2. RELEVANCE TO PUBLIC HEALTH

2.1 BACKGROUND AND ENVIRONMENTAL EXPOSURES TO DICHLOROPROPENES IN THE UNITED STATES

1,3-Dichloropropene is a mixture of volatile cis and trans isomers and is primarily used as a nematocide to fumigate soil before planting. Commercial formulations of 1,3-dichloropropene contain stabilizers to inhibit degradation of the compound (Table 3-1). Older formulations contained chroropicrin or epichlorohydrin, whereas currently, the less toxic epoxidized soybean oil is used as a stabilizer. 1,3-Dichloropropene is released to the atmosphere in fugitive or accidental emissions from industrial sources (e.g., petroleum refineries, sewage treatment facilities, and electricity-generating power facilities) and also during its use as a fumigant. Accidental discharges into surface waters from industrial sources or leaching into groundwater from hazardous waste sites or agricultural uses also occur.

A significant proportion of the 1,3-dichloropropene released into soil or surface waters is expected to volatize into the atmosphere where it is degraded by photooxidation with hydroxyl radicals or reaction with ozone. The half-life of 1,3-dichloropropene in ambient air is expected to range between 7 and 50 hours, depending on the concentrations of cis- and trans- isomers and reactive hydroxyl radicals. 1,3-Dichloropropene may also undergo biodegradation or hydrolysis in natural waters and in soil. Experimental data indicate increased rates of hydrolysis with higher temperature, the hydrolysis half-life in deionized water being about 10 days at 20 °C.

1,3-Dichloropropene is not a widely-occurring atmospheric pollutant. Mean concentrations in positive air samples from urban and rural regions have ranged between 0.088 and 0.33 ppb in one report, but concentrations as high as 35.2 ppb have been measured in high-use agricultural regions. 1,3-Dichloropropene has been detected in 40% of 12,673 water samples, but only 6% of the samples contained 1,3-dichloropropene above the quantifiable limit. The range of quantifiable concentrations in water was 0.002–25 ppb, with a mean of 0.5 ppb. 1,3-Dichloropropene was detected in only 0.1% of 70,631 public water system samples collected in the United States between 1993 and 1997. 1,3-Dichloropropene has not been detected in table-ready foods.

Possible routes of human exposure to 1,3-dichloropropene include inhalation of contaminated air, ingestion of contaminated drinking water, and dermal contact with pesticides containing 1,3-dichloro-

propene. Due to the volatility of 1,3-dichloropropene, inhalation exposure, particularly in regions where the pesticide is used commercially to fumigate soil, appears to be the major route of exposure for the general population. Children residing in regions of pesticide use are likely to be exposed to 1,3-dichloropropene by the same routes that affect adults. Occupational exposure or accidental exposure resulting from a spill is likely to occur through inhalation and dermal contact.

Information on the release, environmental fate and partitioning, concentrations in environmental media, and potential for human exposure is very limited for 1,1-, 1,2-, 2,3-, and 3,3-dichloropropene. Based on their physical and chemical properties, these substances are expected to behave similarly to 1,3-dichloropropene when they are released into the environment. However, hydrolysis of 1,1- and 1,2-dichloropropene is expected to be much slower than hydrolysis of the other dichloropropene isomers due to the inhibiting effect of the vinylic chlorine atoms.

1,1-, 1,2-, 2,3-, and 3,3-Dichloropropene are not commonly found at measurable concentrations in air, surface water, drinking water, groundwater, soil or food. 1,1-Dichloropropene has been detected in 64% of 5,348 water samples collected in the United States, but only 1% of the samples contained 1,1-dichloropropene above the quantifiable limit. The range of quantifiable concentrations in water was 0.001–5 ppb, with a mean of 0.4 ppb. 1,1-Dichloropropene was detected in only 0.01% of 97,698 public water system samples collected in the United States between 1993 and 1997.

The potential for human exposure to 1,1-, 1,2-, and 3,3-dichloropropene is expected to be low because these chemicals are not produced or used in high amounts. Higher amounts of 2,3-dichloropropene may be released from facilities where this substance is produced or used. Individuals who work or live near these facilities may be exposed to 2,3-dichloropropene; however, exposure of the general population to this chemical is not expected to be important.

2.2 SUMMARY OF HEALTH EFFECTS

As volatile halogenated alkenes, dichloropropenes are reactive and cause irritant effects at the point of contact. Their small molecular size and lipid solubility facilitate rapid absorption and distribution throughout the body. Metabolism, primarily in the liver, but also in other tissues, results either in detoxification and elimination, or bioactivation to more a toxic or mutagenic metabolite. Since there is some evidence that the isomers behave differently with respect to metabolic pathways, and the available toxicity data are not necessarily comparable, health effects are discussed for each isomer individually. No

studies have compared the relative toxicity of dichloropropenes in mammals, but limited data suggest that inhaled 2,3-dichloropropene is more damaging to the respiratory tract than 1,3-dichloropropene.

1,3-Dichloropropene. 1,3-Dichloropropene is readily absorbed by all routes of exposure. The compound does not accumulate in the body and is readily excreted in the urine following conjugation to glutathione and metabolic conversion to mercapturic acid derivatives. Consistent with its reactive properties, some of the major effects of exposure occur at the point of contact: nasal epithelium following inhalation exposure, stomach following oral exposure, and skin following dermal exposure. The urinary bladder in mice exposed by inhalation and erythrocytes in dogs exposed orally are also targets of 1,3-dichloropropene.

The available information on the toxicity of 1,3-dichloropropene in humans is largely limited to case reports lacking exposure quantification and occupational studies. Case reports of high level (unquantified) exposures confirm portal-of-entry effects in the respiratory system after inhalation exposure, gastrointestinal effects following accidental ingestion, and contact dermatis leading to sensitization reactions following dermal exposure. Additional effects noted following high-level exposure included cardiovascular effects (tachycardia and hypovolemia) prior to multiorgan failure and death. No hepatic or renal urinary biomarkers were elevated following repeated occupational exposures to cis-1,3-dichloropropene at relatively low levels (0.6 ppm). An association was reported between occupational exposure to 0.06 to 2.1 ppm 1,3-dichloropropene and urinary excretion of biomarkers indicative of renal damage, but the levels were subclinical and could be considered nonadverse.

Experimental studies of 1,3-dichloropropene in animals have been conducted using various commercial formulations, most of which contained chloropicrin (Telone C-17 contains 19–21% chloropicrin) or epichlorohydrin (Telone II®a contains 1% epichlorohydrin) as stabilizers, or significant amounts of 1,2-dichloropropane (DD contains 25–29% 1,2-dichloropropane). More recent studies have tested Telone II®b, which was relatively pure (≥90% 1,3-dichloropropene) and contained 2% epoxidized soybean oil (ESO) as a stabilizer. Comparison of results of the new dietary studies with results of earlier oral gavage studies, suggest that either bolus dosing and/or the presence of epichlorohydrin may have been responsible for some effects in observed in earlier studies.

Results from repeated-dose animal studies indicate that respiratory effects (hyperplasia of the nasal respiratory epithelium in rats and mice) and urinary effects (hyperplasia of the urinary bladder in mice) following chronic inhalation exposure at ≥20 ppm 6 hours/day, 5 days/week, and gastrointestinal

(hyperplasia of the forestomach in rats) and hematological effects (microcytic anemia in dogs) following long-term oral exposure to Telone II®b at ~12–15 mg/kg/day or to Telone II®a at 11 mg/kg/day (25 mg/kg/day, 3 days/week) are the most sensitive effects induced by exposure to 1,3-dichloropropene. Renal effects or urinary bladder hyperplasia were not observed in animals treated in the diet with Telone II®b, but hyperplasia of the urinary bladder was observed in animals treated by gavage with Telone II®a at 21 mg/kg/day (50 mg/kg/day, 3 days/week) for 2 years. These effects are discussed in greater detail below.

Other effects of exposure to 1,3-dichloropropene involve the skin and eyes, liver, and nervous system. Liquid 1,3-dichloropropene is irritating to the eyes of rabbits, a 0.1 mL application causing erythema, lacrimation, or palpbral closure. Liquid application to skin of rats, rabbits, or guinea pigs resulted in erythema/edema from a single 4-hour application at 0.5 mL or repeated applications at 0.1 mL, and necrosis resulted from a single 24-hour application at 200 mg/kg. Contact sensitization was noted in guinea pigs following repeated dermal application at 0.2 mL. Neurological effects included ataxia and loss of the righting reflex in pregnant rabbits exposed by inhalation to 300 ppm for 13 days, but this exposure level was fatal to six of seven does. No direct developmental effects were noted in animals exposed at <120 ppm by inhalation for 10 days or <90 ppm for 3 months, but reduced litter sizes were observed in pregnant rats exposed to 150 ppm, a level causing maternal toxicity (reductions in feed intake, water intake, and body weight). No adverse effect on reproduction was noted in rats exposed by inhalation at <90 ppm for two generations.

Extremely limited data (a few case reports and one epidemiological study) are available for carcinogenic effects of 1,3-dichloropropenes in humans. In chronic animal bioassays using Telone II®b increases in benign tumors (adenomas) were reported in the mouse lung following inhalation exposure and rat liver following oral dietary exposure. A chronic oral gavage bioassay using Telone II®a resulted in more severe carcinogenic effects, but it is not known whether that was a consequence of the presence of epichlorohydrin in Telone II®a or bolus dosing. Carcinogenicity of 1,3-dichloropropene is discussed in greater detail below.

The health effects of 1,3-dichloropropene exposure are discussed in detail in Chapter 3.

The following section discuss the most significant effects of exposure to 1,3-dichloropropene, which involve the gastrointestinal, hematological, respiratory, and urinary systems and cancer.

Respiratory Effects. Due to the reactivity of 1,3-dichloropropene, irritant effects on the respiratory tract can be expected from inhalation exposure in humans and animals. In humans accidentally exposed to presumably high concentrations of 1,3-dichloropropene, respiratory effects included mucous membrane irritation, chest pain, and cough. In one case, repeated exposure for 30 days to pesticide spray from a leaky hose (presumably a combined vapor and droplet exposure) resulted in hyperemia and superficial ulcerations of the nasal mucosa and inflammation of the pharynx. No data are available for effects in humans repeatedly exposed at lower levels.

Respiratory effects in rats exposed to 1,3-dichloropropene vapor at high concentrations in acute lethality studies included atelectasis after 1 hour at 206 ppm for TC-17 (21.1% chloropicrin), and in 4-hour exposures, lung edema at 595 ppm, congestion at 676 ppm for Telone II®a, and hemorrhage at 1,035 ppm. Nasal turbinates were not examined for histopathology in these acute-duration studies. In intermediate-duration studies using sublethal exposures to Telone II®b or Telone II®a vapor, hyperplasia/hypertrophy of the nasal respiratory epithelium was observed in rats at ≥90 ppm or mice at ≥60 ppm and degeneration of the nasal olfactory epithelium was observed in rats at ≥90 ppm. Exposure for 2 years to Telone II®b vapor resulted in hyperplasia/hypertrophy of the nasal respiratory epithelium in mice at ≥20 ppm and rats at 60 ppm and degeneration of the nasal olfactory epithelium in rats and mice at 60 ppm.

Lung effects (congestion, hemorrhage) that were observed in rats during acute lethality studies by the oral or dermal routes may have arisen from inhalation of 1,3-dichloropropene vapor during administration of high doses of the test material.

Gastrointestinal Effects. Irritant effects on the gastrointestinal system have been observed in humans and animals following oral exposure to 1,3-dichloropropene. Gastrointestinal effects observed in one case of fatal ingestion included initial acute gastroenteritis and abdominal pain on deep palpation, subsequent bloody diarrhea, hemorrhagic exudate of the stomach at autopsy, histopathological evidence of congestion of gastric mucosal vessels, autolysis, and mucosal erosions of the stomach. Nausea and vomiting were observed following accidental exposure to a high concentration of 1,3-dichloropropene vapor, but it is possible that these could be a nonspecific effect of neurotoxicity. No data are available for effects in humans repeatedly exposed at lower doses.

Gastrointestinal effects observed in rats following exposure to 1,3-dichloropropene as single oral gavage doses of various pesticide formulations include hyperkeratosis of the forestomach at ≥75 mg/kg and hemorrhaging of the small intestine at ≥110 mg/kg. In repeated-dose oral studies at sublethal exposures,

basal cell hyperplasia of the nonglandular stomach developed in rats ingesting 15 mg/kg/day 1,3-dichloropropene as microencapsulated Telone II®b in the diet for 13 weeks or 12.5 mg/kg/day for 2 years, or in rats and mice exposed by oral gavage to respective TWA doses of 11 or 21 mg/kg (25 or 50 mg/kg/day, 3 days/week) Telone II®a for 2 years. Mice exposed to 60 ppm Telone II®b for 2 years by inhalation developed hyperplasia and hyperkeratosis of the forestomach.

Hematological Effects. Limited human data suggest that hematological malignancies (histiocytic lymphoma, acute myelomonocytic leukemia) may be associated with accidental inhalation exposure to 1,3-dichloropropene vapor or aerosol at relatively high levels. In one of these cases, pallor and a reduced hemoglobin count accompanied the leukemia. The only significant hematological effects reported in animals were reductions in hemoglobin and hematocrit counts consistent with microcytic anemia in dogs exposed to 15 mg/kg/day microencapsulated Telone II®b in the diet for 13 weeks or 1 year. The NOAELs for hematological effects in dogs were 5 mg/kg/day in the 13-week study and 2.5 mg/kg/day in the 1-year study.

Urinary System Effects. Urinary bladder hyperplasia was a consistent finding in mice exposed to ≥60 ppm 1,3-dichloropropene Telone II®b by inhalation for 6 months or ≥20 ppm for 2 years. Oral gavage administration of epichlorohydrin-containing Telone II®a at doses of 21 mg/kg/day (50 mg/kg, 3 days/week) to mice also increased the incidence of urinary bladder hyperplasia, but this lesion was not observed in mice exposed to Telone II®b in the diet at doses up to 50 mg/kg/day. The degree to which oral bolus dosing, which could overwhelm the major detoxification pathway, and/or epichlorohydrin, which is a mutagen, contributed to the different results of the two chronic mouse studies is not known.

Cancer. Evidence for the carcinogenicity of 1,3-dichloropropene in humans is inadequate. Clinical reports describing the development of neoplasms in three men following inhalation (and possibly dermal) exposure suggest a possible association between exposure and cancer in humans, but are inadequate to establish the association. One source of uncertainty is the lack of information about the specific pesticide formulation and possible carcinogenic additives to which the individuals may have been exposed (see discussion of animal studies below). Two of the men were exposed to 1,3-dichloropropene during the cleanup of a tank truck spill. Six years later, both men simultaneously developed and succumbed to histiocytic lymphoma that was refractory to treatment. The same report described a farmer who developed acute myelomonocytic leukemia after being exposed to 1,3-dichloropropene while applying the chemical to his fields. This leukemia was also refractory to treatment, and the man died approximately 1 year later. A case-control study provided suggestive evidence that populations living for 20 years in

regions with high usage of 1,3-dichloropropene pesticide may be at increased risk for death from pancreatic cancer.

Results from several cancer bioassays provide adequate evidence of carcinogenicity in animals. In chronic bioassays using Telone II®b, the only observed increased tumor incidences were for bronchioalveolar adenomas in mice exposed by inhalation to 60 ppm and for hepatocellular adenomas and carcinomas (combined) in rats exposed in the diet at 25 mg/kg/day. In a chronic oral gavage bioassay using Telone II®a, increased incidences were observed for squamous cell papillomas and carcinomas in the forestomach of rats exposed at 11 mg/kg/day (25 mg/kg/day, 3 days/week) and for squamous cell papillomas and carcinomas in the forestomach, bronchioalveolar adenomas, and transitional cell carcinomas of the urinary bladder in mice exposed at 21 mg/kg/day (50 mg/kg/day, 3 days/week). There is some uncertainty as to whether bolus dosing or the presence of epichlorohydrin in Telone II®a contributed to increased incidences of forestomach squamous cell papillomas and carcinomas in rats and mice or urinary bladder transitional cell carcinomas in mice, thyroid adenomas and carcinomas, or adrenal gland pheochromocytomas. Aspiration of Telone II®a may have contributed to the increased incidence of bronchioalveolar adenomas in mice treated by oral gavage for 2 years. Positive development of sarcomas in mice subcutaneously injected with 1,3-dichloropropene and positive results for chromosomal aberration and deoxyribonucleic acid (DNA) fragmentation in short-term genotoxicity assays (see Section 3.3) lend support to the carcinogenic potential of 1,3-dichloropropene. It should be noted that positive results in mutagenicity assays have been attributed to impurities in the test material (see Section 3.3). The Department of Health and Human Services has determined that 1,3-dichloropropene may reasonably be anticipated to be a carcinogen based on sufficient evidence of carcinogencity in experimental animals. The International Agency for Research on Cancer has determined that 1,3-dichloropropene is possibly carcinogenic to humans. In 2000, a study classified 1,3-dichloropropene as a probable human carcinogen.

2,3-Dichloropropene. The toxicokinetic properties of 2,3-dichloropropene appear to be similar to those of 1,3-dichloropropene. It is readily absorbed in animals exposed by the inhalation and oral routes, and once absorbed, is distributed rapidly throughout the body. It is a weakly alkylating compound that can react directly with biological macromolecules. The major metabolic pathway for 2,3-dichloropropene is a detoxifying conjugation to glutathione, leading to the elimination of mercapturic acid metabolites in the urine. Two minor pathways result in the formation of the mutagens 1,2-dichloroacetone or 2-chloroacrolein. Saturation of the detoxifying conjugation pathways, which might occur under high exposure conditions, could result in the production of proportionally more mutagens via the alternate pathways.

Reliable data in rats and mice suggest that the most sensitive effect of repeated acute-duration inhalation exposure to 2,3-dichloropropene at 5 ppm is damage to the respiratory tract. Limited data in 13-week studies appear to confirm the sensitivity of the respiratory tract to inhalation exposure (see below). In these 13-week studies, hepatic and renal organ weight increases and altered serum chemistry or urinalysis parameters occur in rats exposed at 40–80 ppm, but not at 15 ppm. Acute inhalation exposure at high levels (>500 ppm) may result in signs indicative of suppression of the central system (unconsciousness) and/or death. The acute-duration study by Zempel et al. (1987) is the only study that allows reliable identification of NOAELs and LOAELs for all systemic end points. No data are available for developmental or carcinogenic effects of exposure to 2,3-dichloropropene.

Repeated exposure to 5–75 ppm for 6 hours/day for 9 out of 11 days resulted in significant concentration-related increases in the incidence and severity of lesions of the respiratory tract in rats and mice. Nearly all rats and mice were affected at the 5 ppm level, with hyperplasia of the nasal respiratory epithelium in both species and diffuse degeneration of the bronchial/bronchiolar epithelium in mice. At ≥25 ppm, all rats and mice exhibited hyperplasia of the nasal olfactory epithelium and mice had hyperplasia of the laryngeal epithelium. Rats and mice differed in that nasal tissues were the only respiratory tract target in rats, whereas the lungs were also affected in mice. A NOAEL for respiratory effects was not identified in this study.

Intermediate-duration studies provide supportive evidence for respiratory tract effects, but the data do not adequately identify reliable NOAELs or LOAELs. Rats exposed to 15 ppm 6 hours/day, 5 days/week for 13 weeks did not have alterations in lung histology, but did show an increase in red nasal discharge, a sign of nasal irritation. Since the nasal turbinates, the most sensitive target in rats exposed acutely, were not examined for histopathology, a LOAEL for respiratory effects cannot be assigned reliably. An unfinished bioassay, terminated when a drop in U.S. production volumes indicated the compound was of low priority, showed increases in absolute and relative lung weights in female mice exposed at ≥5 ppm and male mice exposed at ≥10 ppm for 6 hours/day, 5 days/week for 13 weeks. Although no histopathology data are available for this bioassay, the fact that the lung was the only organ to show weight increases at 5 ppm appears to confirm that the respiratory tract is a specific target of inhaled 2,3-dichloropropene.

1,2-Dichloropropene. No information is available about the toxicokinetic properties of 1,2-dichloro-propene. Toxicity information is limited to a brief summary of results of acute-duration studies in

animals exposed at high or unreported exposure levels. Rats exposed for a few minutes to a saturated vapor atmosphere estimated at 63,764 ppm experienced unconsciousness, with liver, lung, and kidney injury occurring in those that died. Kidney and liver injury were also observed in rats exposed by oral gavage at 2,000 mg/kg. Irritant effects in eyes and skin were observed following topical application of 1,2-dichloropropene at an unspecified dose. The scant information on this isomer suggests that it shares irritant properties with 1,3-dichloropropene and 2,3-dichloropropene.

1,1-Dichloropropene. No *in vivo* toxicity or toxicokinetic data were located for 1,1-dichoropropene. *In vitro* metabolism results of one study indicate that this isomer differs from 1,3-dichloropropene and 2,3-dichloropropene in that conjugation to glutathione results in bioactivation to a mutagenic metabolite, rather than the production of innocuous mercapturic acid metabolites. This finding indicates that estimates of toxicity based on 1,3- or 2,3-dichloropropene may not necessarily apply to 1,1-dichloropropene.

3,3-Dichloropropene. No toxicity or toxicokinetic data were located for 3,3-dichloropropene.

2.3 MINIMAL RISK LEVELS (MRLs)

Estimates of exposure levels posing minimal risk to humans (MRLs) have been made for 1,3- and 2,3-dichloropropene. An MRL is defined as an estimate of daily human exposure to a substance that is likely to be without an appreciable risk of adverse effects (noncarcinogenic) over a specified duration of exposure. MRLs are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration within a given route of exposure. MRLs are based on noncancerous health effects only and do not consider carcinogenic effects. MRLs can be derived for acute, intermediate, and chronic duration exposures for inhalation and oral routes. Appropriate methodology does not exist to develop MRLs for dermal exposure.

Although methods have been established to derive these levels (Barnes and Dourson 1988; EPA 1990), uncertainties are associated with these techniques. Furthermore, ATSDR acknowledges additional uncertainties inherent in the application of the procedures to derive less than lifetime MRLs. As an example, acute inhalation MRLs may not be protective for health effects that are delayed in development or are acquired following repeated acute insults, such as hypersensitivity reactions, asthma, or chronic bronchitis. As these kinds of health effects data become available and methods to assess levels of significant human exposure improve, these MRLs will be revised.

The following discussion of inhalation and oral MRLs and the supporting databases is organized by isomer. Intermediate- and chronic-duration inhalation and oral MRLs have been derived for 1,3-dichloropropene and an acute-duration inhalation MRL has been derived for 2,3-dichloropropene (Table 2-1). Additional details of MRL derivations are presented in Appendix A.

1,3-Dichloropropene.

Inhalation MRLs.

The data for acute toxic effects in human exposed by inhalation to 1,3-dichloropropene came from accidental exposures for which the concentrations in air were not measured. Acute effects in humans involved the respiratory system (mucous membrane irritation, chest pain, cough, and breathing difficulties) (Flessel et al. 1978; Markovitz and Crosby 1984). Most of the acute-duration inhalation data in animals comes from 1–4-hour acute lethality rat studies that did not employ a control group. Eye irritation was reported at 206 ppm for Telone C-17® (21.1% chloropicrin) (Streeter and Lomax 1988) and 775–1,146 ppm for Telone II®a (Streeter et al. 1987; Yakel and Kociba 1977). Respiratory effects included atelectasis at 206 ppm for Telone C-17® (21.1% chloropicrin) (Streeter and Lomax 1988), lung edema at 595 ppm and congestion at 676 ppm for Telone II®a (Cracknell et al. 1987) and hemorrhage at 1,035 ppm (Streeter et al. 1987). Adrenal congestion was noted at 676 ppm for Telone II®a (Cracknell et al. 1987). The 1-hour LC_{50} for Telone C-17 (21.1% chloropicrin) was 253 ppm (Streeter and Lomax 1988), and 4-hour LC_{50} values of 676 and 904 ppm were reported for Telone II®a (Cracknell et al. 1987; Streeter et al. 1987). In repeated-dose developmental studies, no maternal effects were noted in rat dams exposed to Telone II®a at 300 ppm, but litter sizes were decreased (Kloes et al. 1983). Conversely, 300 ppm had no effect on rabbit development, but resulted in ataxia and death in six of seven does (Kloes et al. 1983). The no-observed-adverse-effect level (NOAEL) of 150 ppm for maternal effects in rats or developmental effects in rabbits exposed to Telone II®a (Kloes et al. 1983) cannot be used as the basis for an acute-duration inhalation MRL, because the lack of histopathological examination of the nasal turbinates, the likely target organ, in dams casts doubt on the reliability of 150 ppm as a NOAEL for systemic effects, although it appears to be a reliable NOAEL for developmental effects.

- An MRL of 0.008 ppm has been derived for intermediate-duration inhalation exposure (15–354 days) to 1,3-dichloropropene.

Table 2-1. Summary of Minimum Risk Levels (MRLs) Derived for Dichloropropenes

Compound	Route	Duration	MRL value	Effect	References
1,3-Dichloropropene	Inhalation	Acute	Insufficient data		
	Inhalation	Intermediate	0.008 ppm	Hypertrophy/hyperplasia of nasal respiratory epithelium	Lomax et al. 1989
	Inhalation	Chronic	0.007 ppm	Hypertrophy/hyperplasia of nasal respiratory epithelium	Lomax et al. 1989
	Oral	Acute	Insufficient data		
	Oral	Intermediate	0.04 mg/kg/day	Basal cell hyperplasia of nonglandular stomach	Haut et al. 1996
	Oral	Chronic	0.03 mg/kg/day	Basal cell hyperplasia of nonglandular stomach	Stebbins et al. 2000
2,3-Dichloropropene	Inhalation	Acute	0.002 ppm	Hyperplasia of nasal respiratory epithelium	Zempel et al. 1987
	Inhalation	Intermediate	Insufficient data		
	Inhalation	Chronic	No data		
	Oral	Acute	Insufficient data		
	Oral	Intermediate	No data		
	Oral	Chronic	No data		
1,2-Dichloropropene	Inhalation	Acute	Insufficient data		
	Inhalation	Intermediate	No data		
	Inhalation	Chronic	No data		
	Oral	Acute	Insufficient data		
	Oral	Intermediate	No data		
	Oral	Chronic	No data		
1,1-Dichloropropene	Both	All	No data		
3,3-Dichloropropene	Both	All	No data		

In the only intermediate-duration inhalation study in humans, no evidence of renal or hepatic damage was detected in clinical chemistry analyses of blood and serum in pesticide applicators using cis-1,3-dichloropropene for an average of 521 (±230) minutes/day at a geometric mean concentration (8-hour TWA) of 2.7 mg/m^3 (range 0.1–9.5 mg/m^3) (0.594 [0.22–2.09] ppm) over a 117-day period compared to unexposed controls (Verplanke et al. 2000). No other end points were examined in this study. Respiratory effects (mucous membrane irritation, chest pain, cough, and breathing difficulties) have been observed following accidental acute exposure to high concentrations (Flessel et al. 1978; Markovitz and Crosby 1984).

The available data from the inhalation exposure animal studies indicate that hypertrophy/hyperplasia of the nasal respiratory epithelium and hyperplasia of the urinary bladder in mice are the most sensitive effects associated with intermediate-duration exposure to 1,3-dichloropropene. Increased incidences of hypertrophy/hyperplasia of the nasal respiratory epithelium occurred in male and female B6C3F1 mice exposed to 60 ppm Telone II®b (92.1% 1,3-dichloropropene with 2% ESO) vapor 6 hours/day, 5 days/week for 6 months (Lomax et al. 1989). Female mice in this study exposed at 60 ppm also had a marginally increased incidence of hyperplasia of the urinary bladder. Fischer 344 rats exposed in this study under the same protocol did not exhibit increased incidences of histologically detected lesions in any organs or tissues after 6 months of exposure (Lomax et al. 1989). Slight reductions in body weights were observed in rats and mice exposed at 60 ppm, but the differences were not biologically significant (<10% lower than controls) at 6 months (Lomax et al. 1989). Nasal lesions were also observed in rats exposed to ≥90 ppm Telone II®b 6 hours/day, 5–7 days/week for 3 months in a reproductive toxicity assay (Breslin et al. 1989). Nasal hyperplasia in rats and mice and urinary bladder hyperplasia in mice occurred in groups exposed to ≥90 ppm Telone II®a (90.9% 1,3-dichloropropene with 1.2% epichlorohydrin) 6 hours/day, 5 days/week for 13 weeks (Stott et al. 1988). One 13-week study by Coate (1979a) reported nasal lesions in rats exposed 6 hours/day, 5 days/week to Telone II®a at 30 ppm, but since the purity of the test material was not reported, the significance of the result is uncertain.

Although increased incidences of hypertrophy/hyperplasia of the nasal respiratory epithelium and hyperplasia of the urinary bladder were both sensitive effects in mice at a LOAEL of 60 ppm, the urinary bladder lesions were observed only in females and at a marginal increase (p=0.043; Fisher Exact Test) over controls. Since the nasal lesions were observed in both sexes at a higher incidence, they are selected as the critical effect for development of the intermediate-duration MRL for 1,3-dichloropropene. The 6-month study with male and female mice exposed to Telone II®b by Lomax et al. (1989) is selected as the principal study because the study was adequately designed and reported and the test material was a relatively high concentration of 1,3-dichloropropene without the confounding presence of

epichlorohydrin. Lomax et al. (1989) exposed groups (10/sex/concentration) of B6C3F1 mice to vapors of 1,3-dichloropropene 6 hours/day, 5 days/week for 6 months at concentrations of 0, 5, 20, or 60 ppm. These were designed as interim satellite groups for a 2-year study. The test material was 92.1% pure (49.5% cis; 42.6% trans) and contained 2.0% ESO as a stabilizer, 0.7% 1,2-dichloropropane, and 5.2% mixtures of hexanes and hexadienes. Mice were examined for clinical signs of toxicity, body weight changes, and terminal hematology and clinical chemistry parameters. Terminal examinations of all animals included gross necropsy, measurement of selected organ weights (brain, heart, kidney, liver, and testes) and histopathological examination of an extensive array of organs and tissues. Exposure to 1,3-dichloropropene for 6 months had no adverse effect on survival, clinical signs, or hematological or clinical chemistry parameters in mice. Significant histological lesions included hypertrophy/hyperplasia of the nasal respiratory epithelium in male and female mice and hyperplasia of the urinary bladder in female mice at 60 ppm. NOAELs of 20 ppm and LOAELs of 60 ppm are identified for hypertrophy/hyperplasia of the nasal respiratory epithelium in male and female mice and hyperplasia of the urinary bladder in female mice. As the increased incidence of hyperplasia of the urinary bladder in female mice was only marginally significant, hypertrophy/hyperplasia of the nasal respiratory epithelium in male and female mice is chosen as the critical effect for MRL derivation.

Potential points of departure for deriving the intermediate-duration MRL were derived using benchmark concentration analysis, the details of which are provided in Appendix A. Before the analysis, exposure concentrations were adjusted for 92.1% purity and discontinuous exposure. For increased incidence of hypertrophy/hyperplasia of nasal epithelium in male and female mice, the potential point of departure was the benchmark concentration limit (BMCL) associated with 10% extra risk, the default benchmark response (BMR) recommended by EPA (2000a). Models for dichotomous data were fit to the incidence data in the key study. The best fitting model for nasal lesions in male and female mice was the gamma model, which generated a BMC_{10} of 2.8 ppm and a $BMCL_{10}$ of 1.3 ppm for males and BMC_{10} of 6.3 ppm and a $BMCL_{10}$ of 3.0 ppm for females.

The respective $BMCL_{10}$ values for nasal lesions in male and female mice were converted to human equivalent concentrations ($[BMCL_{10}]_{HEC}$) by multiplying by the extrathoracic regional gas dose ratio (B6C3F1 mouse/human) for males (0.1779) and females (0.1368) according to EPA (1994) guidance for inhalation dosimetry for a category 1 gas, as a default for a category 2 gas. The resulting $[BMCL_{10}]_{HEC}$ values were 0.23 ppm for male mice and 0.41 ppm for female mice. The lower $[BMCL_{10}]_{HEC}$ value of 0.23 ppm derived from male mice was used as the point of departure for deriving the MRL. A total uncertainty factor of 30 (3 for conversion from animals to humans using dosimetric adjustment and 10 for

human variability) was applied to the male $[BMCL_{10}]_{HEC}$ to calculate an intermediate-duration inhalation MRL of 0.008 ppm for 1,3-dichloropropene.

- An MRL of 0.007 ppm has been derived for chronic-duration inhalation exposure (≥1 year) to 1,3-dichloropropene.

No data are available for effects in humans following chronic-duration inhalation exposure to 1,3-dichloropropene. Fischer F344 rats and B6C3F1 mice were evaluated for chronic-duration inhalation exposure to Telone II®b (92.1% 1,3-dichloropropene stabilized with 2% epoxidized soybean oil, ESO) for 1 or 2 years (Lomax et al. 1989).

The available data from chronic-duration studies indicate that lesions of the nasal epithelium and urinary bladder in mice are the most sensitive effects associated with chronic-duration inhalation exposure to 1,3-dichloropropene. After 1 year, incidences of hypertrophy/hyperplasia of the nasal respiratory epithelium were increased in male mice exposed at ≥20 ppm and female mice at 60 ppm. In addition, the incidences of hyperplasia and inflammation of the urinary bladder were increased in female mice exposed to 60 ppm for 1 year. After 2 years of exposure, increased incidences of hypertrophy/hyperplasia of the nasal respiratory epithelium occurred in female mice at ≥20 ppm and males exposed at 60 ppm, and increased degeneration of the nasal olfactory epithelium occurred in male and female mice exposed at 60 ppm. In rats, nasal lesions (decreased thickness of the olfactory epithelium in males and females, erosion of the olfactory epithelium in males, and submucosal fibrosis in males) were only detected at 60 ppm after 2 years of exposure and at lower incidences than in exposed mice. The incidences of epithelial hyperplasia of the urinary bladder were increased in female mice exposed for 2 years at ≥20 ppm and male mice exposed at 60 ppm; the incidence of inflammation of the bladder epithelium was increased in female mice exposed for 2 years at ≥20 ppm, but not in males. No histopathology of the urinary bladder was observed in rats.

Based on these findings, hypertrophy/hyperplasia of the nasal respiratory epithelium and hyperplasia of the urinary bladder epithelium in mice exposed for 2 years were selected as co-critical effects for the development of the chronic-duration inhalation MRL for 1,3-dichloropropene. The mouse study by Lomax et al. (1989) is the principal study because the test material in this adequately designed and reported study had a purity of 92.1% and did not contain epichlorohydrin or chloropicrin as a possibly confounding toxic additive. Lomax et al. (1989) exposed groups (50/sex/concentration) of B6C3F1 mice to vapors of 1,3-dichloropropene (Telone II®b) 6 hours/day, 5 days/week for 2 years at concentrations of 0, 5, 20, or 60 ppm. Additional satellite groups (10/sex/concentration) were established for interim

sacrifices at 6 and 12 months (results for the 6-month sacrifice are given under the description for the intermediate-duration inhalation MRL). The test material was 92.1% pure (49.5% cis; 42.6% trans) and contained 2.0% ESO as a stabilizer, 0.7% 1,2-dichloropropane, and 5.2% mixtures of hexanes and hexadienes. Mice were examined for clinical signs of toxicity, body weight changes, and terminal hematology and clinical chemistry parameters. Terminal examinations of all animals included gross necropsy, measurement of selected organ weights (brain, heart, kidney, liver, and testes), and histopathological examination of an extensive array of organs and tissues. Exposure to Telone II®b vapor for 2 years had no significant adverse effect on survival, body weight, the incidence of clinical signs, hematology, or clinical chemistry parameters in mice. In the 1-year satellite group, incidences of hypertrophy/hyperplasia of the nasal respiratory epithelium were significantly higher than controls in males at ≥20 ppm and in females at 60 ppm; females at 60 ppm also had increased incidences of epithelial hyperplasia and inflammation of the urinary bladder. After 2 years of exposure, incidences nasal and urinary bladder hyperplasia were elevated in males at 60 ppm and in females at ≥20 ppm. Increases in inflammation of the urinary bladder were not observed in males and were relatively small in females. Degeneration of the nasal olfactory epithelium was not statistically elevated in either sex at concentrations <60 ppm. NOAELs of 5 ppm and LOAELs of 20 ppm were identified for hypertrophy/hyperplasia of the nasal respiratory epithelium and epithelial hyperplasia of the urinary bladder in females.

Potential points of departure for deriving the chronic-duration inhalation MRL were calculated using benchmark concentration analysis, the details of which are provided in Appendix A. Before the analysis, exposure concentrations in ppm were adjusted for 92.1% purity and discontinuous exposure. Models for dichotomous data were fit to the incidence data in the key study. None of the models in the EPA benchmark dose (BMD) software provided an adequate fit to the data for hypertrophy/hyperplasia of the nasal respiratory epithelium in male mice, so no BMCL could be calculated. For increased incidences of hypertrophy/hyperplasia of nasal respiratory epithelium in female mice or hypertrophy of urinary bladder epithelium in male and female mice, the potential points of departure were the 95% lower confidence limits on estimated concentrations (BMCLs) associated with 10% extra risk compared to control values. This benchmark response (BMR) level is the default recommended by EPA (2000a). The log-probit model gave the best fit to data for nasal lesions in female mice, resulting in a BMC_{10} of 1.56 ppm and a $BMCL_{10}$ of 1.0 ppm. The logistic model gave the best fit to data for urinary bladder lesions in male mice, resulting in a BMC_{10} of 2.18 ppm and a $BMCL_{10}$ of 1.78 ppm. The quantal-quadratic model gave the best fit to data for urinary bladder lesions in female mice, resulting in a BMC_{10} of 1.52 ppm and a $BMCL_{10}$ of 1.30 ppm.

Mouse BMCL values were converted to human equivalent concentrations (HECs) using EPA (1994) dosimetry methods. The $BMCL_{10}$ of 1.0 ppm for hypertrophy/hyperplasia of nasal respiratory epithelium in female mice was multiplied by the extrathoracic regional dose ratio (mouse/human) of 0.1999, resulting in a HEC of 0.20 ppm. As no mouse or human blood:air partition coefficients were available for 1,3-dichloropropene, the $BMCL_{10}$ values for urinary bladder lesions in male and female mice were multiplied by the default blood:gas partition coefficient ratio of 1 (for calculating the HECs for the extrarespiratory effects), resulting in $[BMCL_{10}]_{HEC}$ values for male and female mice of 1.78 and 1.30 ppm, respectively. The $[BMCL_{10}]_{HEC}$ value of 0.20 ppm for hypertrophy/hyperplasia of nasal respiratory epithelium in female mice was selected as the more sensitive point of departure. A total uncertainty factor of 30 (3 for extrapolation from animal to human using dosimetric adjustment and 10 for human variability) was applied to the $[BMCL_{10}]_{HEC}$ of 0.20 ppm, resulting in a chronic-duration inhalation MRL of 0.007 ppm for 1,3-dichloropropene.

Oral MRLs. No acute-duration oral MRL was derived for 1,3-dichloropropene. The only information on toxic effects in humans following oral exposure to 1,3-dichloropropene comes from a case report of effects following accidental ingestion of an undetermined fatal dose (Hernandez et al. 1994). The gastrointestinal effects observed in this case (initially acute gastroenteritis and abdominal pain on deep palpation, subsequent bloody diarrhea, hemorrhagic exudate of the stomach at autopsy, histopathological evidence of congestion of gastric mucosal vessels, autolysis, and mucosal erosions of the stomach) support the significance of portal-of-entry effects of ingested 1,3-dichloropropene. Other effects included tachycardia, tachypnea, hypovolemia, adult respiratory distress syndrome, and multiorgan failure prior to death. The database for oral toxicity of 1,3-dichloropropene in animals consists entirely of several acute lethality studies in rats conducted by oral gavage under protocols that do not include a control group. Suppression of the central nervous system following exposure to Telone II®a was indicated by clinical signs such as reduced respiratory rate at ≥75 mg/kg, lethargy at ≥110 mg/kg, and ataxia at ≥170 mg/kg (Jones and Collier 1986a); rats exposed to the cis isomer exhibited ataxia at ≥75 mg/kg (Jones 1988a). Hemorrhaging was observed in the lung, gastrointestinal tract, and liver in rats dosed with ≥110 mg/kg of 97.2% cis-1,3-dichloropropene (Jones 1988a); hemorrhaging was observed in the gastrointestinal tract and lungs of rats dosed at ≥170 or 250 mg/kg, respectively, with 97.2% mixed isomers (Jones and Collier 1986a). Hyperkeratosis of the stomach was observed in rats exposed to ≥75 mg/kg 1,3-dichloropropene (97.2% mixed isomers) (Jones and Collier 1986a) or 100 mg/kg 79.1% 1,3-dichloropropene with 19% chloropicrin (Mizell et al. 1988a). LD_{50} values in rats were 121 mg/kg for the cis isomer (97.2%), 304 mg/kg for 79.1% 1,3-dichloropropene with 19% chloropicrin (Mizell et al. 1988a), and 150–

470 mg/kg for mixed isomer formulations with purities between 92 and 97.54% (Jeffrey et al. 1987a; Jones and Collier 1986a; Lichy and Olson 1975).

- An MRL of 0.04 mg/kg/day has been derived for intermediate-duration oral exposure (15–364 days) to 1,3-dichloropropene.

No data are available for effects in humans following intermediate-duration oral exposure to 1,3-dichloropropene. Intermediate-duration oral exposure studies with rats, mice, and dogs exposed to different commercial formulations of 1,3-dichloropropene isomers have been conducted by oral gavage or dietary exposure.

As shown in the following overview, available data from the oral exposure animal studies indicate that lesions in the nonglandular stomach mucosa in rats and microcytic anemia in dogs are the most sensitive effects associated with intermediate-duration oral exposure to 1,3-dichloropropene. Increased incidences of basal cell hyperplasia of the nonglandular stomach occurred in male Fischer 344 rats exposed to doses ≥15 mg/kg/day Telone II®b microencapsulated in feed for 13 weeks; female rats displayed hyperkeratosis of the nonglandular stomach epithelium at doses of 100 mg/kg/day in this study (Haut et al. 1996). B6C3F1 mice exposed to Telone II®b via the same protocol for 13 weeks did not display any adverse effects on histologic or hematologic end points (Haut et al. 1996). Microcytic anemia (decreased hematocrit, hemoglobin concentration, and corpuscular volume) occurred in beagle dogs exposed to doses ≥15 mg/kg/day Telone II®b encapsulated in feed for 13 weeks (Stebbins et al. 1999). Reductions in terminal body weight were observed in rats, mice, and dogs exposed to Telone II®b in feed for 13 weeks, but reduced food intake associated with decreased palatability may have contributed to these effects (Haut et al. 1996; Stebbins et al. 1999). In an earlier 13-week study with Telone®, a commercial formulation of lesser 1,3-dichloropropene purity than Telone II®b, increased liver or kidney weights were observed in rats at doses as low as 10 and 30 mg/kg/day, respectively, but the lack of renal or kidney adverse noncancer effects in the intermediate- or chronic-duration studies with Telone II®b suggests that these organs are not consistently observed noncancer toxicity targets of 1,3-dichloropropene.

The study describing hematological effects in dogs was not selected for MRL derivation due to the small group sizes (4/sex/group) and the lack of histopathological examination. Therefore, the other sensitive effect, basal cell hyperplasia in the nonglandular stomach of male rats, was selected the critical effect for development of the intermediate-duration MRL for 1,3-dichloropropene. The 13-week study with male rats (Haut et al. 1996) exposed to microencapsulated Telone II®b was selected as the principal study, because the test material in this adequately designed and reported study was the most purified 1,3-di-

chloropropene formulation tested and did not contain potentially confounding toxic materials such as epichlorohydrin or chloropicrin. The test material, Telone II®b, was 95.8% pure 1,3-dichloropropene (50.7% cis; 45.1% trans) and was microencapsulated in a starch/sucrose (80:20) microsphere matrix before addition to the diets for 13 weeks. In the Haut et al. (1996) study, groups of male and female Fischer 344 rats (10/sex/group) received 1,3-dichloropropene at reported doses of 0, 5, 15, 50, or 100 mg/kg/day. Animals were evaluated for clinical signs of toxicity, body weight changes, feed intake, and hematological, clinical chemistry, and urinalysis parameters. All rats received a gross necropsy examination and were evaluated for histopathology in a full array of tissues and organs. Ingestion of Telone II®b had no effect on survival in rats. Significant histopathological lesions in this study included basal cell hyperplasia of the nonglandular stomach in male rats exposed at ≥15 mg/kg/day and hyperkeratosis of the nonglandular stomach epithelium at 100 mg/kg/day. In this study, a NOAEL of 5 mg/kg/day and a LOAEL of 15 mg/kg/day were identified for cell hyperplasia in the nonglandular stomach of male rats (Haut et al. 1996).

Potential points of departure for deriving the intermediate-duration MRL were derived using benchmark dose analysis, the details of which are described in Appendix A. For increased incidence of basal hyperplasia in nonglandular stomach mucosa of rats, the potential point of departure was the BMDL associated with 10% extra risk; this BMR was selected as the default following EPA (2000a) guidance. Models for dichotomous data in the BMD software were fit to the incidence data in the key study. The best fitting model for forestomach lesions in male rats was the multistage model, which generated a BMD_{10} of 9.0 mg/kg/day and a $BMDL_{10}$ of 3.6 mg/kg/day. The $BMDL_{10}$ of 3.6 mg/kg/day for basal cell hyperplasia in male rats was selected as the point of departure for deriving the intermediate-duration oral MRL.

An intermediate-duration oral MRL of 0.04 mg/kg/day was derived by dividing the $BMDL_{10}$ of 3.6 mg/kg/day by an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

- An MRL of 0.03 mg/kg/day has been derived for chronic-duration oral exposure (≥1 year) to 1,3-dichloropropene.

No data are available for effects in humans following chronic-duration oral exposure to 1,3-dichloropropene. Chronic-duration oral exposure studies with rats, mice, and dogs exposed to different commercial formulations of 1,3-dichloropropene isomers have been conducted by oral gavage or dietary exposure.

As shown in the following overview, the available data indicate that lesions in the nonglandular stomach mucosa in rats and microcytic anemia in dogs are the most sensitive effects associated with chronic-duration oral exposure to 1,3-dichloropropene. Basal cell hyperplasia of the nonglandular stomach mucosa was observed in male and female Fischer 344 rats exposed to doses as low as 12.5 mg/kg/day Telone II®b (but not 2.5 mg/kg/day) encapsulated in feed for 1 or 2 years (Stebbins et al. 2000), and in male and female F344 rats and female B6C3F1 mice exposed to gavage doses of 25 mg/kg/day Telone II®a (89% dichloropropene isomers plus 1% epichlorohydrin) 3 times/week for up to 2 years (NTP 1985). Increased incidences of this lesion did not occur in male or female B6C3F1 mice exposed to 2.5, 25, or 50 mg/kg/day Telone II®b encapsulated in feed for 1 or 2 years (Stebbins et al. 2000) or in male or female beagle dogs exposed to 0.5, 2.5, or 15 mg/kg/day Telone II®b encapsulated in feed for 1 year (Stebbins et al. 1999). However, male and female beagle dogs exposed to 15 mg/kg/day, but not 2.5 mg/kg/day, Telone II®b encapsulated in feed for 1 year showed decreased values for mean hematocrit, hemoglobin concentration, and corpuscular volume, compared with control values, which are indicative of microcytic anemia. Exposure-related reductions in terminal body weight were observed in rats, mice, and dogs exposed to Telone II®b in feed for 1 or 2 years, but reduced food intake associated with decreased palatability may have contributed to these effects (Stebbins et al. 1999, 2000).

Adverse noncancer effects on the liver or kidney are not as clearly associated with chronic-duration oral exposure to 1,3-dichloropropene as forestomach basal cell hyperplasia in rats or microcytic anemia in dogs. Exposure-related kidney effects include increased incidence of hydronephrosis in female, but not male, B6C3F1 mice exposed to gavage doses of 100 mg/kg/day Telone II®a, but not 50 mg/kg/day, for up to 2 years (NTP 1985) and increased incidence of nephropathy in female, but not male, Fischer 344 rats exposed to 25 or 50 mg/kg/day Telone II®a for up to 2 years (NTP 1985). However, no exposure-related kidney effects were observed in Fischer 344 rats, B6C3F1 mice, or beagle dogs exposed to Telone II®b encapsulated in feed for 1 or 2 years at doses as high as 25 mg/kg/day for rats, 50 mg/kg/day for mice, and 15 mg/kg/day for dogs (Stebbins et al. 1999, 2000). Observed noncancer effects in the liver include decreased size of hepatocytes in male, but not female, B6C3F1 mice exposed to 50 mg/kg/day, but not 25 mg/kg/day, Telone II®b encapsulated in feed for 1 year, but not in mice exposed for 2 years (Stebbins et al. 2000) and increased incidence of slight or very slight eosinophilic foci of altered liver cells in male and female Fischer 344 rats exposed to 2.5, 12.5, or 25 mg/kg/day Telone II®b encapsulated in feed for 2 years. The toxicological significance of these apparent liver effects is equivocal given the inconsistency of the findings in the mouse study and the common spontaneous occurrence of liver foci (eosinophilic or basophilic) in aged Fischer 344 rats.

Based on the findings from the chronic-duration oral exposure animal studies, basal cell hyperplasia in the nonglandular stomach of male rats and decreased hemoglobin concentration and corpuscular volume in male or female dogs were selected as co-critical effects for development of the chronic-duration MRL for 1,3-dichloropropene. The 2-year rat study (Stebbins et al. 2000) and 1-year dog study (Stebbins et al. 1999) involving exposure to microencapsulated Telone II®b were selected as the principal studies, because the test material in these adequately designed and reported studies was the most purified 1,3-dichloropropene formulation tested (95.8% pure 1,3-dichloropropene—50.7% cis; 45.1% trans—with 2% ESO as a stabilizer) and did not contain potentially confounding toxic materials such as epichlorohydrin or chloropicrin. In the study by Stebbins et al. (2000), the main group of male and female Fischer 344 rats (50/sex/group) received doses of 0, 2.5, 12.5, or 25 mg/kg/day for 2 years and a satellite group of 10/sex/group received the same treatment for 12 months. In the Stebbins et al. (1999) study, groups of beagle dogs (4/sex/dose) had intakes of 0, 0.5, 2.5, or 15 mg/kg/day for 12 months. Both studies evaluated animals for clinical signs of toxicity, body weight changes, feed intake, and hematological, clinical chemistry, and urinalysis parameters. All animals received a gross necropsy examination, with evaluation of a full array of tissues and organs for histopathological examination. Ingestion of Telone II®b had no effect on survival in rats or dogs. The primary histological lesion in rats was basal cell hyperplasia of the nonglandular stomach mucosa observed in males and females exposed to ≥12.5 mg/kg/day. In these studies, a NOAEL of 2.5 mg/kg/day and a LOAEL of 12.5 mg/kg/day were identified for cell hyperplasia in the nonglandular stomach of male rats (Stebbins et al. 2000) and a NOAEL of 2.5 mg/kg/day and a LOAEL of 15 mg/kg/day were identified for decreased hemoglobin concentration and corpuscular volume in male or female dogs (Stebbins et al. 1999).

Potential points of departure for deriving the chronic-duration MRL were derived with benchmark dose analysis, the details of which are described in Appendix A. For decreased hemoglobin concentration, which was as an index of 1,3-dichloropropene-induced microcytic anemia in dogs, potential points of departure were 95% lower confidence limits on estimated doses (i.e., BMDLs) associated with a value lower than 10^{th} percentile values for the distribution of hemoglobin concentrations in a sample of normal beagle dogs. The linear model for continuous data was modeled to the hemoglobin data in dogs, resulting in a $BMD_{10th\%ile}$ of 8.35 mg/kg/day and a $BMDL_{10th\%ile}$ of 6.05 mg/kg/day for male dogs and a $BMD_{10th\%ile}$ of 10.98 mg/kg/day and a $BMDL_{10th\%ile}$ of 8.83 mg/kg/day for female dogs. For increased incidence of basal hyperplasia in nonglandular stomach mucosa of rats, the potential point of departure was the BMDL associated with 10% extra risk. This BMR is the default recommended by EPA (2000a). Models for dichotomous data were applied to the incidence data in rats. The log-probit model gave the best fit to the

data for male rats, resulting in a BMD_{10} of 5.34 mg/kg/day and a $BMDL_{10}$ of 4.26 mg/kg/day. The log-logistic model gave the best fit to the data for female rats, resulting in a BMD_{10} of 5.42 mg/kg/day and a $BMDL_{10}$ of 3.51 mg/kg/day. The lowest BMDL is the $BMDL_{10}$ of 3.51 mg/kg/day for increased incidence of nonglandular stomach basal cell hyperplasia in rats. A chronic-duration oral MRL based on the $BMDL_{10}$ of 3.51 mg/kg/day for basal cell hyperplasia in rats divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability) would be 0.04 mg/kg/day. This value is in agreement with EPA's chronic oral RfD of 0.03 mg/kg/day, which was based on a point of departure of 3.4 mg/kg/day (see Chapter 8 and Appendix A). Therefore, 0.03 mg/kg/day was selected as the chronic oral MRL for 1,3-dichloropropene.

2,3-Dichloropropene

Inhalation MRLs

- An MRL of 0.002 ppm has been derived for acute-duration inhalation exposure (<15 days) to 2,3-dichloropropene.

No information was located regarding the acute inhalation toxicity of 2,3-dichloropropene in humans. The available data from inhalation studies in animals indicate that hyperplasia of the nasal respiratory epithelium in male and female rats and mice and degeneration of the bronchial/bronchiolar epithelium in male and female mice are the most sensitive effects associated with acute-duration exposure to 2,3-dichloropropene. Increased concentration-related incidences and severity (see Table 2-2, the same as Table A-1 in Appendix A) of hyperplasia of the nasal respiratory epithelium occurred in male and female Fischer 344 rats and B6C3F1 mice, and slight diffuse degeneration of bronchial/bronchial epithelium occurred in male and female B6C3F1 mice exposed to 5 ppm 2,3-dichloropropene (>99% purity) vapor 6 hours/day for nine exposures over 11 days (Zempel et al. 1987). Male and female rats and mice in this study exposed at ≥25 ppm had slight-to-moderate hyperplasia of the nasal olfactory epithelium, and male and female mice exposed at ≥25 ppm had very slight-to-slight hyperplasia of the laryngeal epithelium. Reductions (12–25%) in terminal body weights in male and female mice exposed at 25 or 75 ppm appeared to be related to reduced feed intake.

Respiratory lesions were also observed in single-exposure acute lethality studies described in cursory and/or incomplete reports. In a 6-hour exposure study, crusted noses were observed in rats exposed at 250 ppm and bloody noses at 500 ppm, whereas in a 1-hour study, gasping and shallow respiration were observed during exposure at ≥693 ppm and labored respiration was observed after exposure at 1,963 ppm

Table 2-2. Incidence of Significant Lesions in Fischer 344 Rats and B6C3F1 Mice Exposed to 2,3-Dichloropropene (>99%) Vapor 6 Hours/Day, for 9/11 Days[a]

	Control	5 ppm	25 ppm	75 ppm
Rats				
Hyperplasia of nasal respiratory epithelium				
Male rats	0/5	4/5*	5/5**	5/5***
Female rats	0/5	5/5*	5/5**	5/5***
Mice				
Hyperplasia of nasal respiratory epithelium				
Male mice	0/5	3/5*	5/5**	5/5***
Female mice	0/5	4/5*	5/5**	5/5***
Diffuse degeneration of bronchial/bronchiolar epithelium				
Male mice	0/5	5/5**	5/5***	5/5****
Female mice	0/5	5/5**	3/5***+ 2/5****	5/5****

[a]Severity: *very slight; **slight;***moderate;****severe

Source: Zempel et al. 1987

in rats (Dietz et al. 1985b). Exposure to an unquantified concentrated vapor atmosphere resulted in gasping, labored breathing, and nasal discharge as clinical signs, as well as hemorrhagic lungs and inflammation of the nasal mucosal in rats (Younger 1967). In these studies, evidence of suppression of the central nervous system was observed at concentrations in excess of 500 ppm (Dietz et al. 1985b; Younger 1967).

The acute study in male and female rats and mice by Zempel et al. (1987) is selected as the principal study because it was adequately designed and reported, the purity of the test material was high, and it reported critical effects at the lowest tested concentration.

Zempel et al. (1987) exposed (whole body) groups of B6C3F1 mice and F344 rats (5/sex/species/group) to vapors of 2,3-dichloropropene (>99% purity) 6 hours/day for nine exposures over 11 days at concentrations of 0, 5, 25, or 75 ppm. Rats and mice were examined for clinical signs of toxicity, body weight changes, hematology and serum chemistry analyses of terminal blood samples, and, in rats only, urinalyses. Terminal examinations of all rats and mice included a complete necropsy (for rats, including the eyes), measurement of selected organ weights (brain, heart, liver, thymus, kidneys, and testes), and microscopic examination of all tissues for animals in the control and 75 ppm groups, and for target tissues (liver, kidneys, bone marrow, lungs, and nasal tissues, and in mice, thymus, trachea, and larynx) in the 5 and 25 ppm groups. Exposure to 2,3-dichloropropene had no significant effect on survival in rats or mice. No alterations in activity levels or hematology, serum chemistry, or urinalysis results were observed in rats. Alterations in hematology and clinical chemistry parameters observed in mice were ascribed by the study authors to mild dehydration (and resulting hemoconcentration) and stress. Significant histological lesions of the respiratory tract are presented in Table 2-2. Other histopathological lesions were not considered to be compound related: stress-related cortical atrophy of the thymus and dehydration-related reduced extramedullary hematopoeisis in the liver and spleen of mice at 75 ppm. The lowest exposure level, 5 ppm, was a minimal LOAEL for very slight hyperplasia of the nasal respiratory epithelium in male and female rats and mice and slight diffuse degeneration of the bronchial/bronchiolar epithelium in male and female mice.

Potential points of departure for deriving the acute-duration inhalation MRL were obtained by first adjusting for intermittent exposure, resulting in a duration-adjusted LOAEL of 1.25 ppm. Using EPA (1994) dosimetry adjustments, regional gas dose ratios (RGDRs) were calculated for extrathoracic (ET) effects (nasal lesions) in rats and mice and tracheobronchial (TB) effects (bronchial/bronchiolar lesions) in mice. Although 2,3-dichloropropene is a category 2 gas, the equations for a category 1 gas were used

by default since an equation is not available for category 2 gases. The calculated RGDRs were applied to the duration adjusted LOAEL of 1.25 ppm to obtain the human equivalent concentrations ($LOAEL_{HEC}$): 0.20 and 0.14 ppm for extrathoracic effects in male and female rats, respectively, 0.18 and 0.15 ppm for extrathoracic effects in male and female mice, respectively, and 2.22 and 1.79 ppm for tracheobronchial effects in male and female mice, respectively. The lowest $LOAEL_{HEC}$ of 0.14 ppm for hyperplasia of the nasal respiratory epithelium in female rats was chosen as the point of departure for the MRL since it would be protective against all observed effects. A composite uncertainty factor of 90 (3 for the use of a minimal LOAEL, 3 for extrapolation from animals to humans using dosimetric adjustments, and 10 for human variability) was applied to the $LOAEL_{HEC}$ of 0.14 ppm for hyperplasia of the nasal respiratory epithelium in female rats, resulting in an MRL of 0.002 ppm.

No intermediate-duration inhalation MRL was derived for 2,3-dichloropropene because of a lack of suitable data. No studies were located regarding the intermediate-duration inhalation toxicity of 2,3-dichloropropene in humans. Intermediate-duration inhalation studies in animals exposed to 2,3-dichloropropene are not adequate for derivation of an intermediate-duration inhalation MRL because of deficiencies that prevent the accurate determination of reliable NOAELs or LOAELs for respiratory lesions (Johannsen et al. 1991; NTP 1989). NTP (1989) began 13-week studies (Study No. C61881) in Fischer 344 rats and B6C3F1 mice exposed 6 hours/day, 5 days/week to 0, 5, 10, 20, 40, or 80 ppm 2,3-dichloropropene, but terminated the postexposure work on the studies when new data showed that production volumes of 2,3-dichloropropene in the United States had dropped below 100 kg/year (NTP 2006; communication from NTP to SRC). Some data tables are available for this study on the NTP website, providing definitive concentration-response information for body weights and hematology parameters, but not for most other end points because no histopathology data are available. The 13-week systemic toxicity and 13–16-week reproductive toxicity studies by Johannsen et al. (1991), in which Sprague-Dawley rats were exposed 6 hours/day, 5 days/week at concentrations of 0, 1, 5, or 15 ppm or 0, 1, or 5 ppm, respectively, are deficient in the failure to examine the likely target organ, the nasal turbinates.

The following results were reported in the 13-week studies in rats and mice. No effects on survival, hematology, serum chemistry, histopathology, body weight, or organ weights were observed in rats exposed at ≤15 ppm (Johannsen et al. 1991). In rats, respiratory effects in rats included red nasal discharge (increasing in frequency during the study), but no observed lung histopathology, at ≤15 ppm (Johannsen et al. 1991), and no lung weight increases at ≤80 ppm (NTP 1989). Female mice exposed at 5–40 ppm had 25–33% increases in absolute lung weight and 25–47% increases in relative lung weight,

whereas male mice had absolute lung weights increased by 13–36% at 10–80 ppm and relative lung weights increased by 22–33% at 10–40 ppm and by 200% at 80 ppm (NTP 1989). No female mice exposed at 80 ppm survived to 13 weeks (NTP 1989); no mortality data were available for male and female rats or male mice exposed to ≤80 ppm (NTP 1989). Significant concentration-related (>10%) reductions in terminal body weights compared to controls were observed in male rats and male and female mice exposed at 40 or 80 ppm (NTP 1989). Hepatic toxicity was observed in female rats: 33% increased absolute and 37% increased relative liver weights, a 60% increase in serum alkaline phosphatase, and a 6-fold increase in total serum bile acids at 80 ppm, and >3-fold increases in serum alanine aminotransferase (ALT) and sorbitol dehydrogenase (SDH) at 40–80 ppm (NTP 1989). No hepatic weight changes were observed in female mice exposed at ≤40 ppm, or male rats or mice exposed at ≤80 ppm (NTP 1989). A 17% increase in absolute and 23% increase in relative kidney weights were observed in female rats at 80 ppm (NTP 1989); urine volume was increased with exposure in female rats, but decreased in male rats. No kidney weight changes were observed in female mice exposed at ≤40 ppm, or male rats or mice exposed at ≤80 ppm (NTP 1989). No significant compound-related effects were observed on hematology parameters in rats or mice exposed at ≤80 ppm (NTP 1989). No significant effects were observed on reproductive parameters—gonadal weight or sperm parameters in male or estrus cycling in female rats or mice exposed at ≤80 ppm (Johannsen et al. 1991; NTP 1989) or mating and fertility indices in rats exposed at ≤5 ppm (Johannsen et al. 1991). The available limited data provide suggestive evidence that the respiratory system is the primary target of intermediate-duration inhalation exposure to 2,3-dichloropropene, presumably a portal-of-entry effect related to repeated irritation. The lung weight effects at 5 ppm in the NTP study are consistent with the acute-duration inhalation study by Zempel et al. (1987) in that lung effects were observed in mice, but not in rats.

Neither of the available studies provide a suitable basis for derivation of an intermediate-duration inhalation MRL for 2,3-dichloropropene. Although Johannsen et al. (1991) appears to identify irritation of the respiratory tract as the most sensitive effect of exposure, an accurate NOAEL or LOAEL for respiratory effects cannot be determined for this study because no incidence data were reported for red nasal discharge at 15 ppm and no histopathological examination was conducted for the nasal turbinates. Furthermore, the incomplete NTP (1989) study in mice appears to show lung effects in mice at 5 ppm, but also lacks histopathology data for the lung and nasal turbinates. Consequently, no intermediate-duration inhalation MRL was derived.

No chronic-duration inhalation MRL was derived for 2,3-dichloropropene because of a lack of data in humans or animals.

Oral MRLs. No oral MRLs were derived for 2,3-dichloropropene. No information was located regarding the oral toxicity of 2,3-dichloropropene. Animal data are limited to two acute lethality studies in rats that did not include control groups. A study by Younger (1967) was only available as a summary that reported an acute oral LD_{50} of 285 (250–326) mg/kg for male and female rats combined and did not report target organ specificity. A study by Union Carbide Corp. (1958), results of which were published in Smyth et al. (1962), reported an acute oral LD_{50} of 320 (260–400) mg/kg (Smyth et al. [1962] mis-reported the unit as mL/kg). Necropsy results included congestion in lungs, liver, and kidney, and opacity of the gastrointestinal tract. These studies are not suitable for MRL derivation because they provide no dose-response information for nonlethal effects.

1,2-Dichloropropene

Inhalation MRLs. No inhalation MRLs were derived for 1,2-dichloropropene. No information was located regarding the acute inhalation toxicity of 1,2-dichloropropene in humans. Animal data are limited to an unpublished summary of an acute lethality study in which small numbers of rats (3 or 4) were exposed to saturated vapor at an estimated concentration of 63,764 ppm and 1/4 died after 6 minutes and 3/3 died after 12 minutes (Dow 1962); the study included no other exposure levels and no control group. Effects noted in this study were unconsciousness and, in one rat at necropsy, considerable (unspecified) injury to lung, liver, and kidney. The numerous deficiencies in design (small group size, lack of control group, single exposure level, lack of a nonlethal exposure level) and reporting, render this study unsuitable for MRL derivation.

Oral MRLs. No oral MRLs were derived for 1,2-dichloropropene. No information was located regarding the oral toxicity of 1,2-dichloropropene in humans. Animal data are limited to an unpublished summary of a range-finding study in which two rats were given 1,2-dichloropropene by oral gavage in corn oil at a dose of 2,000 mg/kg (Dow 1962). Neither animal died, but necropsy revealed considerable (unspecified) injury to the liver and kidney. This study is unreliable because of the inadequate design (small group size, lack of control group) and inadequate reporting of methods and results.

1,1-Dichloropropene and 3,3-Dichloropropene

No MRLs were derived for 1,1- or 3,3-dichloropropene because of a lack of toxicity data in humans or animals exposed to these isomers by the inhalation or oral routes.