEL doses were:

31.25 mg/kg/day x 2.75 kg = 85.94 mg $\approx$86 mg per 240 cm^2 patch
86 mg/240 cm^2 = 0.36 mg/cm^2 = **360 μg/cm^2 = local NOEL dose**

62.5 mg/kg/day x 2.75 kg = 171.875 mg per 240 cm^2 patch
171.87 mg/240 cm^2 = 0.72 mg/cm^2 = **720 μg/cm^2 = local LOEL dose**

3. Subchronic toxicity

The critical subchronic LED_{10} was established in the 90-day dog oral gavage study of Brammer (1992). As was the case for acute toxicity, the BMD approach was employed to determine a regulatory LED because an empirical NOEL was not defined in the Brammer study. The LOEL of 1 mg/kg/day study was based on an observation of minimal "bile duct proliferation / inflammatory cell infiltration" in a single female, accompanied in the same animal by a precipitous rise in serum alanine transaminase activity between weeks 12 and 13. Taken together, these data indicated that incipient hepatotoxicity and bile duct pathology were coincident, and implied that there may be a relationship between the bile duct effects and the liver effects. Due (a) to the mildness of the bile duct pathology in the single low dose animal, and (b) to the uncertainty surrounding the relationship between this pathologic sign and the hepatitis observed at higher doses, the lower bound on the 10% benchmark response (*i.e.*, the LED_{10}) was considered to be an appropriate cutoff in the establishment of a seasonal regulatory value. Using the bile duct / liver damage incidence curve of 0/4, 1/4, 3/4 and 4/4, 16 algorithms were tested to determine the curve that best approximated the data points. AIC analysis indicated that the quantal linear algorithm provided the best fit. The resulting LED_{10} of 0.163 mg/kg/day (ED_{10} = 0.326) was rounded to **0.2 mg/kg/day** and used to evaluate seasonal health risks.

Designation of 0.2 mg/kg/day and 1 mg/kg/day as the critical subchronic LED_{10} and LOEL, respectively, was directly supported by similar findings in the 1-year dog oral gavage study (Brammer, 1994). In that study, one female treated at 1 mg/kg/day (the high dose) exhibited an ~8-fold rise in alanine aminotransferase at weeks 26, 32, 39, 45 and 52. The same individual exhibited signs of hepatotoxicity (a slight increase in hepatocyte and macrophage/Kupffer cell pigmentation, slight mononuclear cell infiltration, slight telangiectasis). It seems clear, therefore, that occasional beagle dogs exhibit great sensitivity in hepatic responsiveness to relatively low doses of metam sodium.

The critical LED_{10} / LOEL designation was also supported by the NOELs established in the 90-day mouse (Whiles, 1991) and rat (Allen, 1991) studies. Liver toxicity was not a major finding in either of these studies, though pale or accentuated lobular patterns in the liver were noted at as low as 36.05 mg/kg/day in the mouse study, along with increases in adjusted liver weight at the top three doses (*i.e.*, $\geq$4.48 mg/kg/day). Even so, the NOELs in both studies (0.79 mg/kg/day in the mouse, 0.49 mg/kg/day in the rat) approximated the LED_{10} in the dog study. The mouse NOEL was based on a reduction in hemoglobin, hematocrit and red blood cell numbers, indicating possible anemia, as well as on increased liver weights and eosinophilic granules in transitional epithelial cells of the urinary bladder, all at the mid-low dose of 4.48

mg/kg/day. The appearance of eosinophilic granules in the urinary bladder at 4.48 mg/kg/day was predictive of the clearer bladder toxicity (cystitis and mucosal hyperplasia) occurring at the top two doses. The evidence for anemia at the top 3 doses may have understated the magnitude of the effect: the suppression of water consumption noted at those doses, which was possibly due to palatability problems, may have resulted in dehydration. The NOEL in the rat study, 0.49 mg/kg/day, was based on slight decrements in body weight gain and water consumption (the latter also plausibly due to unpalatability) with a consequent lowering of urine volume at 3.10 mg/kg/day. The gravity of the rat endpoints was, however, not clear.

It may be asked why the critical subchronic endpoint was derived from an oral dosing study when skin was the only postulated route of exposure; a 21-day subchronic dermal study was, after all, available using a 42.4% formulation (Leuschner, 1979). No systemic effects due to dermal exposure were detected in that study, resulting in a systemic NOEL $\geq$ 125 mg/kg/day. Based on local erythema, edema and dermatitis, the local NOEL was 31.25 mg/kg/day. (This study was considered "supplemental" because no dosing solution analysis was submitted. However, it was, in the absence of other irritation studies, considered appropriate in the evaluation of dermal irritation risk. See discussion above under "Dermal irritation".) In a study from the open literature, Pruett *et al.* (1992) showed that dermal application of metam sodium at doses as low as 200 mg/kg/day for 4 days resulted in suppressions of NK cell activity and $CD4^{+}CD8^{+}$ lymphocyte populations, as well as lowered spleen weights. The Pruett study generated a dermal NOEL of 100 mg/kg/day.

Unfortunately, neither of these dermal studies investigated the possibility of fetal toxicity, which was very much in evidence in both the rabbit and rat developmental toxicity studies. Without an appreciation of whether or not dermal exposure could provoke embryotoxicity, it was considered prudent to set the critical subchronic NOEL *at or below* the acute value. Consequently, the value of 0.3 mg/kg/day was adopted as the critical subchronic value.

The assumption that toxicity occurring by the oral route is relevant in a situation where only dermal exposure is expected probably represents a health conservative position. Metam absorption by the oral route is considered to be 100%, as opposed to the 2.5% rate of absorption by the dermal route, making the absorbed dose by the oral route much higher than by the dermal route. Based on the lack of systemic toxicity following dermal application in rabbits (Leuschner, 1979), it is unlikely that unique aspects of dermal pharmacokinetics (for example, the absence of first-pass hepatic metabolism, the possible access to organs or tissues not reached after oral exposure, or the creation of toxic metabolites) would create a more toxic scenario than exists after oral exposure. Ultimately, in view of the fact that the MOEs for worker exposures were relatively high (909-2500) even when considering the oral study NOEL as definitive (as is done in this document; see Table 25), it can be reasonably stated that adequate protection against those toxic endpoints was realized.

4. Pre- / post natal sensitivity

Six developmental toxicity studies, 4 in rats and 2 in rabbits, were examined for this document. All utilized the oral route of exposure. Both rabbit studies indicated clear metam sodium-induced increases in early resorptions. In Himalayan rabbits, not only were the resorptions induced at a sub-maternally toxic dose of 10 mg/kg/day, but fetal malformations (meningocele + spina bifida) were documented at the slightly maternally toxic dose of 100 mg/kg/day. In New Zealand White rabbits, resorption incidence was overwhelming at a dose in which only slight

maternal toxicity was observed. Malformations (meningocele, microphthalmia, anophthalmia, skull malformation, hydrocephaly and abnormal zygomatic arch) were also noted in one of the Wistar rat developmental toxicities study at the maternally toxic dose of 60 mg/kg/day. Because of the high pre-natal sensitivity, an additional uncertainty factor or greater MOE should be considered (though see discussion in section V.F.2). It is worth reemphasizing that metam sodium is listed as a reproductive toxicant under Proposition 65.

5. Chronic toxicity (non-oncogenic)

A critical NOEL of **0.1 mg/kg/day** for chronic toxicity was established from the dog 1-year gavage study (Brammer, 1994). Four beagles/sex/dose were administered 0, 0.05, 0.1 or 1 mg/kg/day. One high dose female exhibited an ~8-fold rise in alanine aminotransferase at weeks 26, 32, 39, 45 and 52 (compared to weeks 4, 8, 13 and 19). The same individual exhibited signs of hepatotoxicity (a slight increase in hepatocyte and macrophage / Kupffer cell pigmentation, slight mononuclear cell infiltration, slight telangiectasis) that, in view of similar results in the dog 90-day study, were considered to be test article-related. Other observations, such as an increase in mean alkaline phosphatase activities (up to 47%, both sexes, mostly high dose) and a reduction in mean plasma triglycerides (up to 34%, females, high dose) may also indicate a more generalized liver dysfunction. An increase in kaolin-cephalin time (also known as activated partial thromboplastin time) of up to 15% in both sexes at the high dose indicates some interference with blood clotting.

6. Oncogenicity

Weight of Evidence Considerations. Oral exposure to metam sodium was associated with an increased incidence of angiosarcomas in male mice. There was also a suggestion of an increase in hemangiosarcomas, a subset of angiosarcomas, in male rats. Angiosarcoma is a malignant vascular tumor defined in Dorland's Medical Dictionary (26th ed.) as "formed by proliferation of endothelial and fibroblastic material." The term encompasses "all lesions labeled hemangiosarcoma, lymphangiosarcoma, and malignant hemangiosarcoma, since it remains uncertain whether these lesions are derived from blood vascular or lymphatic endothelium, or perhaps from either" (Fletcher and McKee, 1992).

The increase in hemangiosarcomas in rats did not conform to a conventional dose-response relation; statistical significance by a Fisher Exact test was attained only at the mid dose (see Table 10) (Rattray, 1994). This did not completely negate the possibility that metam sodium exposure was responsible for those tumors. It was possible, for example, that decreased caloric intake at the high dose was responsible for the lowered hemangiosarcoma incidence rate at that dose. Decrements in body weight (~12%) and food consumption (~8%) were noted in males at the high dose. Partial caloric restriction suppresses the development of many kinds of tumors in laboratory animals (Tannenbaum, 1959), though we are unaware of data relating specifically to hemagiosarcoma formation in rats. Because "hemangiomatous" tumor incidence was reported to vary among Wistar rat strains (Carlock and Dotson, 2001), the lack of an historical database from that laboratory made it impossible to claim that the reported incidence rates fell either within or outside an expected range. Nonetheless, these authors held that the data did *not* support a role for metam sodium in the increase noted at the mid dose, primarily because the hemangiosarcoma incidence rates were consistent with historical control levels established in other laboratories. While such a claim was plausible, it did not entirely absolve

metam sodium of a causative role, particularly in view of the results from the mouse study (next paragraph).

A much clearer effect was discerned in male mice (Horner, 1994). The incidence of angiosarcomas in high dose males was very significantly increased compared to controls ($p<0.001$, Fisher Exact Test) (see Table 12). A Cochran-Armitage Trend Test was also positive at the $p<0.001$ level. Furthermore, females also exhibited a positive trend at the $p<0.01$ level. Suggestion of an angiosarcoma induction at the mid dose was noted among decedents of both genders. Angiosarcoma incidence in the spleen also appeared to rise at the mid dose in tallies of all animals (though statistical significance was achieved only in high dose males). Indeed, given the rise in incidence rates between controls and low dose animals in total angiosarcomas in males, an effect even at the low dose could not be discounted unequivocally.

Historical control data, which consisted of nine studies conducted between March 1984 and February 1991, strongly supported a causative role for metam sodium in angiosarcoma induction at the high dose. The mean incidence (± standard deviation) for males in these studies was 10%±4% (range: 5-18%), far lower than the incidence of 50.9% in high dose "at risk" males recorded in the current study (Table 12). The incidence rates even at the low and mid doses (22.6% and 21.8%, respectively), were suggestive of a metam sodium-induced effect at those doses. The mean historical incidence for females was 5%±3% (range: 0-9%), also clearly lower than the "at risk" incidence of 19.2% at the high dose. The mid dose incidence of 13.0% was also higher than the historical mean and range.

It may be argued that the male body weight gain decrement of 16% at the high dose suggested that the maximum tolerated dose, defined by some as a weight gain decrement of more than 5-10% (US EPA, 1999), was exceeded. However, because the occurrence of other toxic signs in high dose males was unremarkable, the dosing regime was considered appropriate for the purposes of the current analysis.

As a vascular tissue disease, it was not surprising that angiosarcomas were found in several mouse organs including liver (where they may have been responsible for the increase in palpable masses), subcutaneous tissues and, especially, spleen (Table 12). Interestingly, non-neoplastic histopathology included findings of increased hepatocytic fat vacuolization and splenic hemosiderosis at the high dose.

Bladder tumors were also noted in the mouse study. A transitional cell papilloma in 1 male and a transitional cell carcinoma in 1 female were observed in the urinary bladders of the high dose mice. As both of these tumor types were considered to be extremely rare by the examining pathologist, a role for metam could not be ruled out despite the low bladder tumor incidence rate. Furthermore, the extensive dose-dependent histopathology in the bladder was clear evidence that bladder was a target organ. This raises the possibility that the observed bladder neoplasia was part of an adaptive response to tissue damage (see discussion in section III.D.2.).

Metam sodium was clastogenic both *in vivo* (Gelbke and Engelhardt, 1987a) and *in vitro* (Gelbke and Engelhardt, 1987b; Mackay, 1996). Other assays for genotoxicity, including gene mutation, DNA damage and micronucleus induction, were either negative or equivocal.

Quantitative Assessment of Oncogenic Effects. Calculation of cancer potency was based on the appearance of angiosarcomas in male mice (Table 12) (Horner, 1994). While a statistically significant increase over controls was noted only at the high dose, no evidence presented in that study was suggestive of a threshold mechanism. As noted above, increased angiosarcoma incidence at the low and mid doses, particularly in males, could not be discounted.

Angiosarcomas were the major contributors to death among those animals that had these tumors; however, there was no statistically significant evidence that metam affected overall survival in the dosed groups. Therefore, oncogenic potency was calculated using the linearized multistage model of tumor development (GLOBAL 86; for a discussion of the pros and cons of using linearized models for low dose risk estimates, see section V.B.3.). In order to calculate the oncogenic potency, it was necessary to exclude all animals not considered to be at risk for developing angiosarcoma, to wit, those that died during the first year of dosing. The remaining animals were considered to be "at risk" for this tumor (Table 12). The first detection of an animal with angiosarcoma occurred during week 68. Indeed, angiosarcoma was considered a factor contributory to death in this individual. It was thus reasonable to assume that the tumor would have been detectable for some time before 68 weeks had a dissection been done in an affected animal. Consequently, one year was chosen as the cut-off time for determining the at risk population.

The mouse internal dose used in the cancer potency calculations was the mean dose over the entire study length. As the weekly internal dose dropped steadily over the first 39-52 weeks, a phenomenon likely due to increases in body weight, there was an implicit assumption that the whole-study mean dose, as opposed to a dose calculated for just the early part of the study, was relevant to angiosarcoma formation. However, there are no data to confirm the assumption. Extrapolation of the mouse doses to humans was done by multiplying the doses by an interspecies scaling factor using the ratio of animal-to-human body weight to the 1/4 power: $(BWt_A / BWt_H)^{0.25} = (0.03 \text{ kg} / 70 \text{ kg})^{0.25} = 0.144$ (US EPA, 1992). Thus the mean male mouse internal doses of 1.9, 7.2 and 28.9 mg/kg/day were converted to equivalent human doses of 0.274, 1.037 and 4.162 mg/kg/day. The resulting estimated oncogenic potency using the incidence rate for all "at risk" male mice (*i.e.*, those surviving beyond 1 year; see discussion above and the footnote to Table 12) ranged from $\mathbf{Q_1 = 8.56 \times 10^{-2}}$ $(\text{mg/kg/day})^{-1}$ (the maximum likelihood estimate or MLE) to $\mathbf{Q_1^* = 1.85 \times 10^{-1}}$ $(\text{mg/kg/day})^{-1}$ (the 95% upper bound or 95% UB). These calculations are detailed in the Appendix to this document.

US EPA has identified metam sodium as a B2 (probable human) carcinogen based on the same mouse study. Their published Q_1^* of 0.198 is close to the Q_1^* calculated here (US EPA, 1997c).

B. EXPOSURE ASSESSMENT

As noted above in section II.C., there were 21 products containing metam sodium registered in California as of June 2004 (DPR, 2004). Metam concentrations in these products range between 15% and 44%. They are intended for use as antimicrobials, bactericides, fungicides, herbicides, insecticides and nematicides in agriculture, sewer lines, sugar mills, potting soil, wood chips and utility poles. One of these products is formulated with 14.5% cyanodithioimido carbonate and 2 products are formulated with 2.2-25% dichlobenil (DPR, 2004). Once in the soil, metam sodium degrades to MITC and other products (see Environmental Fate, section II.G. above).

1. Occupational exposure

Potential occupational exposure estimates to metam sodium following agricultural and other uses were developed by the Worker Health & Safety Branch and are contained in the document Estimation of Exposure of Persons in California During Soil Applications of Products Containing Metam Sodium (DPR, 2004). Data and text from that study are extracted below, and are used in the risk characterization of metam sodium to follow.

Exposure of workers to metam sodium was considered to occur exclusively *via* dermal contact. Due to the unavailability of a worker exposure study specifically utilizing metam sodium, surrogate data were substituted utilizing sodium tetrathiocarbonate applied to grapes and citrus at 3 sites. Because the sodium tetrathiocarbonate was unstable, a known amount of non-labile cesium ion was added before application. Dermal exposure was calculated by measuring the cesium concentration at the site of interest and multiplying by the proportion of cesium-to-tetrathicarbonate in the initial mixture. According to the Exposure Assessment (DPR, 2004),

> The mixers/loaders wore coveralls over normal work clothing, rubber or neoprene boots, and rubber or neoprene gloves, whereas, applicators wore normal work clothing, rubber or neoprene boots, and rubber or neoprene gloves. The requirements on clothing protection are similar to those required for loaders of metam sodium. A mixer/loader of metam sodium is also required to wear a properly fit-tested MSHA/NIOSH-approved half-face respirator with organic vapor cartridges plus nonventing chemical goggles, or a MSHA/NIOSH-approved full-face respirator with organic vapor cartridges. Under the work clothing workers wore long underwear, which served as the dermal sampling matrix. At each site, there were two applicators and one mixer/loader. These workers did not enter the treated area during the application at any of the sites. The application time ranged from 5.75 to 11.33 hours, averaging 8.31 hours per day.

In almost all cases, cesium was either not detected or registered below the level of quantitation, requiring substitution of actual values with values reflecting the limits of detection and of quantitation. This probably resulted in an overestimation of exposure (for a fuller discussion of the inherent weaknesses in this method of exposure assessment, see section V.). The proportion of metam sodium that was absorbed from the skin was 2.5%, a value derived from a study of metam sodium absorption in the rat (Stewart, 1993).

a. Acute exposure: systemic (absorbed) and local

Absorbed doses. Absorbed doses were calculated from estimates of acute dermal exposure using a dermal absorption rate of 2.5%, as noted above. These values appear in Tables 24 and 25. The highest exposure rates and absorbed daily doses were associated with oakroot fungus control, though it should be recognized that this estimate was based solely on the higher maximum allowable application rate.

Table 24. Dermal exposure estimates of adult pest control operators to metam sodium during preplant applications or for oakroot fungus control

Sodium tetrathiocarbonate		Metam sodium		
Rate[a]	Dermal exposure[b]	Work task[c]	Rate[a]	Dermal exposure[b,d]
136	2.27	SI, SC, BR	318	5.3
		RT	346	5.8
		ORF	618	10.3

[a] lb a.i./A
[b] mg/person/day, mean values for nine workers; Haskell (1994a, 1994b)
[c] Shank injection (SI), sprinkler chemigation (SC), bystander/reentry (BR), rotary tiller (RT), oakroot fungus control (ORF).
[d] Assumed dermal exposure is proportional to application rate.

Table 25. Acute, seasonal, annual and lifetime systemic exposures of adult pest control operators to metam sodium during preplant applications or for oakroot fungus control

Work task[a]	Dermal exposure[b]	ADD[c]	Seasonal exposure[d]	SADD[e]	Workdays / year[f]	AADD[g]	LADD[h]
SI, SC, BR	5.3	1.5	yes	1.5	200	0.8	0.4
RT	5.8	1.7	yes	1.7	200	0.9	0.5
ORF	10.3	2.9	no	n/a	15	n/a	n/a

[a] See Table 24, footnote c.
[b] mg/person/day, mean values, from Table 24
[c] ADD, absorbed daily dose, μg/kg/day. Dermal absorption = 2.5%. The average body weight of adult workers participating in the study was 87.5 kg (n=9). ADD = [(dermal exposure) x .025] ÷ average body weight. For the first example, (5.3 x .0250) ÷ 87.5 = 1.5 μg/kg/day. Standard deviations are not presented because most values were estimated from Limit of Detection (LOD) and/or Limit of Quantitation (LOQ).
[d] The seasonal exposure should last about 8 months based on the use of metam sodium in carrots in Kern and adjacent counties (DPR, 2004). It was assumed that there was no seasonal exposure for the control of oak root fungus because there are only five estimated workdays per 120-day season.
[e] SADD, seasonal average daily dose, μg/kg/day. Pesticide use data from 2000 to 2002 (DPR, 2004) showed the use of metam sodium in Kern and adjacent counties in carrots to be essentially continuous for eight months. Consequently, the SADDs for the SI, SC, BR and RT occupational scenarios were considered to be equivalent to the ADD (*i.e.*, the workdays per season were 200/200).

[f] Annual workdays for pest control operators, excluding oakroot fungus control, was 200, as supported by the pesticide use data and a report by Sullivan referenced in the Exposure Assessment document (DPR, 2004). A pest control operator was assumed to treat more than one crop with metam sodium in one or more counties.
[g] AADD, annual average daily dose, μg/kg/day. AADD = ADD x (workdays/year ÷ 365 days/year). For example, for the SI, SC and BR scenarios, 1.5 x 200/365 = 0.8 μg/kg/day.
[h] LADD, lifetime average daily dose, μg/kg/day. Assumes a working lifetime of 40 years (total lifetime = 75 years). LADD = AADD x (40 years of employment / 75-year lifetime). For example, for the SI, SC and BR scenarios, 0.8 x 40/75 = 0.4 μg/kg/day.

Local dermal exposure. Metam sodium's potentially corrosive properties made it necessary to estimate the extent of local exposure in μg/cm^2/day. This was accomplished using the sodium tetrathiocarbonate surrogate data along with a default median surface area assumption of 19,400 cm^2 for adult male workers (median body weight of 76 kg) (Table 26) (DPR, 2004). Local exposure values for females were expected to be similar to the male values; their smaller body size would be proportional to lower exposure values in mg/person/day, making the quotient of dermal exposure over body surface area the same for males and females. These estimates assume an even distribution of pesticide over the skin, an assumption that may not be valid if particular areas are disproportionally exposed.

Table 26. Estimated daily local dermal exposures of adult pest control operators during preplant applications and oakroot fungus control

Work task[a]	Dermal exposure[b]	Daily dermal exposure[c]
SI, SC, BR	5.3	0.27
RT	5.8	0.30
ORF	10.3	0.53

[a] See Table 24, footnote c.
[b] mg/person/day, from Table 24.
[c] μg/cm^2/day, based on a surface area of 19,400 cm^2 for adult male workers.

b. Seasonal (subchronic) exposure
As with acute exposures, seasonal average daily doses (SADDs) were calculated from the surrogate sodium tetrathiocarbonate data (Table 25). Pesticide use data from 2000 to 2002 (DPR, 2004) showed the use of metam sodium in Kern and adjacent counties in carrots to be essentially continuous for eight months (i.e., ~200 days). Consequently, the SADDs for the SI, SC, BR and RT occupational scenarios were considered to be equivalent to the ADD (*i.e.*, the workdays per season were 200/200). While the highest acute exposure rates, absorbed daily doses, and dermal doses were associated with oakroot fungus control, the limited number of workdays associated with the latter task was not considered consistent with an expectation of seasonal or annual exposure.

c. Annual (chronic) exposure
Because of its long potential seasonal use pattern, chronic exposure to metam sodium for non-oncogenic effects was also expected. These estimates appear in Table 25 as the annual

average daily dose (AADD). The relevant calculations assumed a 200 day/year exposure pattern.

d. Lifetime exposure

Because of the evidence for induction of angiosarcomas by metam sodium in male mice and supporting evidence for induction of hemangiosarcomas in male rats, both after chronic exposures through drinking water, a lifetime average daily dose (LADD) was calculated for the various work tasks (Table 25). These calculations assumed a 40-year exposure pattern out of a 75-year lifetime. As with the SADD and AADD estimates, oakroot fungus control was not expected to generate lifetime exposure. For a discussion of the inherent uncertainties in postulating lifetime exposrue, see section V.C.).

2. Residential exposure

Metam sodium is used outside of agriculture in the treatment of lumber and structural wood, sewage and drainage systems, food processing water systems and industrial waste disposal systems. The possibility of residential exposure was, however, considered to be unlikely (DPR, 2004). Therefore, a non-occupational (*i.e.*, resident / bystander) risk characterization was not undertaken.

3. Dietary exposure

Dietary exposure to metam sodium was considered to be unlikely for the following reasons:

1. Metam sodium is highly unstable, degrading quickly to MITC and other compounds.
2. It is used agriculturally only as a pre-plant biocide.

Because there are no established food use tolerances for metam, a dietary risk characterization was not conducted for this document. Combined or aggregate risk characterization was also not conducted since potential exposure is limited to occupational scenarios.

C. RISK CHARACTERIZATION

The assessment of non-cancer health effects resulting from exposure to metam sodium is expressed as the Margin of Exposure (MOE). The MOE is the ratio of the critical NOEL or LED from the definitive acute or subchronic studies over the estimated exposure dosages from the metam sodium surrogate dermal exposure studies. A MOE of 10 is generally considered to be protective of human health for adverse effects observed in human studies, while a margin of exposure of 100 is considered to be protective of human health for adverse effects observed in animal studies.

$$\text{Margin of Exposure (MOE)} = \frac{\text{NOEL or LED}}{\text{Exposure dose}}$$

1. Occupational exposure

a. Acute exposure

The mean 24-hour dermal absorbed exposure of workers ranged from 1.5 to 2.9 μg/kg/day. The critical acute LED_{01}, derived from the rabbit developmental toxicity study of Hellwig (1987), was 1 mg/kg, based on increased early resorptions at the LOEL dose of 10 mg/kg. Acute MOEs ranged from 345 to 667 (Table 27).

Table 27. Mean 24-hr absorbed daily doses and acute MOE values for various work tasks

Work task[a]	ADD (μg/kg/day)[b]	MOE[c]
SI, SC, BR	1.5	667
RT	1.7	588
ORF	2.9	345

[a] See Table 24, footnote c.
[b] ADD, absorbed daily dose, μg/kg/day. For sample calculation, see Table 25.
[c] MOE = LED_{01} (=1 mg/kg/day) / ADD.

Risk of dermal irritation. The risk of acute occupational dermal irritation was assessed because primary dermal irritation studies in animals (Table 5d) as well as incident reports in the California Pesticide Illness Surveillance Program (PISP) indicated that metam is corrosive and may have caused irritation in the field. The only available semiquantitative indicator of dermal irritability was the 21-day dermal toxicity study of Leuschner (1979). This study produced a local irritation NOEL of 31.25 mg/kg/day, based on a finding of erythema, edema and dermatitis in a majority of animals at 62.5 mg/kg/day. Conversion to units of local concentration resulted in NOEL and LOEL values of 360 and 720 μg/cm^2/day, respectively (section IV.A.3.).

Table 28 provides irritation MOEs based on dermal exposure rates calculated for the various work tasks. The lowest MOE was 679 for oakroot fungus control operations. Values as high as 1333 were calculated for other work tasks. Note, however, that the NOEL value was derived in what amounted to a "sub-acute" study (*i.e.*, exposures were longer than one day, but notably shorter than a conventional subchronic exposure regime), where dermal irritation at the LOEL dose of 720 μg/cm^2/day was not observed until day 4 (irritation was observed on day 1 at the

high dose of 1440 μg/cm^2/day). In all probability the acute dermal irritation NOEL would be higher under a true acute exposure scenario, raising the corresponding MOE. However, as noted above in the explication of the local exposure calculation (section IV.A.3), the assumption of even distribution over the body surface may underestimate higher local exposures, consequently overestimating the MOEs.

Table 28. Mean dermal daily doses and acute dermal irritation MOE values for various work tasks.

Work task[a]	Daily dermal exposure (μg/cm^2/day)	MOE[b]
SI, SC, BR	0.27	1333
RT	0.30	1200
ORF	0.53	679

[a] See Table 24, footnote c.
[b] MOE = dermal irritation NOEL (360 μg/cm^2/day) / daily dermal exposure

b. Seasonal (subchronic) exposure

Mean seasonal average daily doses for the various work categories ranged from 1.5 to 1.7 μg/kg/day. Using the estimated critical seasonal LED_{10} of 0.2 mg/kg/day established in the 90-day dog oral gavage study (based on bile duct proliferation / inflammatory cell infiltration and elevated plasma alanine aminotransferase activity in 1/4 females at the LOEL dose of 1 mg/kg/day), the range of seasonal MOE values was 118-133. These values appear in Table 29. While oakroot fungus control represented the highest risk from the standpoint of acute exposure, seasonal risk was not estimated because the limited number of workdays associated with this task was not considered consistent with an expectation of seasonal exposure.

Table 29. Seasonal average daily doses and seasonal MOE values for various work tasks

Work task[a]	SADD (μg/kg/day)	MOE[b]
SI, SC, BR	1.5	133
RT	1.7	118
ORF	n/a[c]	n/a[c]

[a] See Table 24, footnote c.
[b] MOE = LED_{10} (=0.2 mg/kg/day) / SADD.
[c] The limited number of workdays associated with oakroot fungus control was not considered consistent with an expectation of seasonal exposure.

c. Annual (chronic) exposure

Mean annual average daily doses for the various work categories ranged from 0.8 to 0.9 μg/kg/day. Using the critical chronic NOELof 0.1 mg/kg/day established in the dog 1-year oral

gavage study (based on elevated plasma alanine aminotransferase activity and signs of hepatotoxicity in 1/4 females), the range of annual MOEs was 111-125 (Table 30).

Table 30. Annual average daily doses and annual MOE values for various work tasks

Work task[a]	AADD (μg/kg/day)	MOE[b]
SI, SC, BR	0.8	125
RT	0.9	111
ORF	n/a[c]	n/a[c]

[a] See Table 24, footnote c.
[b] MOE = LED_{10} (=0.1 mg/kg/day) / AADD.
[c] The limited number of workdays associated with oakroot fungus control was not considered consistent with an expectation of annual exposure.

d. Lifetime exposure - oncogenicity

The risk of oncogenic effects was calculated as the product of the oncogenic potency and the lifetime average daily dose (LADD), assuming a dermal absorption of 2.5% and exposure for 40 working years over a 75-year lifespan. Risk values were calculated for both the maximum likelihood estimate (MLE) and the 95% upper bound of that estimate (95% UB). As shown in Table 31, the estimated risk using the MLE ranged between 3.42×10^{-5} and 4.28×10^{-5}, with rotary tiller operations incurring the highest risk, followed closely by shank injection and sprinkler chemigation operations, and bystander reentry situations. Using the 95% UB, the risk was as high as 9.25×10^{-5}.

Analysis of oncogenic potency by the Weibul time-to-tumor method was not considered appropriate in this assessment because, while angiosarcoma was often a factor contributory to death, there was no evidence that (1) it decreased the survival time or (2) that the death from angiosarcoma of high dose animals occurred sooner than the death from angiosarcoma of control animals.

Table 31. Lifetime average daily doses and oncogenic risk values for various work tasks

Work task[a]	LADD (μg/kg/day)	Oncogenic risk MLE[b]	95% UB[c]
SI, SC, BR	0.4	3.42×10^{-5}	7.40×10^{-5}
RT	0.5	4.28×10^{-5}	9.25×10^{-5}
ORF	n/a	n/a	n/a

[a] See Table 24, footnote c.
[b] This risk calculation was performed using the maximum likelihood estimate (MLE) of potency (Q_1), 8.56×10^{-2} (mg/kg/day)$^{-1}$. For example, MLE oncogenic risk for rotary tiller operators was (5×10^{-4} mg/kg/day) x (8.56×10^{-2} mg/kg/day^{-1}) = 4.28×10^{-5}.
[c] This risk calculation was performed using the 95% upper bound (95% UB) estimate of potency (Q_1*), 1.85×10^{-1} (mg/kg/day)$^{-1}$. For example, 95% UB oncogenic risk for rotary tiller operators was (5×10^{-4} mg/kg/day) x (1.85×10^{-1} mg/kg/day^{-1}) = 9.25×10^{-5}.

2. Risk from exposure to MITC

Monitoring of MITC levels under occupational scenarios, in towns near regions of heavy agricultural metam sodium use ("ambient" levels), and near fields that were recently treated ("application site" levels) demonstrated the potential for exposure of workers and the general public. Occupational and application site air levels were generally higher than ambient levels, thus generating lower MOE values. Nonetheless, MOEs calculated under all three scenarios indicated the potential for human health impacts. Because the critical acute NOEL was based on a human study, MOEs over 10 were considered health-protective. On the other hand, the critical subchronic and chronic NOELs were based on an animal study. Consequently, seasonal and chronic MOEs over 100 were considered health-protective. Under acute exposure conditions a range of occupational MOEs between <1 and 8 was noted, while the application site range was <1-59 and the ambient range was 15-2200. Under seasonal exposure conditions, occupational MOEs ranged between 3 and 1429, application site MOEs between 1 and 333, and ambient MOEs between 28 and 166,667. Under chronic exposure conditions, occupational MOEs ranged between <1 and 143, application site MOEs between <1 and 33, and ambient MOEs between 5 and 25,000.

Reference Exposure Levels (RELs). The REL is defined by the Office of Environmental Health Hazard Assessment as "the concentration level at or below which no adverse health effects are anticipated for a specified exposure duration." RELs are based on the best available medical and toxicological studies and "are designed to protect the most sensitive individuals in the population by the inclusion of margins of safety." The REL for acute effects of MITC was calculated by dividing the critical NOEL, 220 ppb, by 10 to account for intrahuman variability when the NOEL was determined in a human study. Because the eye irritation NOEL was stable at 1, 4 and 8 hours in the critical laboratory study, the REL was relevant for potential exposure times of up to 8 hours. The resultant value, 22 ppb, was well below many of the anticipated acute exposure levels established in the occupational and application site air monitoring studies, indicating a potential human health hazard. Estimated ambient exposure estimates for 1 and 8 hours did not exceed 14.6 ppb. A human health concern was therefore not indicated under those conditions.

The subchronic REL of 1 ppb was generated by dividing the 24-hour critical subchronic rat inhalation NOEL of 100 ppb by an uncertainty factor of 100 (10-fold to account for intrahuman variability and 10-fold for the assumption that humans are more sensitive than animals). Seasonal ambient time-weighted average MITC concentration determinations indicated some cause for human health concern. A health concern clearly existed for occupational and application site scenarios where the REL values were frequently exceeded.

The chronic REL of 0.1 ppb was generated by dividing the subchronic REL by an uncertainty factor of 10 (to extrapolate from subchronic to chronic exposure). Chronic occupational and application site air levels nearly always exceeded this value, indicating a human health concern. Ambient values were also frequently in excess of 0.1 ppb, indicating a health concern.

Despite evidence that MITC exposure through the drinking water may have induced mammary fibroadenomas and carcinomas in female rats and fibrosarcomas in male and female mice, the data were not considered sufficient to trigger a quantitative oncogenic risk evaluation.

V. RISK APPRAISAL

A. INTRODUCTION

Risk assessment is the process used to evaluate the potential for human exposure and the likelihood that the adverse effects of a substance will occur in humans under the specific exposure conditions. Every risk assessment has inherent limitations on the application of existing data to estimate the potential risk to human health. Therefore, certain assumptions and extrapolations are incorporated into the hazard identification, dose-response assessment, and exposure-assessment processes. These, in turn, result in uncertainty in the risk characterization, which integrates all the information from the previous three processes. Qualitatively, risk assessments for all chemicals have similar uncertainties. However, the degree or magnitude of the uncertainty can vary depending on the availability and quality of the data, and the types of exposure scenarios under assessment.

Specific areas of uncertainty associated with this risk assessment for potential occupational exposure to metam-sodium are discussed in the following sections.

B. HAZARD IDENTIFICATION

1. Acute systemic and local toxicity

Consideration of the critical Hellwig (1987) rabbit developmental toxicity study. The critical acute LED_{01} of 1 mg/kg was established in the Himalayan rabbit developmental toxicity study of Hellwig (1987). It was based on an increase in early resorptions throughout the dose range, with an effect arguably present even at the low dose of 4.2 mg/kg, where statistical significance was not achieved. The LED_{01} was determined by applying benchmark dose methodology to the incidence curve, using fetal incidence per dose as the data source (DPR, 2003b). Sixteen BMD algorithms were tested to determine the curve that best fit the early resorption data. Of these, the quantal linear model and the probit model (non-log transformed) had equivalent low AIC numbers (a measure of goodness of fit). For the quantal linear model, the LED_{01} and ED_{01} were 0.79 and 1.01 mg/kg, respectively, while for the non-log probit model the LED_{01} and ED_{01} were 2.56 and 3.32 mg/kg. Thus the quantal linear model was chosen to represent the acute risk from metam sodium because it predicted a more health-protective (*i.e.*, lower) LED value. The LED_{01} of 0.79 mg/kg was rounded to 1 mg/kg, and used in this document in place of a NOEL value to calculate margins of exposure.

Confidence in this acute regulatory value is affected by a number of considerations:

1. As noted, the increased incidence of early resorptions at 4.2 mg/kg did not achieve the 95% level of statistical confidence (*i.e.*, $p<0.05$ by the Fisher Exact test) generally required to assign statistical significance. While it is true that the Fisher “p” value was 0.08 for the incidence of early resorptions compared to controls, and 0.06 for the number of litters with early resorptions, the failure to achieve statistical significance may indicate that the apparent effect represented only normal variation in control populations. Nonetheless, recognition of the low (but not formally statistically significant) “p” values, in combination with the dose-dependent rise in incidence, was sufficient to set the LOEL at 4.2 mg/kg.

2. Choice of the quantal linear algorithm over the non-log probit algorithm, two models with virtually equal AIC numbers (*i.e.*, their respective curves represented equivalent fits to the data points using this parameter) was based solely on its more health-protective consequence in the risk characterization due to its lower LED_{01}. Thus the acute MOEs, which range between 345 to 667 using the quantal linear LED_{01} (1 mg/kg), would have ranged between 1035 and 2001 using the rounded non-log probit LED_{01} (3 mg/kg).

3. Choice of 1% as the benchmark response level reflected the seriousness by which the early resorption endpoint was regarded. It might nonetheless be argued that, in view of the relatively common occurrence of this endpoint in rabbit and the lack of statistical significance at the low dose, 5% might have been a reasonable choice. This would have resulted in LED_{05} and ED_{05} values of 4.04 and 5.13 mg/kg, respectively, by the quantal linear approach, with consequent MOEs of four times the range based on LED_{01} determination.

4. As discussed above in section III.G.4, early resorptions were also observed in the Zeneca rabbit developmental toxicity study (Hodge, 1993), but at a considerably higher dose (LOEL = 60 mg/kg, NOEL = 20 mg/kg). This could be interpreted both as support for using early resorptions as an endpoint, and as an argument against the critical LOEL being set at 4.2 mg/kg (as it was for the Hellwig [1987] study). Early resorptions may also have been increased in the Wistar rat developmental toxicity study of Hellwig and Hildebrand (1987), though the dose at which this occurred was unclear (see discussion below).

5. There was an apparent lack of dose responsiveness for early resorptions if the data are expressed on a litter basis, which is commonly held to be more toxicologically valid, rather than the fetal basis relied upon in this assessment. In this conception, the litter incidence at increasing doses (1/14, 5/13, 5/14, 13/15), with its lack of increase between the low and mid doses, casts question on the nature of the increase between the controls and the low dose. The counter-argument is, however, that because the fetal incidence at the low dose was spread among several litters, it was considered to express, at least partially, a litter-wide effect. This lends validity to the use of fetal data.

Some reasoning should be provided as to why the acute LED_{01} of 1 mg/kg from Hellwig (1987) was relied upon for the critical acute endpoint rather than calculating an appropriate LED from the developmental LOEL of 4.2 mg/kg established in the Wistar rat developmental toxicity study (lowest dose tested; Hellwig and Hildebrand, 1987). The latter value was based on a statistically significant increase in resorptions at that dose. Most of the resorptions occurred within two days of the advent of dosing on gestation day 6. Three considerations were primary in deemphasizing the Hellwig and Hildebrand study as a possible source for the critical acute value:

1. The incidence of resorptions did not exhibit dose responsiveness in the Hellwig and Hildebrand study. Despite the statistically significant increase recorded at the low dose of 4.2 mg/kg/day, there was a *decrease* in resorptions at 16.9 mg/kg/day to control levels (Table 16). In addition, no further increase compared to the 4.2 mg/kg/day group was observed at the

high dose of 50.6 mg/kg/day. A similar situation was evident when the data were expressed as a percentage of litters exhibiting at least one resorption. Thus it appeared impossible to distinguish between random variation and a metam-induced increase at any dose.

2. The later developmental toxicity study of Tinston (1993), using the same strain of rat, did not show increased resorptions at least through 20 mg/kg/day, and very probably through the high dose of 60 mg/kg/day. In this light, it is very hard to place great confidence in the acute developmental LOEL value of 4.2 mg/kg/day from Hellwig and Hildebrandt (1987).

3. Historical control data neither supported nor negated an embryotoxic effect for metam in the Hellwig and Hildebrand study. BASF company data summarizing control group tallies from 21 studies conducted between 1982 and 1988 showed a range of resorption incidence between 4.5% and 12.7%, with a mean of 8.3% ± 2.3% (BASF, 1989). The values observed in the current study at 4.2 and 50.6 mg/kg/day, 17.89% and 14.79%, respectively, exceeded that range. However, supplier data from 10 studies contributed by BASF indicated a range from 3.51% to 22.57%, encompassing the current study values. (*Note*: BASF did not define the term "supplier", though it may refer to data from the breeding facility. BASF also did not provide a mean value for the supplier range.)

Consideration of the Tinston (1993) rat developmental toxicity study. The Tinston study established maternal and developmental NOELs of 5 mg/kg. These were based on clinical signs and decrements in maternal weight and food consumption in the dams, and skeletal developmental delays and suppression of fetal weights at the mid dose of 20 mg/kg/day. Although the incidence of non-ossification at two sites (calcaneum and 2nd centrum) was statistically significantly increased over controls at the low dose, these signs were not adequate to determine a LOEL. For one thing, they were not of sufficient magnitude or severity for regulatory consideration. In addition, the maternal hypophagia and weight gain decrements that were their likely cause, were themselves relatively slight at the low dose. Without knowing the cause of the hypophagia, it is difficult to discern the toxicologic significance of the resultant effects. We were faced with a situation where, in all likelihood, a train of slight effects (*i.e.*, maternal weight gain decrements and fetal ossification delays) was put into motion by a slight decrement in food consumption. In light of the fact that there is at least some question about whether there was an ossification delay at all at the low dose (see discussion in the next paragraph and in section III.G.2), it appeared unwise to rely upon this effect to set a regulatory LOEL.

Finally, the non-ossification incidence rates at the two sites (1) did not exceed the historical control ranges even at the *mid* dose of 20 mg/kg, and (2) did not even exceed the historical control means at the low dose of 5 mg/kg. While invoking historical control data is not meant to delegitimize the ossification effects at the low dose, or to infer that they were not metam sodium related, comparison to historical data does illustrate how minor those effects were at the low dose.

Consideration of the Leuschner (1979) 21-day rabbit dermal toxicity study. It might be argued that the use of data from oral exposures is irrelevant when actual exposure in the field is

postulated to occur only through the skin. Indeed, the available 21-day rabbit dermal toxicity study (Leuschner, 1979) did not produce systemic toxicity even at the high dose of 125 mg/kg/day. Immunotoxicity was present at 200 mg/kg/day in the 4-day dermal exposure study of Pruett *et al.* (1992), though none was observed at 100 mg/kg/day. However, neither dermal study examined possible effects on embryos or fetuses. Orally administered metam sodium induced resorption of early embryos, particularly in the rabbit, and fetal malformations in the Himalayan rabbit and Wistar rat, effects which were not clearly attributable to maternal toxicity. Such effects were considered sufficiently serious to warrant the level of protection provided by the oral NOEL value.

Dermal irritation. The risk of acute dermal irritation to workers was estimated by calculating MOEs for each of the indicated occupational categories. The irritation NOEL used to calculate the MOE, 360 $\mu g/cm^2$/day (calculated from the applied dose of 31.25 mg/kg; see section IV.A.3.), was derived from the 21-day dermal toxicity study in rabbits (Leuschner, 1979). Estimates of occupational dermal exposure were derived from the same sodium tetrathiocarbonate surrogate study used to estimate systemic exposure (DPR, 2004). The main source of uncertainty with respect to the NOEL determination resided in the decision to consider irritation at the LOEL dose of 720 $\mu g/cm^2$, which evolved after 4 days of exposure, to constitute an acute response. It could be argued that the appropriate acute NOEL was actually 720 $\mu g/cm^2$, based on a LOEL of 1440 $\mu g/cm^2$. The latter dose generated an irritation response within a single day, conventionally considered an appropriate acute scenario. Designation of 720 $\mu g/cm^2$ as the NOEL would have resulted in MOE values twice as high as those reported here using 360 $\mu g/cm^2$. However, as 4 days was considerably shorter than a conventional subchronic scenario, it was considered prudent for health conservative reasons to classify this exposure period as acute.

It is also relevant to recall that the Leuschner study did not include a dosing solution analysis, normally required under federal guidelines for studies of this nature. If metam degradation occurred after application to the dermal surface (as is plausible), or if the initial concentration of metam had declined from the label-stated value, then the amount of metam required to initiate an irritation response was also lower. The risk estimates in this document would thus be understated (*i.e.*, the MOEs would be inappropriately high).

Finally, the results of the primary dermal irritation studies were quite variable, with 4 of 7 studies showing metam sodium to be a Category I dermal irritant (indicative of corrosiveness, with tissue damage or scarring), one study showing Category II (severe irritation at 72 hours), and 2 studies at Category IV (mild irritation at 72 hours) (see Table 5d and the associated text discussion). While the reason for this inconsistency was not known (though it was plausibly related to uncontrolled lability of metam sodium at the test site), a further level of uncertainty regarding the representativeness of the Leuschner study should be recognized.

2. Subchronic toxicity

The critical subchronic endpoint LED_{10} of 0.2 mg/kg/day was established in the dog 90-day oral gavage study of Brammer (1992b). As noted in Sections III.C.5 and IV.A.3, this value was estimated from the low dose LOEL of 1 mg/kg/day using benchmark dose methodology (DPR, 2003b). Sixteen BMD algorithms were tested to determine the curve that best fit the liver data. Of these, the quantal linear model had the lowest AIC number, and thus was considered to be the best representation of the data points. The quantal linear model generated LED_{10} and ED_{10}

values of 0.163 mg/kg/day and 0.326 mg/kg/day, respectively. The LED_{10} was rounded to 0.2 mg/kg/day for use in the subchronic risk characterization.

The critical subchronic LOEL was based on an observation of bile duct proliferation / inflammatory cell infiltration and elevated plasma alanine aminotransferase activity in 1/4 females at that dose, interpreted as evidence of liver damage. The most obvious uncertainty in this designation was whether or not an effect detected in a single animal was indeed due to metam sodium exposure (as has been postulated in this document). Increases in apparent toxicity in single animals can be difficult to ascribe to test article exposure and are often discounted as unreliable in risk analyses. The alternative of designating 1 mg/kg/day as the NOEL based on clear liver damage at 5 mg/kg/day would result in MOEs that are 5-fold higher (*i.e.*, 5-fold lower risk estimates) than those reported here. However, in light of a similar incidence (1/4 females) of liver damage by 26 weeks at the *same dose* in the dog chronic study (Brammer, 1994), and the clear dose responsiveness of the liver damage in the subchronic study, it was considered probable that the liver effects at 1 mg/kg/day in the subchronic study were due to metam sodium. It is worth mentioning that, in their review of metam sodium toxicity, Carlock and Dotson (2001) also considered the liver effect at 1 mg/kg/day in this study to be test article related, setting the NOEL for females at <1 mg/kg/day.

From the data in the two dog studies (Brammer, 1992b and 1994), it appears that a fraction of beagles may be particularly sensitive to the hepatotoxic effects of metam sodium by the oral route. Use in this document of a benchmark dose response level of 10%, instead of 5% or 1%, was, in effect, a recognition of the apparent mildness of the single-animal response at that dose. Of course the opposite argument can be made, that a single response was *not* necessarily evidence of a low incidence rate, since there were only four dogs / sex / dose group.

The bile duct proliferation / inflammatory cell infiltration seen in one low dose female, as well as in one mid dose male and one mid dose female, were considered to reflect an early form of the hepatitis that developed in other animals at the higher doses. This assumption was supported by the inflammatory nature of the hepatitis and the presumed co-location of the liver and bile ducts in the histologic preparations. In addition, the study report lists “biliary proliferation” as one of the indicators of hepatitis in the mid and high dose animals, implying a link between the “bile duct proliferation” at the low dose and the hepatitis at the higher doses. Nonetheless, the report is *not* clear on what the difference between “biliary proliferation” and “bile duct proliferation” is, nor why, with biliary proliferation listed as an indicator of hepatitis, it is not tabulated as a bile duct effect similar to the bile duct proliferation at the low dose. This increased the uncertainty in designating the low dose effect as part of a process that resulted ultimately in hepatitis.

The argument that the oral route is irrelevant because, according to the Exposure Assessment (DPR, 2004), exposure is only expected by the dermal route, is not convincing. Such an argument would state that, as the 21-day dermal study of Leuschner (1979) established a systemic NOEL of $\geq$125 mg/kg/day, and assuming a metam sodium dermal absorption rate of 2.5% (DPR, 2004), the systemic dose would have been ~3 mg/kg/day. This was well above the critical oral LED_{10} of 0.2 mg/kg/day and even above the critical oral LOEL of 1 mg/kg/day (which, as has been discussed here, was based on liver toxicity). While this is superficially reassuring (in the sense that liver damage apparently does not occur after dermal exposure at

this dose), it nonetheless represented only a 3-week exposure, not 13 weeks as in the oral study.

Also, 3 mg/kg/day approximated the oral LOEL dose for embryotoxicity of 4.2 mg/kg/day in Himalayan rabbits, illustrating the potential for metam sodium to achieve toxicologically meaningful concentrations within the body even after dermal exposure. In view of the severity of the potential teratologic effects, it was considered prudent to keep the critical subchronic NOEL below the acute LED_{01}. Consequently, the orally derived value of 0.2 mg/kg/day was relied upon for this risk analysis for the seasonal risk evaluation.

The Brammer (1992b) study carried additional weight by virtue of the fact that it was conducted in dogs and used a gavage dosing regime. The precise dose was, therefore, known, in contrast to the supporting studies in rats and mice, where the drinking water exposure regimen necessitated calculation of internal doses using unverified assumptions about the metam sodium degradation rate in water bottles (see below). However, as these studies supported the critical LED_{10} designation of 0.2 mg/kg/day, it is relevant to explore their weaknesses.

The rat 90-day drinking water study (Allen, 1991) established the lowest empirical NOEL at 0.49 mg/kg/day (*i.e.*, extrapolation from a LOEL was not necessary). However, the toxicologic significance of the determining endpoints (body weight, water consumption, and urinary effects) was unclear.

The mouse 90-day drinking water study of Whiles (1991) established a NOEL of 0.79 mg/kg/day based on reduction in hemoglobin, hematocrit and red blood cell numbers (an anemic effect), increased liver weights, and eosinophilic granules in transitional epithelial cells of the urinary bladder, at the next higher dose of 4.48 mg/kg/day.

However, several factors bear on the legitimacy of the mouse NOEL determination:

1. 0.79 mg/kg/day may underestimate the amount of metam sodium consumed at the NOEL dose, and thus underestimate the NOEL. The value was calculated by multiplying the initial (nominal) dose by the percentage of the dose remaining after 24 hours in a water bottle (for a detailed description of this calculation, see footnote #1, section III.C.3.). As explained in section IV.A.2., at nominal concentrations less than 0.1 mg/ml, more than 60% of the metam sodium was no longer detectable by 24 hours. Moreover, detailed degradation curves were not established in the study. Since the drinking water containing the test article was changed daily, such determinations for times less than 24 hours would have been critical for an accurate estimation of the internal dose. It was, therefore, not possible to determine the metam sodium concentration in the bottles at the time of exposure. It can only be said that the mice were *possibly* exposed to higher concentrations than those calculated for the NOEL and LOEL doses, as they would likely have consumed a significant portion of their water before the end of the 24-hour period that each batch of water / metam sodium was available to them.

2. The significance of the mouse NOEL value was further undermined by the likely contamination of the water bottles with metam sodium breakdown products. This would be particularly problematic at the lower doses where, as

noted above, metam sodium degradation was greater than 60% in a 24-hour time period and where the NOEL and LOEL values were set.

3. As was the case with the rat study, the "adverseness" of the endpoint determinants in the mouse drinking water study (anemia, increased liver weights, and eosinophilic granules in transitional epithelial cells) may be questioned, particularly because overt clinical signs were not observed at any dose (though further histopathologic damage was evident in the bladder at higher doses).

3. Oncogenicity

Incidence of angiosarcoma, a multi-organ malignant vascular tumor, was increased by exposure of male mice to metam sodium. As it was clear that angiosarcoma incidence increased in several organ systems at the high dose, it was assumed that tumor development in all of those systems was reflective of the same basic process. Additive data, *i.e.*, data from all organ systems, were thus invoked to generate the oncogenic potency values. In a calculation that was based on incidence rates in the total population of male mice at risk (that is, all mice surviving the first year of exposure), the risk to workers for development of angiosarcoma was $3.42x10^{-5}$ - $4.28x10^{-5}$ when expressed as the maximum likelihood estimate and $7.40x10^{-5}$ - $9.25x10^{-5}$ when expressed as the 95% upper bound estimate. These estimates, derived as they were from the GLOBAL86 approach, were based on assumptions that multistage, non-threshold-dependent mechanisms were valid. Such a situation is generally thought to obtain in cases such as this one where genotoxicity is apparent - metam sodium was clastogenic in 3 of 4 structural chromosome aberration tests, including 2 *in vitro* and 1 *in vivo* test - and contravening evidence for a threshold mechanism was not supplied. Nonetheless, actual evidence for linearized kinetics was not forthcoming; because of the limited number of animals tested, there was no certainty that metam sodium induced tumors at the lower two doses. Linearized kinetics were thus invoked as a health-protective default assumption.

There are several more reasons why oncogenic risk, as currently stated, may be overstated:

1. Oncogenic risk was calculated using oral exposure studies. The relevance of such studies to the current situation, where exposure is expected to occur only by the dermal route, is very much in question. However, as no long-term dermal toxicity studies were available, it was considered prudent to retain the risk values derived from the oral studies.

2. Metam sodium may not be absorbed *as such* through the skin, but may be absorbed as MITC or other breakdown products. As noted above in the summary treatment of MITC toxicity (section III.J.2.), MITC by the oral route did not cause angiomatous tumors, though there was an association with mammary fibroadenomas and carcinomas in female rats exposed to MITC chronically through the drinking water study and with cutaneous fibrosarcomas in both sexes in a similarly exposed mice. Thus conversion to MITC at the skin surface may decrease the angiomatogenic potential of metam sodium.

3. The oncogenic risk estimate derives from an unverified assumption that

acute, seasonal or annual dermal exposure (themselves estimated using surrogate data) can be validly amortized to generate a lifetime average daily dose.

4. Finally, as mentioned above in the Risk Characterization section (IV.C.1.d.), it may be argued that, based on the 16% weight gain decrement in high dose males, the maximum tolerated dose was exceeded. However, this was discounted due to lack of convincing overt toxic signs.

Support for a causative role for metam in angiosarcoma induction was provided in the observation that incidence of hemangiosarcoma, a malignant vascular tumor regarded as a type of angiosarcoma, appeared to increase in male rats. As mentioned above under Risk Characterization, the incidence decreased in the rat from the mid to the high dose, calling into question conclusive statements of metam causation (see section IV.A.5.). However, in the context of the much clearer data from the mouse for the same tumor type, a metam-based etiology in the rat is credible.

Evidence for increases in meningioma in the rat and bladder dysplasias in the mouse was also credible, but potency calculations were not carried out due to the very low incidence rates in both cases. Nonetheless, the considerable evidence for bladder histopathology in the mouse (both sexes) strengthens the argument that the bladder dysplasias observed were indeed the result of metam exposure (see discussion of in section III.D.2). In addition, as noted by the examining pathologist, the extreme rarity of these tumors supported a metam causation.

C. EXPOSURE ASSESSMENT

1. Occupational exposure

Uncertainties associated with the assessment of occupational exposure to metam sodium are covered in the Exposure Assessment document (DPR, 2004). It is, nonetheless, worth reiterating that the exposure estimates were based on surrogate data, since no studies on metam sodium itself were available. Like metam sodium, the surrogate, sodium tetrathiocarbonate, was labile. Estimation of dermal exposure per day was based on a proportionality between the initial tetrathiocarbonate concentration and the level of non-labile cesium ions that were added to the formulation. Several factors have a bearing on the reliability of this data:

1. As discussed in section IV.B., cesium ions were either not detected or were below the level of quantitation in the occupational tasks examined in the surrogate exposure study. Consequently, values which reflected the limits of detection or quantitation were substituted for actual exposure values. This likely resulted in an overestimation of exposure, with a consequent underestimation of systemic and dermal irritation MOEs, and an overestimation of oncogenic risk.

In the latter case, lifetime adjusted daily doses (LADDs) were estimated by amortizing subchronic exposure data which was originally calculated for seasonal work of 200 days/season. The seasonal exposures were themselves amortized from acute exposure estimates. Thus the lifetime daily MITC exposure value was based on an improbable circumstance, to wit, that exposure values determined over a single day were validly translated into daily exposure

values occurring over a 40-year working career. The risk values calculated using such exposure terms should be viewed almost certainly as overestimates. Nonetheless, DPR has used this approach in at least one previous risk characterization document (DPR, 1998). The seasonal and annual exposure estimates occasion similar concerns, as they too were dependent on the short term surrogate measurements.

2. Because the exposure estimates were based on levels of quantitation or detection, *ranges* of exposure were not provided. Any *appearance* of exactitude due to the absence either of ranges or of standard deviations is misleading.

3. The exposure assessment assumes that none of the metam sodium will have degraded prior to absorption through the skin. In view of the lability of this compound, a property that is dependent on specific environmental conditions such as temperature, moisture, light availability and pH, an assumption of non-degradation is neither supported nor refuted by any data. The resultant systemic exposure values may thus be overestimates. Overestimation of exposure would, in turn, result in an overestimation of the toxicity risk.

4. The 2.5% dermal absorption factor derived from a rat study (Stewart, 1992) may overestimate the amount of absorption occurring in humans. A study directly comparing metam absorption *in vitro* in full thickness (epidermis + dermis) rat and human skin was reviewed recently by DPR (DPR, 2000). At the high dose of 940 μg/cm^2, rat skin absorbed 4.1 times more metam sodium than human skin. However, as the dose was lowered, the rat and human values began to converge. At the low dose of 94 μg/cm^2, only 1.4 times more metam sodium was absorbed by rat than human skin. As stated in the DPR review (DPR, 2003c), "It is likely that the ratio could approach 1.0 when a lower dose level was used, *eg.* 8.6 μg/cm^2, which was employed in the *in vivo* dermal absorption study." DPR therefore advocated a 1:1 correspondence between rat and human at doses relevant to field exposures.

5. Calculation of local dermal exposure assumed that the pesticide was evenly distributed over the body surface. It did not take into account the possibility that exposures of particular areas such as the hands or face might be disproportionally high. Consequently, the risk of dermal irritation in putative highly exposed areas may be underestimated.

2. Exposure of the general public

Exposure of the general public to metam sodium was not anticipated in DPR's Exposure Assessment document (DPR, 2004).

D. RISK CHARACTERIZATION

Generally, an MOE of at least 100 is considered sufficiently protective of human health when the NOEL for an adverse systemic effect is derived from an animal study. The MOE of 100 allows for the possibility that humans are 10 times more sensitive than animals and exhibit a 10-fold range in sensitivity among individuals. The acute systemic MOEs for metam sodium ranged between 690 and 1333 depending on the occupational task. The corresponding seasonal systemic MOEs ranged between 118 and 133, also depending on the occupational task, though as noted, oakroot fungus control was not considered a likely seasonal (or annual) exposure scenario. Annual systemic MOEs had a range of 111-125. Acute dermal irritation MOEs ranged between 679 and 1333. While none of these MOEs fell below the benchmark of 100, clearly the seasonal and annual systemic MOEs were close to that value, occasioning concern. Uncertainties in the establishment of MOEs, both from the hazard identification and exposure perspectives, were covered in the preceding sections.

Because of the seriousness of the oncogenic endpoint (angiosarcomas in mice), it is of interest to look once more at the risk calculations for oncogenesis. Metam sodium was clearly oncogenic in the 2-year mouse drinking water study. An oncogenic risk estimate was formulated based on GLOBAL86, one of the currently preferred models for extrapolating quantal animal toxicity data to low doses using the linearized multistage model. This model generates a *maximum likelihood estimate* (Q1) and a *95% upper bound* estimate (Q1*) of cancer potency, expressed as the slope of the dose-response curve (both numbers derive from the same polynomial approximation of the dose-response curve), with units of $(mg/kg/day)^{-1}$. Risk, a unitless expression, was then calculated as the potency x the lifetime adjusted daily dose (LADD). Generally, a risk value of 10^{-6} or less is considered to be negligible. As shown above, the risk for development of angiosarcoma following 40 years of occupational exposure to metam sodium at the highest LADD was 4.28×10^{-5} when expressed as the maximum likelihood estimate and 9.25×10^{-5} when expressed as the 95% upper bound estimate.

Considerable uncertainty exists with respect to the exposure assumptions used to calculate oncogenic risk in this case. In particular, a seasonal exposure of 200 days over the course of a year, calculated from surrogate, single-day exposure data using substitution values reflecting the limits of detection and quantitation, may not be sufficient to calculate a valid lifetime average daily dose (LADD). However, several considerations favor use of the LADD in this way so that a risk value may be calculated for metam sodium:

1. The mode of action by which metam sodium induced angiosarcomas in mice and rats is unknown. Hence the time / exposure requirements for potential tumor induction in humans are also unknown.

2. Metam sodium is clastogenic in 3 or 4 chromosome aberration assays, including one *in vivo* assay in which the effect was induced after a single exposure (Gelbke and Englehardt, 1987b).

3. Reflecting the seriousness of this condition, angiosarcoma was a leading cause of death in the mouse oncogenicity study. Humans are known to have similarly grave clinical outcomes from this tumor type (Fletcher and McKee, 1992).

As noted above, inherent in any linearized low dose extrapolation is the assumption that the endpoint has no biological threshold for tumor induction. The original notion that tumor induction had no threshold came from studies suggesting that radiation could theoretically induce carcinogenesis at "one-hit" doses. This assumption has also been postulated to apply to DNA-reactive carcinogens. Nonetheless, one-hit carcinogenesis has never been conclusively proven with respect to chemicals, and, in fact, appears to be incorrect in some circumstances (Williams and Weisburger, 1986).

E. METAM SODIUM CRITICAL TOXICITY ENDPOINTS, USEPA vs. DPR

In May 2004, the United States Environmental Protection Agency released a series of documents evaluating the risks associated with exposure to metam sodium and MITC. Critical toxicity endpoints established for metam sodium by USEPA appear in USEPA (2004). These values are summarized below in Table 32. The parallel values established by DPR in the present document are included for the sake of comparison.

Table 32. Comparison of critical endpoints for metam sodium set by DPR and USEPA

Exposure scenario	DPR	USEPA
Acute, systemic	**1 mg/kg** (LED_{01}), based on ⇑ early resorptions @ 4.2 mg/kg in rabbits (gavage) Ref.: Hellwig (1987)	**4.22 mg/kg** (NOEL), based on ⇓ wt. gain & ⇓ food consumption @ 16.88 mg/kg in maternal rats (gavage) Ref.: Hellwig & Hildebrandt (1987)
Acute, irritation	**360 μg/cm^2/day** (NOEL), based on dermal irritation @ 720 μg/cm^2/day in rabbits (21-day dermal) Ref.: Leuschner (1979)	USEPA did not set an irritation-based endpoint
Subchronic, systemic	**0.2 mg/kg/day** (LED_{10}), based on incipient hepatotoxicity and bile duct pathology @ 1mg/kg/day in dogs (3-month gavage) Ref.: Brammer (1992b)	**0.1 mg/kg/day** (NOEL), based on ⇑ ALT and liver histopathology @ 1mg/kg/day in dogs (1-yr gavage) Ref.: Brammer (1994)
Chronic, systemic	**0.1 mg/kg/day** (NOEL), based on ⇑ ALT activity and evidence of hepatotoxicity @ 1 mg/kg/day in dogs (gavage) Ref.: Brammer (1994)	**0.1 mg/kg/day** (NOEL), based on ⇑ ALT and liver histopathology @ 1mg/kg/day in dogs (1-yr gavage) Ref.: Brammer (1994)
Oncogenicity	**1.85x10^{-1} (mg/kg/day)$^{-1}$** (Q_1*), based on angiosarcomas in mice Ref.: Horner (1994)	**1.98x10^{-1} (mg/kg/day)$^{-1}$** (Q_1*), based on angiosarcomas in mice Ref.: Horner (1994)

F. ISSUES RELATED TO THE FOOD QUALITY PROTECTION ACT

1. Introduction

The Food Quality Protection Act of 1996 mandated the US EPA to "upgrade its risk assessment process as part of the tolerance setting procedures" (US EPA, 1997a and b). The improvements to risk assessment were based in part on the recommendations from the 1993 National Academy of Sciences report, Pesticides in the Diets of Infants and Children (NRC, 1993). The Act required an explicit finding that tolerances are safe for children. US EPA was required to use an extra 10-fold safety factor to take into account both potential pre- / post-natal developmental toxicity and the completeness of the data unless US EPA determined, based on reliable data, that a different margin would be safe. In addition, US EPA must consider available information on: 1) aggregate exposure from all non-occupational sources; 2) effects of cumulative exposure to the pesticide and other substances with common mechanisms of toxicity; 3) the effects of *in utero* exposure; and 4) the potential for endocrine disrupting effects.

Because no tolerances have been designated for metam sodium (see section VI: Tolerance Assessment), FQPA is not directly applicable. However, the issues under FQPA are addressed for metam because of their general toxicologic importance.

2. Pre- / post natal sensitivity

Six developmental toxicity studies, 4 in rats and 2 in rabbits, were examined for this document. All utilized the oral route of exposure. In both rabbit studies, metam sodium induced early resorptions. In Himalayan rabbits, resorptions were induced at the sub-maternally toxic dose of 10 mg/kg/day. Fetal malformations (meningocele + spina bifida) occurred at the slightly maternally toxic dose of 100 mg/kg/day. In New Zealand White rabbits, resorption incidence was overwhelming at a dose in which only slight maternal toxicity was observed. In Wistar-derived Alpk:APfSD rats, malformations (meningocele, microphthalmia, anophthalmia, skull malformation, hydrocephaly and abnormal zygomatic arch) were noted at the maternally toxic dose of 60 mg/kg/day.

Because the acute risk evaluation was based on a developmental endpoint (increased resorptions in rabbits - Hellwig, 1987), an extra uncertainty factor to protect from developmentally toxic effects may not be necessary. On the other hand, such an uncertainty factor might be considered in the case of seasonal risk, which was evaluated using an endpoint (liver damage) established in adult dogs (Brammer, 1992b).

3. Aggregate exposures

"Aggregate exposures" refers to the possibility that an individual could be exposed to a particular chemical by more than one route. In the case of metam sodium this is considered unlikely, as exposure is expected only under occupational circumstances and only by the dermal route (see DPR, 2003c).

4. Cumulative exposures

"Cumulative exposures" refers to the possibility that an individual could be exposed to multiple chemicals that have similar mechanisms of toxicity. Other dithiocarbamates such as maneb and mancozeb do not appear to share mechanisms of toxicity with metam. The former 2 compounds are broken down to ethylene thiourea, which is considered to be the proximate mediator of toxicity. Ethylene thiourea is not an intermediate of metam breakdown.

Dazomet, a thiadiazine soil sterilant and anti-microbial, is similar to metam in that it is broken down to MITC and thus may share aspects of MITC's toxicology. However, dazomet use rates are low compared to metam, making the potential for cumulative exposure to MITC also likely to be low. If and when a risk characterization document for dazomet is done, the potential combined exposure to MITC from both dazomet and metam should be considered after the use patterns for dazomet have been clarified.

As mentioned above (section III.J.7.), the volatile breakdown products of metam sodium, particularly MITC, MIC and H_2S, may exert additive or synergistic irritative effects, particularly on lung and eye tissues. An assessment of the likelihood of such effects is currently not possible. It is worth noting that dermally applied metam has been demonstrated to produce sensitization not only to itself, but to MITC (Mutter, 1987). Challenge application of MIC would also likely produce a sensitization reaction following an initial exposure to metam sodium. Finally, it is possible that dermal, eye or respiratory tract irritation caused by MITC could be exacerbated by co-exposure to the more potent irritant MIC. It is possible that both irritants would be present at toxicologically meaningful concentrations after metam sodium applications.

5. Endocrine effects

At relatively high doses, metam sodium, the precursor and parent compound of MITC, was shown to suppress the [norepinephrine-dependent LH] surge and decrease norepinephrine levels in rats, presumably by inhibiting the conversion of dopamine to norepinephrine (Goldman *et al.*, 1994). It was not known if MITC mediated this response. Nonetheless, a clear effect either of metam sodium or MITC on reproduction in a guideline study was not observed.

VI. TOLERANCE ASSESSMENT

A. BACKGROUND

A tolerance is the maximum amount of a pesticide residue that may remain in or on a food, or animal feed (US EPA, 1991). The U.S. EPA tolerance program was developed as an enforcement mechanism to identify illegal residue concentrations resulting from potential non-compliance with the product label requirements (e.g., improper application rates or methods, inadequate pre-harvest intervals, direct or indirect application to unapproved commodities). Tolerances are enforced by Food and Drug Administration (FDA), the US Department of Agriculture (USDA), and state enforcement agencies (e.g. Pesticide Enforcement Branch of DPR).

The data requirement established by U.S. EPA for tolerances include: (1) residue chemistry which includes measured residue levels from field studies, (2) environmental fate studies, (3) toxicology studies which evaluate the potential hazards to humans, domestic animals, and non-target organisms, (4) product performance such as efficacy, and (5) product chemistry which includes physico-chemical characteristics and analytical method (CFR, 1992). The field studies must reflect the proposed use with respect to the rate and mode of application, number and timing of applications, and formulations proposed (US EPA, 1992b).

Currently, the tolerances set by the US EPA are at levels necessary for the maximum application rate and frequency, and are not expected to produce deleterious health effects in humans from chronic dietary exposure (US EPA, 1991).

Assembly Bill 2161 (Bronzan and Jones, 1989) requires the DPR to "conduct an assessment of dietary risks associated with the consumption of produce and processed food treated with pesticides". In the situation where "any pesticide use represents a dietary risk that is deleterious to the health of humans, the DPR shall prohibit or take action to modify that use or modify the tolerance....." As part of the tolerance assessment, a theoretical dietary exposure for a specific commodity and specific population subgroups can be calculated from the product of the tolerance and the daily consumption rate.

B. METAM SODIUM

No federal food or commodity tolerances exist for metam sodium. Pesticides used prior to planting that are not still present at planting are classified as "non-food use" pesticides by the US EPA, and residue tolerances are not required. Metam sodium is used prior to planting of numerous food crops, but the MITC produced must dissipate prior to planting or the planted crop itself will be damaged. For these reasons a tolerance assessment for metam sodium was not undertaken.

VII. CONCLUSIONS

The critical acute LED_{01}, established using the benchmark dose approach, was 1 mg/kg. It was based on a dose dependent increase in early resorptions in Himalayan rabbits at a LOEL dose of 10 mg/kg. Based on the use scenarios examined, occupational dermal exposure was the sole projected exposure route. The mean 24-hour dermal absorbed dose for workers ranged from 1.5 to 2.9 μg/kg/day, resulting in acute margins of exposure (MOEs) ranging from 345 to 667.

A rabbit 21-day dermal toxicity study was used to assess acute irritation risk. Based on a finding of erythema, edema and dermatitis in a majority of animals at 62.5 mg/kg/day, a local irritation NOEL of 31.25 mg/kg/day was set (LOEL=62.5 mg/kg/day), equivalent to a local NOEL concentration of 360 $\mu g/cm^2$/day. Using estimated dermal exposure rates based on various work tasks, the MOE range was 679-1333. Because the NOEL and LOEL values were set using exposure times longer than a single day (but shorter than a conventional subchronic exposure regime), the MOE estimates were likely to overestimate acute dermal irritation risk.

Two rabbit oral developmental toxicity studies evidenced metam sodium-induced increases in early resorptions. In Himalayan rabbits, not only were the resorptions induced at a sub-maternally toxic dose of 10 mg/kg/day, but fetal malformations (meningocele + spina bifida) were documented at the slightly maternally toxic dose of 100 mg/kg/day. In New Zealand White rabbits, resorption incidence was overwhelming at a dose in which only slight maternal toxicity was observed. Malformations (meningocele, microphthalmia, anophthalmia, skull malformation, hydrocephaly and abnormal zygomatic arch) were also noted in the Wistar-derived Alpk:APfSD rat developmental toxicity study at the maternally toxic dose of 60 mg/kg/day. Because the acute risk evaluation was based on a developmental endpoint (increased resorptions in rabbits), an extra uncertainty factor to protect from acute developmentally toxic effects may not be necessary. On the other hand, such an uncertainty factor might be considered in the case of seasonal risk, which was evaluated using an endpoint (liver damage) established in adult dogs

The critical subchronic LED_{10} of 0.2 mg/kg/day was established using benchmark dose methodology from the dog 90-day oral gavage study. The LOEL of 1 mg/kg/day was based on an observation of bile duct proliferation / inflammatory cell infiltration and elevated plasma alanine aminotransferase activity in 1/4 females at that dose. These signs were considered progenitors of the severe hepatitis (hepatocyte degeneration and necrosis, inflammation, and increased pigmentation, collapse of hepatic cords with an influx of blood, and biliary proliferation) present in all animals at 10 mg/kg/day, and the similar, if less severe, hepatitis present at 5 mg/kg/day. This observation was directly supported by similar findings in a 1-year dog oral gavage study conducted by the same laboratory. Seasonal dermal absorbed doses (SADDs) for the various work categories ranged from 1.5 to 1.7 μg/kg/day. These resulted in a range of seasonal MOE values between 118 and 133.

The critical chronic NOEL of 0.1 mg/kg/day was established in a 1-year dog gavage study. The LOEL of 1 mg/kg/day was based on evidence for hepatotoxicity, including a slight increase in hepatocyte and macrophage/kupffer cell pigmentation, slight mononuclear cell infiltration, slight telangiectasis, elevated plasma alanine aminotransferase and alkaline phosphatase activities, and lowered plasma triglycerides. Also, an increased kaolin-cephalin time indicated some interference with blood clotting. Annual dermal absorbed doses (AADDs) for the various work

categories ranged from 0.8 to 0.9 μg/kg/day. These resulted in a range of annual MOE values between 111 and 125.

Metam exposure was associated with an increased incidence of angiosarcomas (also referred to as hemangiosarcomas) in male mice. These tumors were noted in several organ systems. The estimated oncogenic potency using the total incidence rate for male mice surviving one year of exposure ranged from 8.56×10^{-2} $(mg/kg/day)^{-1}$ (the maximum likelihood estimate or MLE) to 1.85×10^{-1} $(mg/kg/day)^{-1}$ (the 95% upper bound or 95% UB). These estimates, derived as they were from the GLOBAL86 approach, were based on assumptions of a multistage, non-threshold-dependent tumorigenic process. The risk of oncogenic effects was calculated as the product of the oncogenic potency and the highest lifetime average daily dose (LADD). The risk to workers for development of angiosarcoma was 3.42×10^{-5} - 4.28×10^{-5} when expressed as the maximum likelihood estimate and 7.40×10^{-5} - 9.25×10^{-5} when expressed as the 95% upper bound estimate.

Dietary exposure to metam sodium was not anticipated, consistent with the fact that no tolerance currently exists for metam sodium. Finally, the exposure of residents and bystanders was considered to be unlikely.

Finally, the major hazard associated with the application of metam sodium to soil may derive from the formation and release into the air of its degradation product MITC. MITC is highly irritating to eyes, lungs and skin, and may cause a chemically-induced asthma-like condition known as reactive airways dysfunction syndrome. A separate risk characterization document on MITC has been prepared (DPR, 2003a). Other degradation products of metam sodium include MIC, H_2S, CS_2, COS and methylamine. Toxic effects may result from exposure to any of these compounds, either alone or in concert with metam sodium and MITC.

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APPENDIX I. Benchmark dose run, early resorptions in rabbits (Hellwig, 1987)

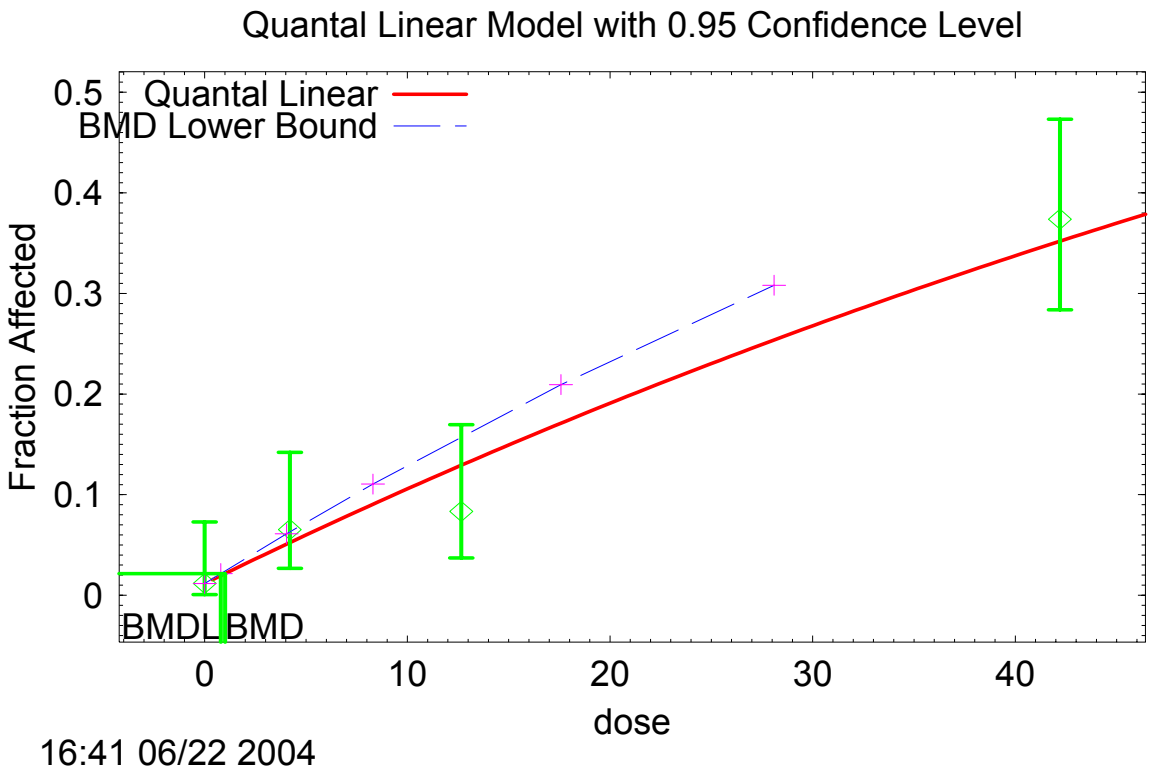
==========

Quantal Linear Model $Revision: 2.2 $ $Date: 2000/03/17 22:27:16 $
Input Data File: D:\BMDS\UNSAVED1.(d)
Gnuplot Plotting File: D:\BMDS\UNSAVED1.plt
Tue Jun 22 16:41:21 2004

==========

BMDS MODEL RUN

~~~~~~~~~~



The form of the probability function is:

P[response] = background + (1-background)*[1-EXP(-slope*dose)]

Dependent variable = #e.resorptions
Independent variable = dose
~~~~~~~~~~

Total number of observations = 4
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

Default Initial (and Specified) Parameter Values
Background = 0.0174419
Slope = 0.0107206
Power = 1 Specified

Asymptotic Correlation Matrix of Parameter Estimates

(*** The model parameter(s) -Power
have been estimated at a boundary point, or have been specified by the user,
and do not appear in the correlation matrix)

	Background	Slope
Background	1	-0.33
Slope	-0.33	1

Parameter Estimates

Variable	Estimate	Std. Err.
Background	0.0116995	0.0105233
Slope	0.00999625	0.00154616

Analysis of Deviance Table

Model	Log(likelihood)	Deviance	Test DF	P-value
Full model	-122.434			
Fitted model	-123.572	2.27619	2	0.3204
Reduced model	-153.46	62.0516	3	<.0001

AIC: 251.145

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Scaled Size	Residual
0.0000	0.0117	0.994	1	85	0.005592
4.2000	0.0523	4.815	6	92	0.5549
12.6600	0.1292	10.851	7	84	-1.253
42.2000	0.3518	37.646	40	107	0.4765

Chi-square = 2.10 DF = 2 P-value = 0.3491

Benchmark Dose Computation

Specified effect = 0.01

Risk Type = Extra risk

Confidence level = 0.95

BMD = 1.00541

BMDL = 0.791738

APPENDIX II. Benchmark dose run, liver damage in & dogs (Brammer, 1992)

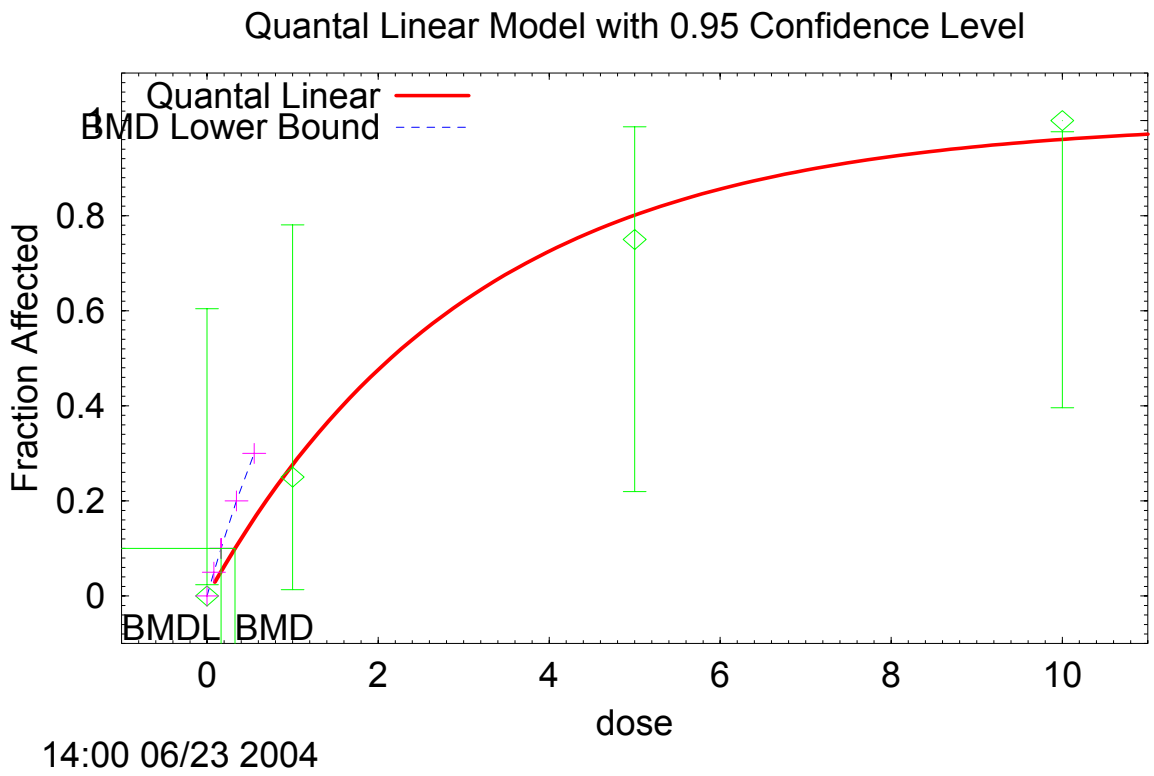
==========

Quantal Linear Model $Revision: 2.2 $ $Date: 2000/03/17 22:27:16 $
Input Data File: D:\BMDS\UNSAVED1.(d)
Gnuplot Plotting File: D:\BMDS\UNSAVED1.plt
Wed Jun 23 14:00:29 2004

==========

BMDS MODEL RUN

~~~~~~~~~~



The form of the probability function is:

P[response] = background + (1-background)*[1-EXP(-slope*dose)]

Dependent variable = #liverpath.
Independent variable = dose
~~~~~~~~~~

Total number of observations = 4
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

Default Initial (and Specified) Parameter Values
Background = 0.1
Slope = 0.219722
Power = 1 Specified

Asymptotic Correlation Matrix of Parameter Estimates

(*** The model parameter(s) -Background -Power
have been estimated at a boundary point, or have been specified by the user,
and do not appear in the correlation matrix)

	Slope
Slope	1

Parameter Estimates

Variable	Estimate	Std. Err.
Background	0	NA
Slope	0.322887	0.141498

NA - Indicates that this parameter has hit a bound
implied by some inequality constraint and thus
has no standard error.

Analysis of Deviance Table

Model	Log(likelihood)	Deviance	Test DF	P-value
Full model	-4.49868			
Fitted model	-4.69798	0.398593	3	0.9405
Reduced model	-11.0904	13.1833	3	0.004256

AIC: 11.396

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Scaled Size	Residual
0.0000	0.0000	0.000	0	4	0
1.0000	0.2759	1.104	1	4	-0.1161
5.0000	0.8010	3.204	3	4	-0.2555
10.0000	0.9604	3.842	4	4	0.4061

Chi-square = 0.24 DF = 3 P-value = 0.9702

Benchmark Dose Computation

Specified effect = 0.1

Risk Type = Extra risk

Confidence level = 0.95

BMD = 0.326308

BMDL = 0.16258

APPENDIX III. Oncogenic potency calculations (Horner, 1994)

The following printout provides the potency calculations for angiosarcoma incidence in male mice from the study of Horner (1994), using the human equivalent doses of metam sodium (see discussion of this calculation in section IV.A.6.). The Q_1 value (the maximum likelihood estimate or MLE) of 8.56×10^{-2} $(mg/kg/day)^{-1}$ and Q_1^* value (the 95% upper bound or 95% UB) of 1.85×10^{-1} $(mg/kg/day)^{-1}$ were derived by these calculations. They are indicated below in **bold** typeface.

```
        DATE: 11/02/2001                    TIME: 14:46:45

                              GLOBAL 86 (MAY 1986)

      BY RICHARD B. HOWE AND CYNTHIA VAN LANDINGHAM


CLEMENT ASSOCIATES
1201 GAINES STREET
RUSTON, LA   71270
(318) 255-4800



   Horner, 1994; metam sodium; mouse-2 yr; males


        POLYNOMIAL DEGREE SELECTED BY PROGRAM, (POLY-DEGREE=0)
             MONTE CARLO TEST USED IN SELECTION

                           #RESPONSES                  #RESPONSES
 GROUP       DOSE          OBSERVED/#ANIMALS           PREDICTED

   1        .000000              7/ 53                    8.57
   2        .274000             12/ 53                    9.60
   3       1.03700              12/ 55                   12.81
   4       4.16200              27/ 53                   27.00

        CHI-SQUARE GOODNESS OF FIT STATISTIC IS   1.1425

        P-VALUE FOR THE MONTE CARLO TEST IS    .3750000000

   FORM OF PROBABILITY FUNCTION:
        P(DOSE) = 1 - exp( -Q0 - Q1 * D - Q2 * D^2 - ... - Q 6 * D^ 6 )
```

MAXIMUM LIKELIHOOD ESTIMATES OF DOSE COEFFICIENTS

Q(0) = .176461320752
Q(1) = 8.559682480678E-02 (**the MLE**)
Q(2) = .000000000000
Q(3) = .000000000000
Q(4) = .000000000000
Q(5) = .000000000000
Q(6) = 3.452742162416E-05

MAXIMUM VALUE OF THE LOG-LIKELIHOOD IS -115.177228516

CALCULATIONS ARE BASED UPON EXTRA RISK
LINEARIZED MULTISTAGE CONFIDENCE LIMITS

RISK	MLE DOSE	LOWER BOUND ON DOSE	UPPER BOUND ON RISK	CONFIDENCE LIMIT SIZE
.10000	1.2295	.61836	.18900	90.0
		.56852	.20376	95.0
		.53092	.21651	97.5
		.49228	.23137	99.0
1.00000E-02	.11741	5.89851E-02	1.98073E-02	90.0
		5.42312E-02	2.15247E-02	95.0
		5.06449E-02	2.30313E-02	97.5
		4.69589E-02	2.48165E-02	99.0
1.00000E-03	1.16885E-02	5.87190E-03	1.98960E-03	90.0
		5.39866E-03	2.16382E-03	95.0
		5.04164E-03	2.31687E-03	97.5
		4.67471E-03	2.49850E-03	99.0
1.00000E-04	1.16833E-03	5.86926E-04	1.99049E-04	90.0
		5.39623E-04	2.16495E-04	95.0
		5.03937E-04	2.31824E-04	97.5
		4.67261E-04	2.50019E-04	99.0
1.00000E-05	1.16827E-04	5.86899E-05	1.99058E-05	90.0
		5.39598E-05	2.16507E-05	95.0
		5.03915E-05	2.31838E-05	97.5
		4.67239E-05	2.50036E-05	99.0
1.00000E-06	1.16827E-05	5.86897E-06	1.99058E-06	90.0
		5.39596E-06	2.16508E-06	95.0
		5.03912E-06	2.31839E-06	97.5
		4.67237E-06	2.50037E-06	99.0
1.00000E-07	1.16827E-06	5.86896E-07	1.99059E-07	90.0
		5.39596E-07	2.16508E-07	95.0
		5.03912E-07	2.31840E-07	97.5
		4.67237E-07	2.50037E-07	99.0

1.00000E-08	1.16827E-07	5.86897E-08	1.99059E-08	90.0
		5.39595E-08	2.16508E-08	95.0
		5.03913E-08	2.31840E-08	97.5
		4.67237E-08	2.50038E-08	99.0

END OF LINEARIZED MULTISTAGE CONFIDENCE LIMITS

****

GLOBAL 86 LOWER CONFIDENCE LIMITS ON DOSE FOR FIXED RISK
****

RISK	MLE DOSE	LOWER BOUND ON DOSE	CONFIDENCE LIMIT SIZE	COEFFICIENTS FOR CONFIDENCE LIMIT
5.00000E-02	.59922	.27678	95.0%	Q(0) = .13559
				Q(1) = .18532 (**the 95% UB**)
				Q(2) = .00000
				Q(3) = .00000
				Q(4) = .00000
				Q(5) = .00000
				Q(6) = .00000

NORMAL COMPLETION!