Appendix B

FUMIGANTS' HEALTH EFFECTS

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Telone™ (composed primarily of *cis* and *trans* isomers of 1,3-dichloropropene), metam sodium, and chloropicrin are key fumigant pesticides used in California. These fumigants are often applied in combination, or marketed as a fumigant product mixture. Because these pesticides are highly toxic, their use in California poses health risks to pesticide applicators as well as to people who live near sites where these fumigants may drift into neighboring properties. While United States Environmental Protection Agency (U.S. EPA) and/or California Department of Pesticide Regulation (CDPR) have conducted risk assessments for these three agents on a chemical by chemical approach, neither agency has addressed the impact of potential interactive effects among these fumigants on health risks in exposed populations.

To assess health risks from simultaneous or sequential exposures to 1,3-dichloropropene, metam sodium, and chloropicrin, we review identified health effects reported for each of these chemicals and indicate the basis for potential interactive effects. In addition, we identify critical data gaps that impede full evaluations of the cumulative health risks from exposure to these three fumigant pesticides. Chemical products formed by the reaction of metam sodium with chloropicrin or Telone isomers have not been fully identified or evaluated for their toxicologic or carcinogenic potential.

Toxicity (including immunotoxicity)
Chloropicrin. The primary effects observed in humans exposed short- or long-term to chloropicrin are sensory and respiratory irritation (DPR, 2010). Multiple episodes of community illnesses in California have been associated with the use of chloropicrin for agricultural pest control (Oriel et al., 2009). Because of its irritant and corrosive properties, chloropicrin was used as a warfare agent during World War I. In healthy young adult human volunteers exposed to chloropicrin, ocular and nasal irritation, increased nitric oxide production (indicative of inflammation), and decreased nasal inspiratory flow were observed (Cain, 2004). Inflammation and epithelial hyperplasia of the nasal cavity and lungs were observed in rats and mice exposed to 2.9 ppm chloropicrin by inhalation for 90 days (Chun and Kintigh, 1993). Respiratory effects of chloropicrin may pose greater health risks in persons with a pre-existing respiratory disease. In oral studies of chloropicrin in rats, hematological changes (including reduction in red blood cell counts, hemoglobin levels, and hematocrits) and histopathological changes in the forestomach (inflammation, necrosis, hyperplasia, and ulceration) were observed (Condie et al., 1994). Though exposure to chloropicrin caused a decrease in thymus weight and reduction in white blood cell counts (Condie et al., 1994), no studies were reported on the effect of chloropicrin on immune system function (DPR, 2010).

Metam. In soil after the first day of application, metam sodium is rapidly converted to the degradation product, methyl isothiocyanate (MITC). Subsequently, MITC is volatilized resulting in potential inhalation and dermal exposures to workers and the general public. MITC is the likely causal agent of illnesses associated with soil-incorporated applications of metam sodium in Arvin, California (O'Malley et al., 2005). Metam sodium and MITC are reactive chemicals that can be converted to other toxic chemicals, including methyl isocyanate (MIC), carbon disulfide (CS_2), and hydrogen sulfide (H_2S). Formulations containing metam are eye and dermal irritants (DPR, 2004). In oral studies, metam caused hepatocyte degeneration and necrosis and bile duct cell proliferation in dogs, stomach ulcerations and disorganization of the nasal cavity olfactory epithelium (at doses of 0.44 mg/ml of drinking water) in rats, and inflammation and bladder mucosal hyperplasia in mice exposed to 0.35 or 0.62 mg/ml (DPR, 2004). In inhalation studies, (10-30 ppm) metam caused erosive gastritis, pulmonary histiocytosis, and inflammation and epithelial hyperplasia of the nasal mucosal membrane in rats (Knapp, 1983).

Degradation products and metabolites of metam are also highly toxic. Ocular and respiratory irritation have been observed in animals and in humans exposed to MITC. The immunotoxicity of metam sodium in mice (a decrease in thymus weight and percentage of CD4+CD8+ thymocytes, an increase in spleen weight, an increase in the percentage of neutrophils in the blood, a decrease in the percentage of lymphocytes in the blood, and a decrease in natural killer cell activity in the spleen) is due to MITC and/or the parent compound and other decomposition products (Keil et al., 1996). Photolysis of MITC produces MIC, which causes tissue damage in multiple organ systems (respiratory, circulatory, gastrointestinal, and central nervous) by reacting with sulfhydryl, carboxyl, and hydroxyl groups (Bajaj et al., 1993). MIC also causes spontaneous abortions and resorptions, suppresses fetal skeletal growth, decreases female fertility, induces chromosomal aberrations, chromatid exchanges, and micronucleus formation, and suppresses cell-mediated immunity (Varma *et al.*, 1987; Saxena *et al.*, 1988). CS_2 is a developmental and reproductive toxin. Central nervous system, cardiovascular, gastrointestinal and immune toxicity have also been reported in humans exposed to CS_2 (DPR, 2004).

Telone (1,3-dichloropropene). In oral studies, Telone at doses of 15 mg/kg or higher caused a regenerative hypochromic microcytic anemia (depressed erythrocyte counts, hemoglobin concentrations, and hematocrit values) in beagle dogs (Stebbins et al., 1999), and doses of 25 mg/kg or higher produced increased incidences of basal cell hyperplasia of the forestomach in rats and mice, nephropathy in rats, and epithelial hyperplasia of the urinary bladder in mice (NTP, 1985). In inhalation studies, Telone produced increased incidences of degeneration and hyperplasia of the nasal epithelium in rats and mice exposed to 20 or 60 ppm, and epithelial hyperplasia of the urinary bladder and forestomach in mice exposed to 20 ppm or higher concentrations (Stott et al., 1988; Lomax et al., 1989). No studies have been reported on the effect of Telone on immune system function (US EPA, 2008; ATSDR, 1992).

Database deficiencies. No studies have been reported on the toxicity of fumigant mixtures containing chloropicrin, metam sodium, and 1,3-dichloropropene. Because these agents

target the respiratory tract and sensory organs with inhalation exposure and the gastrointestinal tract with oral exposure, interactive effects from simultaneous or sequential exposures to these three agents may occur. Mixture studies of these three fumigants in rodent models are needed, with inclusion of early life exposures to assess health risks in children. Though immunotoxicity studies are required by US EPA for conventional pesticide products (US EPA, 2007), this requirement has not been satisfied for the three fumigants included in this review. Because degradation products of metam are immunotoxic, there is a need for an evaluation of the potential immunotoxicity of this fumigant mixture and its individual components.

Carcinogenicity

Chloropicrin. A positive trend and increased incidences of lung adenomas and carcinomas were observed in female CD-1 mice exposed to chloropicrin vapors (0, 0.1, 0.5 or 1.0 ppm or 6 hours/day, 5 days/week) for 78 weeks (Burleigh-Flayer *et al.*, 1995). The increase in lung tumors in male mice was not significant. The unusually high incidence of lung tumors in control male and female mice as well as the short exposure duration reduced the power of this study to detect exposure related effects. Further, the short exposure duration (78 weeks versus conventional carcinogenicity studies of 104 weeks) precluded the ability of this study to detect chloropicrin-induced late developing tumors in the lung or in other organs. Increases in mammary gland fibroadenomas were observed in female CD rats exposed by inhalation to chloropicrin vapors (0, 0.1, 0.5 or 1.0 ppm or 6 hours/day, 5 days/week) for 107 weeks; no neoplastic effects were reported in exposed male rats (Burleigh-Flayer and Benson, 1995).

Technical-grade chloropicrin was administered by gavage in corn oil to Osborne-Mendel rats and B6C3F$_1$ mice for 78 weeks at time-weighted average doses of approximately 20-25 mg/kg/day in rats and 33 or 66 mg/kg in mice (NCI, 1978). Because of high incidences of early deaths in dosed animals, the study in rats was considered to be inadequate for evaluation of carcinogenicity. No conclusive evidence of carcinogenicity was reported in mice; however, the study had low statistical power because survival of the high dose groups decreased rapidly after the first year of the study and there was an inadequate number of control animals. In a 2-year gavage study of chloropicrin administered by gavage to Sprague-Dawley rats at doses of 0, 0.1, 1, and 10 mg/kg/day, an increased incidence of mammary gland fibroadenomas was observed in females (Slauter, 1995). The increase was statistically significant even though animal group size was only 30.

Metam sodium. In Wistar rats administered metam sodium in the drinking water for 104 weeks at doses of 0, 0.019, 0.056 or 0.19 mg/ml, a significant increase in the incidence of hemangiosarcomas was observed in the mid-dose group of males (Rattray, 1994). Because metam degrades in water, the doses of metam sodium received by exposed animals is much lower than values estimated from measurements of water consumption and the initial concentration of metam in water bottles. Hemangiosarcomas are cancers of cells that line the walls of blood vessels. In C57BL mice administered metam sodium in the drinking water for up to 2 years, the incidence of angiosarcomas (a malignant vascular tumor) was significantly increased (Horner, 1994). The doses of metam sodium in the mouse study were 0, 0.019, 0.074 or 0.23 mg/ml. A nonsignificant increase in angiosarcomas was also

observed in the high dose group of female mice. The increase in angiosarcomas in males was observed in several organs, including the liver, spleen, and subcutaneous tissues. In addition, high incidences of epithelial hyperplasia of the urinary bladder were observed in male and female mice (plus an extremely rare bladder tumor in a male mouse and in a female mouse at 0.23 mg/ml).

A 2-year drinking water study of MITC (at concentrations of 0, 2, 10, or 50 ppm), a degradation product of metam, provided some evidence for exposure related induction of mammary gland fibroadenomas and carcinomas in female rats (DPR, 2004). Cutaneous fibrosarcomas were also increased in mice exposed to MITC in drinking water for two years.

Telone (1,3-dichloropropene). Clary and Ritz (2003) examined the relationship between the use of pesticides in California communities and the incidence of pancreatic cancer mortality. Among long-term residents, pancreatic cancer mortality was elevated in areas with the highest use of four pesticides, including 1,3dichloropropene.

Telone is carcinogenic in laboratory animals by oral or inhalation routes of exposure (NTP, 1985; Lomax et al., 1989). In the NTP studies, Telone II was administered by gavage in corn oil (3 times per week for 104 weeks) at doses of 0, 25, or 50 mg/kg to F344 rats and at doses of 0, 50, or 100 mg/kg to B6C3F1 mice. In rats there were increased incidences and/or trends for forestomach squamous cell papillomas and carcinomas, neoplastic nodules of the liver, and adrenal gland pheochromocytomas; in mice there were increased incidences of forestomach squamous cell papillomas and carcinomas, urinary bladder transitional cell carcinomas, lung alveolar/bronchiolar adenomas and carcinomas, and liver (hepatocellular) adenomas and carcinomas. Though this formulation contained 1.0% epichlorohydrin, exposure to this stabilizer was not high enough to account for the multiple-organ tumor response of this fumigant. Telone administration also produced a high incidence of epithelial hyperplasia in the urinary bladder of male and female mice.

In 2-year feed studies in which F344 rats or B6C3F1 mice were exposed to Telone II (stabilized with 2% epoxidized soybean oil) in starch/sucrose microcapsules at doses of 0, 2.5, 12.5, or 25 mg/kg/day, the incidence of liver tumors was increased in males and females; there was no oncogenic effect reported in mice (Stebbins et al., 2000). The US EPA (2008) suggested that the discrepancy between the results of this study and that of the NTP (1985) might be due to instability of the loaded microcapsules during their use in the feed studies.

In the inhalation study (Lomax et al., 1989), F344 rats and B6C3F1 mice were exposed to 0, 5, 20, or 60 ppm of Telone II (stabilized with 2% epoxidized soybean oil) 6 hr/day, 5 days/week for 2 years. A significant increase in the incidence of lung tumors was observed in male mice. In addition, incidences of hyperplasia of the transitional epithelium lining the urinary bladder were increased in exposed mice. The US EPA (2008) has concluded that 1,3-dichloropropene is clearly a rodent carcinogen, and is "likely to be carcinogenic to humans".

Database deficiencies. The results of the cancer studies discussed above, indicate that a fumigant mixture containing chloropicrin, metam sodium, and Telone represents a multiple organ carcinogenic risk to exposed populations. Telone II produced tumors at more organ sites than chloropicrin or metam sodium. The cancer potency of chloropicrin was greater than that of the other two fumigants. A deficiency in the current cancer database for these agents is the lack of studies on cancer risk from early life (neonatal) exposures. In addition, chloropicrin has not been fully evaluated for its carcinogenic potential in mice. The inhalation studies of chloropicrin in mice had low statistical power because of the short exposure duration and the unusually high incidence of lung tumors in the controls groups; the gavage study of chloropicrin in mice had low statistical power because of reduced survival of the high dose groups and an inadequate number of control animals. Chloropicrin has not been adequately evaluated for its carcinogenic potential in rats by the oral route of exposure. Cancer potency estimates for metam sodium are likely underestimated because of the degradation of metam in drinking water, the route of exposure used in the carcinogenicity studies of this chemical. The lack of chronic/carcinogenicity inhalation studies on MITC is a serious deficiency in the database of these fumigants. MITC is the primary degradation product of metam sodium, and inhalation is a potential route of human exposure to this fumigant.

Although the mechanisms of tumor induction for these three agents have not been elucidated, a synergistic effect may arise when two or more agents affect the same organ (e.g., the mammary gland by chloropicrin and the metam degradation product, the lung by chloropicrin and Telone, or the urinary bladder by metam and Telone). Furthermore, by reacting with protein sulfhydryl groups or by reducing glutathione tissue levels each fumigant may affect the metabolic clearance or alter critical steps that affect the carcinogenic outcome of the other agents in the mixture. The combined effect of mutagenicity and hyperplasia in the same organ by two different agents in a mixture can result in a carcinogenic response greater than that of either agent alone.

Carcinogenicity: Sites of tumor induction by chloropicrin, metam sodium, or Telone (1,3-dichloropropene) in rats or mice [a] The increase in mammary gland tumors was observed in a study of MITC, a degradation product of metam.

Chloropicrin	Metam sodium	Telone II
Rats		
Mammary gland	Mammary gland (MITC)[a]	Forestomach
		Liver
		Adrenal gland
Mice		
Lung	Blood vessels - angiosarcoma	Urinary bladder
	Cutaneous fibrosarcoma (MITC)[a]	Forestomach
		Lung
		Liver
Cancer potency (mg/kg/day)$^{-1}$		
2.2 based on lung tumors in female mice (DPR, 2010)	0.19 based on angiosarcomas in male mice (DPR, 2004)	0.1 based on bladder tumors in mice (U.S. EPA, 2008)

Reproductive toxicity

Chloropicrin. In a two-generation study in which CRL:CD rats were exposed to chloropicrin vapors at 0, 0.5, 1.0, or 1.5 ppm, no treatment-related reproductive or developmental effects were reported (Schardein, 1994). In CRL:CD rats exposed to chloropicrin vapors at 0, 0.4, 1.0, or 2.0 ppm beginning 2 weeks prior to mating and continuing through gestation day 20, litter size in the 2 ppm group was reduced due to a reduction in the number of implantation sites (Denny, 1996).

Metam sodium. Similar to other dithiocarbamates, metam sodium blocks the conversion of dopamine to norepinephrine. At ip doses of 50-300 mg/kg, metam sodium produced a decrease in in the percentage of ovulating Long-Evans rats; this effect is likely due to suppression of the norepinephrine-dependent LH surge (Goldman et al., 1994). No significant reproductive effects were observed in a two-generation study of metam sodium administered to Sprague Dawley rats in drinking water at concentrations of 0, 0.01, 0.03 or 0.10 mg/ml (Milburn, 1993). Because of the instability of metam in water, doses received by treated rats could not be accurately estimated.

Telone. No lesions were observed in reproductive organs of rats or mice that were administered oral doses of Telone II (rats: 0, 25, or 50 mg/kg; mice: 0, 50, or 100 mg/kg) for 2 years (NTP, 1985). No exposure related reproductive effects were observed in a two-generation inhalation study of 1,3-dichloropropene (0, 10, 30, or 90 ppm) in F344 rats (Breslin et al., 1989).

Database deficiencies. No data are available on the potential reproductive toxicity of mixtures containing these three fumigants.

Developmental toxicity

Chloropicrin. Exposure of pregnant rats to chloropicrin (0.4-3.5 ppm) by inhalation induced skeletal variations in the developing fetus (Shardein, 1993). Fetal effects induced by inhalation exposure of pregnant rabbits to chloropicrin (0.4-2.0 ppm) included pre- and post-implantation losses, reduction in fetal body weights, and induction of visceral and skeletal variations (York, 1993).

Metam sodium. Oral administration of metam sodium by gavage to pregnant Wistar rats at doses ranging from 4 to 60 mg/kg/day caused increases in resorptions due to early post implantation loss, suppression of fetal weights, and skeletal developmental delays (Hellwig and Hildebrandt, 1987; Tinston, 1993). Gestational exposure of rabbits to metam sodium by oral administration at doses of 4 to 60 mg/kg/day induced early resorptions, fetal malformations (Hellwig, 1987), and skeletal variants (Hodge, 1993).

Telone (1,3-Dichloropropene. No developmental effects were observed in F344 rats or New Zealand white rabbits after gestational exposure of pregnant dams to 1,3-dichloropropene by inhalation at concentrations up to 300 ppm (Hanley et al., 1988).

Database deficiencies. Gestational exposures to chloropicrin or metam sodium are toxic to the developing fetus. No data are available on the developmental toxicity of mixtures of these three fumigants. Because mixed exposures might alter dose response relationships of the individual agents, a developmental toxicity study of this fumigant mixture is needed.

Neurotoxicity

Chloropicrin. No studies were reported on the neurotoxicity of chloropicrin.

Metam sodium. Metam sodium was administered as a single gavage dose (0, 22, 324 or 647 mg/kg) in water to Sprague-Dawley rats (Lamb, 1993). 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. Ambulatory and total motor activities were decreased at all doses on day 0. CS_2, a degradation product of metam, has long been known to be a human neurotoxicant (Spencer and Schaumburg, 1985). Psychosis and peripheral neuropathy have been observed in CS_2 exposed workers and neurological dysfunction has been demonstrated in experimental animals. In rats, CS_2 exposure causes cross-linking in neurofilament proteins prior to the onset of central and peripheral nervous system lesions suggesting that cross-linking contributes to the development of the neurofilamentous axonal swellings characteristic of carbon disulfide neurotoxicity (Sills et al., 2005).

Telone (1,3-Dichloropropene). Several studies of 1,3-dichloropropene (Jones and Collier, 1986; Jeffrey et al., 1987; Mizell et al., 1988), reported clinical signs in rats and rabbits that are indicative of possible neurological effects; these signs included lethargy, salivation,

lacrimation, and labored respiration. Ataxia of the hind limbs and loss of the righting reflex were also observed in pregnant rabbits exposed to 300 ppm of Telone II during gestation days 6-18 (Kloes et al., 1983). No clinical signs of neurotoxicity were observed in rats, guinea pigs, rabbits, or dogs after inhalation exposure to 3 ppm Telone II a for 6 months (Torkelson and Oyen, 1977) or in rats or mice exposed to 150 ppm Telone II for 13 weeks. Sensitive tests for neurological effects, however, were not included in these studies (US EPA, 2008; ATSDR, 1992).

<u>Database deficiencies</u>. The US EPA requires 90-day neurotoxicity studies for conventional pesticide products (US EPA, 2007) and developmental neurotoxicity studies if the pesticide causes neurological effects in adult animals or humans. The three fumigants included in this review have not been adequately tested for potential neurotoxicity. Thus, the EPA requirement has not been satisfied for these three pesticides. Because CS_2, a degradation product of metam is a neurotoxicant in humans, there is a clear need for developmental neurotoxicity studies of metam sodium as well as of the fumigant mixture.

Mechanistic considerations
Metabolism
Chloropicrin is a strong electrophilic agent that reacts with glutathione or protein thiol groups including those of hemoglobin. The initial reaction of chloropicrin with glutathione forms GS-CCl2NO2; this metabolite can react further with glutathione to form dichloro- and monochloro metabolites or react with cysteine. Thiophosgene, a highly toxic and reactive compound, may also be an intermediate of chloropicrin biotransformation.

Metam degrades in soil as well as in the stomach of exposed laboratory animals or humans to methyl isothiocyanate (MITC) and carbon disulfide (CS2). Subsequent metabolism of MITC involves conjugation with glutathione forming mercapturic acid conjugates that are excreted in the urine. Other degradation products formed in soil after application of metam include methyl isocyanate (MIC) and hydrogen sulfide (H2S). Thus, use of metam as a fumigant can results in exposure of farm workers and neighboring residents to multiple reactive chemicals.

The major metabolic pathway for 1,3-dichloropropene involves conjugation with glutathione (GSH) via glutathione S-transferase (GST); the resulting mercapturic acid metabolite is excreted in the urine. A second metabolic pathway involves cytochrome P450-catalyzed epoxidation to 1,3-dichloropropene oxide, which can be detoxified by GST-catalyzed conjugation with glutathione. However, this epoxide intermediate can also undergo an internal rearrangement to 2,3-dichloropropanal (2,3-DCPA), which spontaneously eliminates HCl and forms the mutagenic carcinogen 2-chloroacrolein (Eder et al. 2006).

Genotoxicity
Chloropicrin is a mutagenic and clastogenic chemical; the parent compound or its metabolites induced mutations in Salmonella, chromosomal aberrations in CHO cells, sister

chromatid exchanges in human lymphocytes, and DNA strand breaks in TK6 cells. These results are consistent with the electrophilic nature of this fumigant. Though conjugation with glutathione detoxifies chloropicrin, it also results in activation of this compound to a mutagenic intermediate (Schneider et al., 1999).

Metam was negative in gene mutation studies, but positive for clastogenicity in *in vivo* and *in vitro* studies. In Chinese hamsters and in cultured human lymphocytes (in the absence or presence of metabolic activation), metam produced increases in the frequency of chromosome aberrations (Gelbke and Engelhardt, 1987).

1,3-Dichloropropene is mutagenic in the Ames Salmonella test with or without metabolic activation. 1,3-Dichloropropene is also a clastogen; it induced DNA damage in multiple organs of mice (Sasaki et al., 1998) and increased the frequencies of micronuclei in the bone marrow of mice and sister chromatid exchanges in cultured human lymphocytes, Chinese hamster V79 cells, and Chinese hamster ovary cells. DNA fragmentation induced by 1,3-dichloropropene has been observed in Chinese hamster V79 cells and in the liver and stomach of Sprague-Dawley rats (US EPA, 2008).

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