1,3-Dichloropropene (DCP); CASRN 542-75-6

Human health assessment information on a chemical substance is included in the IRIS database only after a comprehensive review of toxicity data, as outlined in the IRIS assessment development process. Sections I (Health Hazard Assessments for Noncarcinogenic Effects) and II (Carcinogenicity Assessment for Lifetime Exposure) present the conclusions that were reached during the assessment development process. Supporting information and explanations of the methods used to derive the values given in IRIS are provided in the guidance documents located on the IRIS website.

STATUS OF DATA FOR 1,3-Dichloropropene (DCP)

File First On-Line 09/30/1987

Category (section)	Assessment Available?	Last Revised
Oral RfD (I.A.)	yes	05/25/2000
Inhalation RfC (I.B.)	yes	05/25/2000
Carcinogenicity Assessment (II.)	yes	05/25/2000

I. Chronic Health Hazard Assessments for Noncarcinogenic Effects

I.A. Reference Dose for Chronic Oral Exposure (RfD)

Substance Name — 1,3-Dichloropropene (DCP)
CASRN — 542-75-6
Last Revised — 05/25/2000

The oral Reference Dose (RfD) is based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis. It is expressed in units of mg/kg-day. In general, the RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. Please refer to the Background Document for an elaboration of these concepts. RfDs can also be derived for the noncarcinogenic health effects of substances that are also carcinogens. Therefore, it is

essential to refer to other sources of information concerning the carcinogenicity of this substance. If the U.S. EPA has evaluated this substance for potential human carcinogenicity, a summary of that evaluation will be contained in Section II of this file.

I.A.1. Oral RfD Summary

The current RfD for 1,3-dichloropropene is a revision of the value placed on-line on 10/01/1990

Critical Effect	Benchmark Doses	UF	MF	RfD
Chronic irritation **Rat chronic feeding study** **(Stott et al.,1995)**	$BMDL_{10}$: 3.4 mg/kg/day BMD_{10}: 5.1 mg/kg/day	100	1	3E-2 mg/kg/day

$BMDL_{10}$ - 95% lower confidence limit on the maximum likelihood estimate of the dose corresponding to 10% risk.
BMD_{10} - Maximum likelihood estimate of the dose corresponding to 10% risk.

I.A.2. Principal and Supporting Studies (Oral RfD)

There are no chronic human studies suitable for dose-response assessment. Chronic feeding studies in rats (Stott et al., 1995) and mice (Redmond et al., 1995) and chronic gavage studies (NTP, 1985)using both species are available. The feeding studies are favored over the gavage studies because the route of administration is more relevant to human exposure. The gavage studies (NTP, 1985) were previously rejected by EPA for RfD development (IRIS, online 10/01/90) because the dosing regimen (high doses by gavage three times/week) was not well designed to study chronic toxicity. Another problem with the gavage study (NTP, 1985) is that the dichloropropene formulation contained epichlorohydrin, which NTP acknowledged as a possible contributor to tumorigenic effects in the forestomach. Of the two feeding studies available, the rat study of Stott et al. (1995) is the most appropriate choice of a principal study for derivation of toxicity values for nonneoplastic effects. The dosing in the mouse dietary study by Redmond et al. (1995) is uncertain owing to the lack of cancer (urinary bladder

tumors) and noncancer effects (urinary bladder hyperplasia, forestomach hyperplasia, and hydronephrosis) observed in the mouse gavage study (NTP, 1985).

Stott, WT; Johnson, KA; Jeffries, TK; et al. (1995) Telone II soil fumigant: two-year chronic toxicity/oncogenicity study in Fischer 344 rats. The Dow Chemical Company. Midland, Michigan. Study # M-003993-0311.

Stott et al. (1995) fed male and female Fischer 344 rats (50/sex/dose) a microencapsulated formulation of Telone II (96% 1,3-dichloropropene) in the diet at doses of 0, 2.5, 12.5, or 25 mg/kg/day for 24 months. Satellite groups of rats (10/sex/dose) were administered Telone II for 12 months. Standard bioassay data including body weights, food consumption, clinical chemistry, hematology, urine analysis, organ weights, pathology, and histopathology were collected. Body weights were decreased in a dose-dependent manner in treated animals. Decreases were statistically and toxicologically significant in both sexes at 25 mg/kg/day. Average organ weight changes in males and females were associated with decreased body weight. The only histopathology observed was in the forestomach, which exhibited a mild basal cell hyperplasia of the mucosal lining. The incidence of forestomach lesions was statistically increased in both sexes at 12.5 mg/kg/day and higher. There were no indications of basal cell hyperplasia at 2.5 mg/kg. Incidences were 3/100, 4/100, 40/100, and 67/100 for control, 2.5, 12.5, and 25 mg/kg groups, respectively. The forestomach hyperplasia is believed to be a manifestation of chronic irritation, which is consistent with the observation of primary dermal irritation (Nater and Gooskens, 1976) and other portal-of-entry effects from 1,3-dichloropropene exposure (Haut et al., 1996; Breslin et al., 1989; Lomax et al., 1989; Linnett et al., 1988; Stott et al., 1988). Of the two critical effects, body weight decrease and chronic irritation (as evidenced by the forestomach hyperplasia), data from the most sensitive effect, chronic irritation, were used to develop the RfD.

Redmond, JM; Stebbins, KE; Stott, WT. (1995) Telone II soil fumigant: two-year dietary chronic toxicity/oncogenicity study in B6C3F1 mice - final report. Dow Chemical Company, Midland, MI. Study # M-003993-032.

Male and female B6C3F1 mice (50/sex/dose) were administered a microencapsulated formulation of Telone II (96% 1,3-dichloropropene) in the diet at doses of 0, 2.5, 25, or 50 mg/kg/day for 24 months. Satellite groups of mice (10/sex/dose) were administered Telone II for 12 months. Standard bioassay data including body weights, food consumption, clinical chemistry, hematology, urine analysis, organ weights, pathology, and histopathology were collected. Mean body weights were significantly and toxicologically decreased in a dose-dependent manner in male mice at 25 and 50 mg/kg/day. Changes in mean organ weights were considered to be secondary to decreased body weights. No consistent treatment-related changes in hematologic, clinical chemistry, and urine analysis parameters were observed in

any of the treated groups. Treatment-related pathology and histopathology were not observed in any treated groups. Although the dosing in this study is suspected to be insufficient, the decrease in body weight in mice supports the same finding in Stott et al. (1995) because it was observed in rats at the same dose. The lack of other significant effects in Redmond et al. (1995) supports the use of Stott et al. (1995) as the principal study because chronic irritation was observed at a lower dose than decreased body weight.

Haut, KT; Stebbins, KE; Johnson, KA; et al. (1996) Subchronic toxicity of ingested 1,3-dichloropropene in rats and mice. Fundam Appl Toxicol 32:224-232.

Male and female F344 rats and B6C3F1 mice (10/sex/group) were given 0, 5, 15, 50, or 100 mg/kg/day (rats) or 0, 15, 50, 100, or 175 mg/kg/day (mice) microencapsulated Telone II (96% 1,3-dichloropropene) in their diets for 13 weeks. Satellite groups of rats (10/sex/group) from 0 and 100 mg/kg/day groups were retained for observation for 4 weeks following treatment in order to examine recovery. Food consumption in rats was consistently decreased for 100 mg/kg/day male and female rats and occasionally depressed at lower doses relative to control values. Food consumption in mice was generally unchanged and only occasionally depressed at the higher doses relative to controls. A dose-related, statistically significant decrease in body weight was observed in male rats at 15 mg/kg/day and higher, in female rats at 50 mg/kg/day and higher, and in male and female mice at all doses. Changes in mean organ weights were consistent with decreases in body weight and were not considered toxicologically significant. At necropsy, no gross pathology was observed in treated animals. Mild basal cell hyperplasia and a slight prominence of mononuclear cells in the basement membrane of the forestomach, reflections of the irritant effect of 1,3-dichloropropene, were noted in all treated male and female rats at 50 mg/kg/day and higher. After 4 weeks of recovery, animals in the 100 mg/kg/day group (the only treated group continued through recovery) exhibited basal cell hyperplasia; however, the severity and incidence were diminished compared with that observed immediately following cessation of treatment. In mice, the only noted histopathological change was a decrease in vacuolation of tubular epithelial cells of the kidney in males at 175 mg/kg/day, the highest dose. Haut et al. (1996) supports the findings of Stott et al. (1995) by providing additional evidence of decreased body weight and chronic irritation (i.e., forestomach lesions) in response to dietary 1,3-dichloropropene.

I.A.3. Uncertainty and Modifying Factors (Oral RfD)

UF = 100. The default uncertainty factor of 10 for interspecies extrapolation is applied because there are no data on the relative sensitivity of rats and humans to stomach irritation. Because there are no data documenting the nature and extent of variability in human susceptibilities to 1,3-dichloropropene, the default uncertainty factor of 10 is used for within-

species variation. The database for 1,3-dichloropropene is substantial and includes studies of genotoxicity, mode of action, pharmacokinetics, reproductive and developmental toxicity, systemic toxicity, and cancer. Therefore, no additional uncertainty factors are needed.

MF = None

I.A.4. Additional Studies/Comments (Oral RfD)

The only repeated-exposure human toxicity data for 1,3-dichloropropene are case studies showing that dermatitis occurred as a result of direct contact (Bousema et al., 1991; Nater and Gooskens, 1976). Accidental high-dose poisoning following chemical spills or accidental release has caused a dose- related range of acute neurotoxic symptoms, and accidental ingestion of 1,3-dichloropropene has been fatal (Hernandez et al., 1994).

The toxicokinetics in humans are similar to those observed in rats. Inhalation studies with both humans and rats have shown that 1,3-dichloropropene is readily absorbed. Biotransformation of 1,3-dichloropropene leads largely to its detoxification and excretion. In rats and humans, the major metabolic pathway is glutathione conjugation to form mercapturic acid metabolites, which are rapidly excreted in the urine (Hutson et al., 1971; Climie et al., 1979; Dietz et al., 1984a,b; Osterloh et al., 1989; van Welie et al., 1991, Waechter et al., 1992). Half-lives for disappearance from the blood and for excretion of mercapturic acid metabolites are similar for rats and humans.

Distribution studies in rats indicate that the forestomach, glandular stomach, kidney, and liver are primary organs of distribution for oral 1,3-dichloropropene (Dietz et al., 1984b). Climie et al. (1979) determined that a glutathione-dependent biotransformation is the major metabolic pathway of cis-1,3-dichloro[^{14}C]propene. A hepatic glutathione S-transferase catalyzes the conjugation of 1,3-dichloropropene with glutathione. The conjugate is further metabolized to a mercapturic acid and is excreted in the urine as N-acetyl-(S-3-chloroprop-2-enyl)cysteine (3CNAC). No evidence of saturation of dichloropropene metabolism in rats at oral gavage doses of 50 mg/kg or less was observed by Dietz et al. (1984b). 1,3-Dichloropropene underwent substantial first-pass metabolism, following linear pharmacokinetics over an oral gavage dose range of 1-100 mg/kg for mice and 1-50 mg/kg for rats (Dietz et al., 1984b). Mutagenic epoxide metabolites, from a minor metabolic pathway, have been detected at lethal doses (Schneider et al., 1998) in mice. Animal studies show that 1,3-dichloropropene is unlikely to accumulate in the body (Hutson et al., 1971; Dietz et al., 1984a).

Waechter et al. (1992) showed that the absorption of 1,3-dichloropropene from inhalation exposure of humans (72%-82%) was similar to absorption in rats 82%; Stott and Kastl, 1986). The same major urinary metabolite, 3CNAC, is produced in humans, rats, and mice, and

urinary elimination half-lives, 4-6 hours, are similar (Waechter et al., 1992; Dietz et al., 1985; van Welie et al., 1991; Osterloh et al., 1989). Two biological monitoring studies in humans have demonstrated that there is a dose-dependent relationship between respiratory occupational exposure to 1,3-dichloropropene and excretion of 3CNAC (Van Welie et al., 1991; Osterloh et al., 1989). Van Welie et al. (1991), studying workers in the flower bulb industry, found that urinary excretion of 3CNAC followed first-order elimination kinetics following exposure.

No toxicologically significant adverse effects were observed in a two- generation rat reproductive inhalation study (Breslin et al., 1989) or in developmental toxicity inhalation studies with rats and rabbits (Hanley et al., 1988). On the basis of similar toxicokinetics, the reproductive/developmental and systemic toxicity of ingested 1,3-dichloropropene is likely to be similar to that of inhaled 1,3-dichloropropene. Owing to the absence of animal studies examining the effect of 1,3-dichloropropene exposure on juvenile animals, the effects of 1,3-dichloropropene on children cannot be predicted.

For more detail on Susceptible Populations, exit to [the toxicological review, Section 4.7](#) (PDF).

I.A.5. Confidence in the Oral RfD

Study — High
Database — High
RfD — High

The overall confidence in this RfD assessment is high. The confidence in the principal study is high. The study was well designed and well conducted and followed standard guidelines for chronic bioassays. Results from a chronic ingestion study with mice (Redmond et al., 1995) and a subchronic ingestion study with rats and mice (Haut et al., 1996) are consistent with the findings in the 2-year rat bioassay. Chronic irritation, as evidenced by forestomach histopathology, and body weight decrease were the critical effects. The relevance of the chronic irritant effects in the forestomach to humans is supported by a case report of gastric mucosal erosion produced by a fatal accidental ingestion of an unknown quantity of 1,3-dichloropropene (Hernandez et al., 1994). In addition, the forestomach lesions are consistent with observations of other irritant effects produced by 1,3-dichloropropene at the portal of entry (Nater and Gooskens, 1976; Haut et al., 1996; Breslin et al., 1989; Lomax et al., 1989; Linnett et al., 1988; Stott et al., 1988). Studies on reproductive and developmental toxicity, toxicokinetics, inhalation toxicity, and genotoxicity support high confidence in the database. Although studies on reproductive and developmental toxicity used inhalation as the route of

administration, sufficient toxicokinetic data are available to demonstrate that 1,3-dichloropropene is well absorbed and metabolized via the same pathway for both routes.

For more detail on Characterization of Hazard and Dose Response, exit to [the toxicological review, Section 6](#) (PDF).

I.A.6. EPA Documentation and Review of the Oral RfD

Source Document — U.S. EPA, 2000

This assessment was peer reviewed by external scientists. Their comments have been evaluated carefully and incorporated in the finalization of this IRIS Summary. A record of these comments is included as an appendix to the Toxicological Review for 1,3-Dichloropropene.

[To review this appendix, exit to the toxicological review, Appendix B, Summary of and Response to External Peer Review Comments (PDF)](#).

Agency Consensus Date — 04/20/00

Screening-Level Literature Review Findings — A screening-level review conducted by an EPA contractor of the more recent toxicology literature pertinent to the RfD for 1,3-Dichloropropene (DCP) conducted in August 2003 identified one or more significant new studies. IRIS users may request the references for those studies from the IRIS Hotline at hotline.iris@epa.gov or 202-566-1676.

I.A.7. EPA Contacts (Oral RfD)

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202)566-1676 (phone), (202)566-1749 (fax) or hotline.iris@epa.gov (Internet address).

I.B. Reference Concentration for Chronic Inhalation Exposure (RfC)

Substance Name — 1,3-Dichloropropene (DCP)
CASRN — 542-75-6
Last Revised — 05/25/2000

The inhalation Reference Concentration (RfC) is analogous to the oral RfD and is likewise based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis. The inhalation RfC considers toxic effects for both the respiratory system (portal-of-entry) and for effects peripheral to the respiratory system (extrarespiratory effects). It is expressed in units of mg/m^3. In general, the RfC is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily inhalation exposure of the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. Inhalation RfCs were derived according to the Interim Methods for Development of Inhalation Reference Doses (EPA/600/8-88/066F, August 1989) and subsequently, according to Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry (EPA/600/8-90/066F, October 1994). RfCs can also be derived for the noncarcinogenic health effects of substances that are carcinogens. Therefore, it is essential to refer to other sources of information concerning the carcinogenicity of this substance. If the U.S. EPA has evaluated this substance for potential human carcinogenicity, a summary of that evaluation will be contained in Section II of this file.

I.B.1. Inhalation RfC Summary

The current RfC for 1,3-dichloropropene is a reevaluation of an assessment placed on-line on 01/01/1991. Although the current assessment uses benchmark dose modeling for the dose-response analysis, the dosimetric adjustment for animal-to-human exposure concentration was similar to that reported earlier. The resulting RfC is the same as that reported in the 1991 assessment.

Critical Effect	Benchmark Concentrations	UF	MF	RfC
Hypertrophy/hyperplasia of the nasal respiratory epithelium **Chronic inhalation study in B6C3F1 mice (Lomax et al., 1989)**	$BMCL_{10}(ADJ)$[1]: 3.7 mg/m^3 $BMCL_{10}(HEC)$[2]: 0.72 mg/m^3 $BMC_{10}(ADJ)$[1]: 5.9 mg/m^3 $BMC_{10}(HEC)$[2]: 1.2 mg/m^3	30	1	2E-2 mg/m^3

$BMCL_{10}$ — 95% lower confidence limit on the maximum likelihood estimate of the dose corresponding to 10% risk.
BMC_{10} — Maximum likelihood estimate of the dose corresponding to 10% risk.

Conversion Factors and Assumptions — [1]Prior to BMC analysis, exposure concentrations were converted from intermittent exposure to continuous exposure and adjusted for purity of formulation (92%): 22.7 mg/m^3 × 6/24 hrs × 5/7 days × 0.92 = 3.7 mg/m^3. [2]Adjusted BMC and BMCL were converted to human equivalent concentration (HEC) for interspecies dosimetric adjustment. BMC(HEC) was calculated for an effect in the extrathoracic (ET) region. Minute volume$_{mouse}$ = 0.041 L/min, Minute volume$_{human}$ = 13.8 L/min, Surface area(ET)$_{mouse}$ = 3 cm^3, Surface area(ET)$_{human}$ = 200 cm^2. Regional gas dose ratio(ET) = (Minute volume$_{mouse}$/surface area(ET)$_{mouse}$)/(minute volume$_{human}$/surface area(ET)$_{human}$) = 0.198. BMC(HEC) = BMC(ADJ) × Regional gas dose ratio(ET) = 3.66 mg/m^3 × 0.198 = 0.72 mg/m^3.

I.B.2. Principal and Supporting Studies (Inhalation RfC)

Lomax, LG; Stott, WT; Johnson, KA; et al. (1989) The chronic toxicity and oncogenicity of inhaled technical-grade 1,3-dichloropropene in rats and mice. Fundam Appl Toxicol 12:418-431.

There are no chronic human inhalation studies suitable for dose-response assessment. The only chronic animal study available was chosen as the principal study. Lomax et al. (1989) exposed male and female F344 rats and B6C3F1 mice (50/sex/dose) via whole-body chamber inhalation to 0, 5, 20, or 60 ppm (0, 22.7, 90.8, or 272 mg/m^3) technical-grade 1,3-dichloro-propene for 6 hours/day, 5 days/week for 2 years. Two satellite groups of rats and mice (10/sex/dose group) were exposed to 1,3-dichloropropene for 6 and 12 months, respectively. Standard protocols for chronic toxicity and carcinogenicity bioassays were followed. In rats, the only treatment-related effects were histopathological changes in the nasal tissues of both sexes, primarily in the olfactory epithelium, after exposure to 272 mg/m^3 for 24 months, but not after exposure for 6 or 12 months. These microscopic changes were located in the olfactory mucosa covering the upper portions of the nasal cavity, nasal septum, and turbinates, and were characterized by degeneration, erosion, and fibrosis. In mice, gross pathological examination showed an increase in lung masses in males exposed to 272 mg/m^3. Histopathology revealed an increased incidence of hypertrophy and hyperplasia of the respiratory epithelium and/or degeneration of the olfactory epithelium in mice of both genders at 90.8 and 272 mg/m^3. In all cases, changes were graded as "slight," involved approximately 10% or less of the total respective epithelium, and did not progress in severity or extent of distribution from one time period to the next. Statistically significant hyperplastic changes in the urinary bladder were noted in female mice exposed to 90.8 mg/m^3 or higher and in males exposed to 272 mg/m^3. Generally, the hyperplasia increased in severity with increasing exposure concentration, and in the 272 mg/m^3 females, with increasing periods of exposure. Additional microscopic changes noted in mice in the 272 mg/m^3 group were (1) focal hyperplasia and hyperkeratosis in the forestomach of 8/50 males exposed for 24 months; (2)

decreased vacuolation of renal proximal tubular epithelial cells in males exposed for 24 months; and (3) decreased hepatocyte vacuolation in males exposed for 6 and 12, but not 24, months and in females exposed for 24 months.

Stott, WT; Young, JT; Calhoun, LL; et al. (1988) Subchronic toxicity of inhaled technical grade 1-3 dichloropropene in rats and mice. Fundam Appl Toxicol 11:207-220.

Male and female F344 and B6C3F1 mice (10/sex/group) were exposed to vapors of technical-grade 1,3-dichloropropene for 6 hours/day, 5 days/week for 13 weeks at nominal concentrations of 0, 10, 30, 90, or 150 ppm (0, 45.4, 136, 409, or 681 mg/m^3). The only treatment-related clinical effects observed during the study were transient brown discoloration of the fur about the muzzles of rats exposed to 150 ppm immediately following exposure and a strong mercaptan odor associated with the coats and urine of all rats and mice exposed to 409 or 681 mg/m^3. There were no treatment-related differences in survival. The body weights of male and female rats exposed to 409 or 681 mg/m^3 were significantly depressed in an exposure-related manner relative to control rats. Changes in mean organ weights were considered to be secondary to decreased body weights. In 2/10 male rats at 136 mg/m^3, minimally detectable hyperplasia of the respiratory epithelium was present, whereas all male and female rats in the 409 and 681 mg/m^3 groups exhibited mild histopathologic changes in the nasal respiratory epithelium. Rats exposed to 681 mg/m^3 also exhibited slight degeneration of the olfactory epithelium. In mice, exposure-related histopathology of the nasal mucosa was similar to that observed in rats and consisted of slight to very slight degeneration of the olfactory neuroepithelium and hyperplasia of the respiratory epithelium in most of the males and females in the 409 and 681 mg/m^3 groups. The urinary bladders of 7/10 and 6/10 female mice in the 409 and 681 mg/m^3 groups, respectively, exhibited large confluent areas of moderate hyperplasia of the transitional epithelium. Mild aggregates of lymphoid cells in the subepithelial tissues were found to be associated with these areas of hyperplasia in about half of the affected mice. Stott et al. (1988) supports the Lomax et al. (1988) study by providing additional evidence of the ability of 1,3-dichloropropene to produce nasal respiratory and olfactory epithelial histopathology in rats and mice. Additionally, Stott et al. (1988) confirm that the urinary bladder is also a target organ in mice exposed via inhalation.

Breslin, WJ; Kirk, HO; Streeter, CM; et al. (1989) 1,3-Dichloropropene: two-generation inhalation reproduction study in Fischer 344 rats. Fundam Appl Toxicol 12:129-143.

In a two-generation reproductive/developmental study, F344 rats (30/sex/group) were exposed via whole-body inhalation to 0, 10, 30, or 90 ppm (0, 45.4, 136, or 409 mg/m^3, respectively; converted by ppm × MW/24.45 with MW = 110.98) 1,3-dichloropropene for 6 hours/day, 5 days/week for 10 weeks before mating and for 6 hours/day, 7 days/week during mating, gestation, and lactation. No effects in any animals were noted at 10 or 30 ppm. At 90 ppm,

males in the F_0 and F_1 generations exhibited a statistically significant decrease in body weight compared to controls. In adults and litters, no toxicologically significant changes in mating or fertility indices, including cohabitation time required for mating, gestation length, litter size, pup survival, and pup body weights, were observed. There were no increases in either physical or behavioral abnormalities of the pups. Parental toxicity was observed only at 90 ppm and consisted of histopathological changes of the nasal mucosa of the adult male and female rats. The alterations consisted of slight focal hyperplasia of the respiratory epithelium and/or focal degenerative changes of the olfactory epithelium. The findings of Breslin et al. (1989) support the use of Lomax et al. (1989) as the critical study by affirming that epithelial effects in the nasal cavity are more sensitive to 1,3-dichloropropene exposure than other effects.

I.B.3. Uncertainty and Modifying Factors (Inhalation RfC)

UF = 30. In general, the default uncertainty factor for interspecies extrapolation is 10. Half of that factor, $10^{1/2}$, or 3, reflects the pharmacokinetic component of interspecies uncertainty and half represents the pharmacodynamic component of interspecies uncertainty. For 1,3-dichloropropene, the pharmacokinetic component of interspecies uncertainty is accounted for by the similarity in toxicokinetics between rodents and humans (U.S. EPA, 2000, Sections 3.1, 3.2, and 3.4) and by the dosimetric adjustment to convert animal exposure concentrations to human equivalent concentrations (HEC). Thus, an uncertainty factor of 3 is used for interspecies extrapolation to reflect the pharmacodynamic component of interspecies uncertainty. There are few data documenting the nature and extent of variability in human susceptibility to 1,3-dichloropropene; therefore, the default uncertainty factor of 10 is used for within-species variation. The database is substantial and includes studies of genotoxicity, mode of action, pharmacokinetics, reproductive and developmental toxicity, systemic toxicity, and cancer. Therefore, no additional uncertainty factors are needed.

MF = None

I.B.4. Additional Studies/Comments (Inhalation RfC)

1,3-Dichloropropene is rapidly absorbed, conjugated with glutathione to mercapturic acids, and subsequently excreted, mainly in the urine (Stott and Kastl, 1986; Fisher and Kilgore 1988a,b, 1989). Toxicokinetics are similar in humans and in rodents (Osterloh, 1989; van Welie et al., 1991; Brouwer et al., 1991; Waechter et al., 1992). 1,3-Dichloropropene does not bioaccumulate in the body.

The weight and strength of evidence of one two-generation inhalation reproductive study with rats (Breslin et al., 1989) and two developmental toxicity studies with rats and rabbits by Hanley et al. (1988) demonstrate that 1,3-dichloropropene is not a reproductive or

developmental toxicant. Owing to the absence of studies examining the effect of 1,3-dichloropropene exposure on juvenile animals, the effects of 1,3-dichloropropene on children cannot be predicted.

For more detail on Susceptible Populations, exit to [the toxicological review, Section 4.7](#) (PDF).

I.B.5. Confidence in the Inhalation RfC

Study — High
Database — High
RfC -- High

The overall confidence in this RfC assessment is high. The confidence in the principal study is high. The study used two species, was well designed and well conducted, and followed standard guidelines for chronic bioassays. The nasal histopathology findings of the principal study were supported by similar findings in a subchronic inhalation study and a two-generation reproductive/developmental study. Rats and mice of both genders were tested in both the subchronic and chronic studies. Confidence in the database is high because there are supporting toxicokinetic, reproductive, developmental, and ingestion studies in animals.

For more detail on Characterization of Hazard and Dose Response, exit to [the toxicological review, Section 6](#) (PDF).

I.B.6. EPA Documentation and Review of the Inhalation RfC

Source Document — U.S. EPA, 2000

This assessment was peer reviewed by external scientists. Their comments have been evaluated carefully and incorporated in finalization of this IRIS Summary. A record of these comments is included as an appendix to the Toxicological Review for 1,3-Dichloropropene. *[To review this appendix, exit to the toxicological review, Appendix B, Summary of and Response to External Peer Review Comments (PDF)](#).*

Agency Consensus Date — 04/20/00

Screening-Level Literature Review Findings — A screening-level review conducted by an EPA contractor of the more recent toxicology literature pertinent to the RfC for 1,3-Dichloropropene conducted in August 2003 did not identify any critical new studies. IRIS

users who know of important new studies may provide that information to the IRIS Hotline at
hotline.iris@epa.gov or 202-566-1676.

I.B.7. EPA Contacts (Inhalation RfC)

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in
general, at (202)566-1676 (phone), (202)566-1749 (fax) or hotline.iris@epa.gov (Internet
address).

II. Carcinogenicity Assessment for Lifetime Exposure

Substance Name — 1,3-Dichloropropene
CASRN — 542-75-6
Last Revised — 05/25/2000

Section II provides information on three aspects of the carcinogenic assessment for the
substance in question; the weight-of-evidence judgment of the likelihood that the substance is
a human carcinogen, and quantitative estimates of risk from oral exposure and from inhalation
exposure. The quantitative risk estimates are presented in three ways. The slope factor is the
result of application of a low-dose extrapolation procedure and is presented as the risk per
(mg/kg)/day. The unit risk is the quantitative estimate in terms of either risk per µg/L drinking
water or risk per µg/m^3 air breathed. The third form in which risk is presented is a
concentration of the chemical in drinking water or air associated with cancer risks of 1 in
10,000, 1 in 100,000, or 1 in 1,000,000. The rationale and methods used to develop the
carcinogenicity information in IRIS are described in The Risk Assessment Guidelines of 1986
(EPA/600/8-87/045) and in the IRIS Background Document. IRIS summaries developed since
the publication of EPA's more recent Proposed Guidelines for Carcinogen Risk Assessment
also utilize those Guidelines where indicated (Federal Register 61(79):17960-18011, April 23,
1996). Users are referred to Section I of this IRIS file for information on long-term toxic
effects other than carcinogenicity.

II.A. Evidence for Human Carcinogenicity

The current carcinogenicity assessment for 1,3-dichloropropene is a revision of the assessment
placed on-line on 10/01/1993.

II.A.1. Weight-of-Evidence Characterization

Human data are inadequate for assessment of the potential human carcinogenicity of 1,3-dichloropropene because the only human data available are case studies. In chronic animal bioassays, 1,3-dichloropropene produced tumors in F344 rats (forestomach, liver) and B6C3F1 mice (forestomach, urinary bladder, and lung) at high gavage doses, liver tumors in F344 rats at lower dietary doses, and benign lung tumors in male mice exposed via inhalation. Although 1,3-dichloropropene elicited a positive response for mutagenicity in bacterial assays with the addition of S9, the most compelling evidence for mutagenicity is the isolation of mutagenic epoxide metabolites from mouse liver at high ($\sim LD_{50}$) doses. Thus, under the current Risk Assessment Guidelines (U.S. EPA, 1987), 1,3-dichloropropene is a B2, probable human carcinogen, because of the lack of data in humans and sufficient evidence of carcinogenicity in animals.

Although the available human data are inadequate, 1,3-dichloropropene is characterized as "likely" to be a human carcinogen in accordance with the Proposed Guidelines for Carcinogen Risk Assessment (U.S. EPA, 1996). This characterization is based on tumors observed in chronic animal bioassays for both inhalation and oral routes of exposure. Although the chronic dietary and inhalation bioassays suggest that tumors may not occur at low doses, a nonlinear mechanism of tumor formation is not supported by the available mechanistic data. In fact, the mutagenic properties of 1,3-dichloropropene suggest a genotoxic mechanism of action. The mutagenic properties and the absence of data to support a nonlinear mechanism of tumor formation require that the quantitative assessment default to a linear model.

For more detail on Characterization of Hazard and Dose Response, exit to the toxicological review, Section 6 (PDF).

For more detail on Susceptible Populations, exit to the toxicological review, Section 4.7 (PDF).

II.A.2. Human Carcinogenicity Data

Inadequate. Human data are inadequate for assessment of the potential human carcinogenicity of 1,3-dichloropropene. The human data on 1,3-dichloropropene consist of anecdotal reports of three cases of cancer (two non-Hodgkin's lymphomas and one acute myelomonocytic leukemia). Case studies do not provide a basis for inferring a causal association between exposure to 1,3-dichloropropene and blood cancers because the possibility of confounding factors has not been considered or ruled out (U.S. EPA, 1987).

II.A.3. Animal Carcinogenicity Data

Sufficient. Four lifetime animal studies have been conducted to examine the carcinogenicity of 1,3-dichloropropene. There are three oral studies in rats and/or mice and one inhalation study in rats and mice. In the NTP (1985) study, F344 rats of each sex were gavaged with Telone II (92% 1,3-dichloropropene, 1% epichlorohydrin) in corn oil at doses of 0, 25, and 50 mg/kg 3 times/week while B6C3F1 mice of each sex were gavaged with 0, 50, and 100 mg/kg 3 times/week for 104 weeks. A total of 52 rats/sex and 50 mice/sex were used for each dose group in the main oncogenicity study; an additional 5 rats/sex/group were sacrificed after 9, 16, 21, 24, and 27 months of dosing, respectively. Doses were based on earlier short-term studies that observed body weight reduction. Standard bioassay data including clinical signs, body weights, clinical chemistry, hematology, pathology, and histopathology were collected. No increased mortality occurred in treated animals. In rats, elevated incidences of the following tumors were observed at 50 mg/kg: (1) forestomach squamous cell papillomas in males and females; (2) forestomach squamous cell papillomas and carcinomas combined in males; and (3) liver adenomas/carcinomas in males. The highest dose level tested in rats, 50 mg/kg, approximated a maximum tolerated dose level. The portion of the bioassay using male mice was inadequate because of premature deaths from myocardial inflammation in the control group. Elevated incidences of the following tumors were observed in mice either at the highest dose or at both doses tested: (1) forestomach squamous cell papillomas and carcinomas in males and females, and squamous cell carcinomas in females; (2) urinary bladder transitional cell carcinomas in males and females; and (3) lung adenomas/ carcinomas in males and females. The highest dose level tested in mice, 100 mg/kg, exceeded a maximum tolerated dose level. NTP concluded that there was "clear evidence of carcinogenicity" for female B6C3F1 mice, as the administration of Telone II had caused an increased incidence of transitional cell carcinomas of the urinary bladder, as well as an increased incidence of bronchioalveolar adenomas of the lung and of squamous cell papillomas and carcinomas of the forestomach in female mice. Although the NTP study was rejected by the Agency for RfD development (IRIS, online 10/1/90) because the thrice-weekly gavage dosing regime was not well designed to study chronic toxicity, the study provides evidence that 1,3-dichloropropene is a carcinogen at high bolus doses. Current test guidelines recommend gavaging seven times weekly, but indicate that five times/week is acceptable (U.S. EPA, 1998). Another problem with the NTP study (1985) is that the dichloropropene formulation contained epichlorohydrin, which NTP acknowledged as a possible contributor to tumorigenic effects in the forestomach. In addition, gavage administration is less relevant to human exposure than is dietary administration.

In the feeding studies, Fischer 344 rats (50/sex/dose) were administered Telone II (96% 1,3-dichloropropene without epichlorohydrin) in the diet at 0, 2.5, 12.5, or 25 mg/kg/day for 24 months (Stott et al., 1995) while B6C3F1 mice (50/sex/dose) received doses of 0, 2.5, 25, or

50 mg/kg/day for 24 months (Redmond et al., 1995). In both studies, satellite groups of rats and mice (10/sex/species/dose) were administered Telone II for 12 months. Standard bioassay data including body weights, food consumption, clinical chemistry, hematology, urine analysis, organ weights, pathology, and histopathology were collected. Ophthalmologic examinations were conducted at the start of the study and prior to necropsy. In the rat study, a late-onset, statistically significant increase in the incidence of benign liver cell tumors, i.e., hepatocellular adenomas, was observed in males in the 25 mg/kg/day group (9/50 vs. 2/50 in control males). One nonfatal hepatocellular carcinoma was observed in a male rat in the 25 mg/kg/day group. Although the incidence of hepatocellular adenomas in 25 mg/kg/day female rats increased (4/50 vs. 0/50 in concurrent controls), pairwise comparison showed that the increase was statistically nonsignificant. A slight, statistically nonsignificant increase in the incidence of tumors in the 12.5 mg/kg/day male rat group was also noted (6/50 vs. 2/50 in concurrent controls). Female rats in the 25 mg/kg/day group showed a statistically significant decrease in the incidence of benign mammary gland fibroadenomas. In the mouse study, no increases in tumor incidence were observed in treated animals of either gender.

Though more relevant to human exposure, the dietary studies are limited by the lack of in-cage stability studies of the food mixture. The absence of such information leaves doubt as to the actual dose received by the animals. The gavage study, however, also had limitations: the thrice-weekly high-dose gavage and possible confounding of forestomach tumors by epichlorohydrin. In the absence of a single best study, both the NTP (1985) and Stott et al. (1995) studies will be evaluated separately and used for the quantitative oral cancer assessment. The most conservative value is recommended.

The inhalation bioassay involved exposing male and female F344 rats and B6C3F1 mice (50/sex/dose) via whole-body, chamber inhalation to 0, 5, 20, or 60 ppm technical-grade 1,3-dichloropropene (92% 1,3-dichloropropene without epichlorohydrin) for 6 hours/day, 5 days/week for 2 years (Lomax et al., 1989). Two satellite groups of rats and mice (10/sex/dose group) were also exposed to 1,3-dichloropropene for 6 or 12 months, respectively. Standard protocol for chronic toxicity and carcinogenicity bioassays was followed. No clinical signs indicative of toxicity were observed in treated animals throughout the study. There were no significant differences in survival between control and treated animals. In rats, there were no statistically significant increases in primary, benign, or malignant tumors in either males or females exposed to 1,3-dichloropropene for 6, 12, or 24 months. In male mice, a statistically significant increase in the incidence of late-onset bronchioalveolar adenomas was observed in the 60 ppm group at 24 months of exposure (22/50 vs. 9/50 in controls). The increase in the incidence of benign adenomas was higher than historical control values for this tumor type (7%-32%) in B6C3F1 male mice in the same laboratory. No other treatment-related tumor effects were observed in mice of either gender.

II.A.4. Supporting Data for Carcinogenicity

In early in vitro mutagenicity testing, 1,3-dichloropropene was repeatedly screened in the Ames *Salmonella* test and usually tested positive for mutagenicity (e.g., Vithayathil et al., 1983; Stolzenberg and Hine, 1980; Haworth et al., 1983). However, in 1984, Talcott and King demonstrated that preparations of 1,3-dichloropropene assayed in vitro for mutagenic activity contained direct- acting mutagenic polar impurities. Samples of 1,3-dichloropropene tested before silicic acid chromatography were positive for mutagenic activity, whereas those tested after such purification were negative. Polar impurities isolated from 1,3-dichloropropene samples were mutagenic in the Ames *Salmonella* test. These data suggest that the mutagenic activity of 1,3-dichloropropene preparations in earlier prokaryotic tests was due to mutagenic polar impurities and not to 1,3-dichloropropene. NTP (1985) tested purified and unpurified samples of 1,3-dichloropropene for mutagenic activity and confirmed the finding of Talcott and King (1984) that uncontaminated 1,3-dichloropropene was not mutagenic in the Ames *Salmonella* test. Watson et al. (1987) also confirmed these results and reported that purification by gas chromatography can produce trace impurities that are mutagenic in bacterial assays. Although purified 1,3-dichloropropene was not directly mutagenic, Watson et al. (1987) observed mutagenic activity after the addition of washed microsomes from rat liver and showed that mutagenicity was abolished when glutathione, at normal physiological concentration, was added to the bacterial cultures. Watson et al. (1987) have suggested that 1,3-dichloropropene undergoes monooxygenase-dependent bioactivation to mutagenic metabolites only in the absence of glutathione. Schneider et al. (1998a) subsequently found that epoxidation of 1,3-dichloropropene is a minor metabolic pathway in mouse liver after administration of LD50 doses of 1,3-dichloropropene. In mouse liver microsomes in vitro, formation of the epoxides, which were mutagenic in the *Salmonella* TA100 assay, was decreased by the conjugation of 1,3-dichloropropene with glutathione. Thus, glutathione appears to provide protection against the formation of mutagenic epoxide metabolites of 1,3-dichloropropene.

Even in the absence (verified or assumed) of mutagenic impurities, 1,3-dichloropropene has produced mixed results in mammalian in vitro and in vivo genotoxicity studies. In vitro tests for DNA fragmentation in mammalian cells were positive for both V79 cells and rat hepatocytes at concentrations of 1,3-dichloropropene much larger than measured blood concentrations in pharmacokinetic studies (Martelli et al., 1993). Increased DNA fragmentation was associated with decreased glutathione. In vivo DNA fragmentation studies using doses of 62.5 mg/kg and higher in rats found DNA fragmentation in the liver, stomach mucosa, and kidney, but not in the lung, bone marrow, or brain (Ghia et al., 1993). The same study observed no increases in micronuclei in bone marrow, spleen, or hepatocytes. Ghia et al. (1993) also found no evidence of DNA repair induction in assays for unscheduled DNA synthesis.

1,3-Dichloropropene does not produce dominant lethal mutations in Wistar or F344 rats or New Zealand White rabbits, as evidenced by the absence of reproductive effects in inhalation studies by Hanley et al. (1988) and Linnett et al. (1988).

Stott et al. (1997) studied the in vitro binding potential of 1,3-dichloropropene to calf thymus DNA in the presence or absence of S9, and in the presence of S9 and glutathione. Although no evidence of DNA binding was observed under any of these treatment conditions, Schneider et al. (1998b) showed that 1,3-dichloropropene epoxides bind to deoxyguanosine in vitro.

Several genotoxicity studies indicate that 1,3-dichloropropene is mutagenic. Although some in vitro studies indicate that glutathione may protect against the mutagenic effects, there is no clear evidence that it prevents tumor formation in vivo. Thus, the presumed mechanism of action for 1,3-dichloropropene is via DNA toxicity.

II.B. Quantitative Estimate of Carcinogenic Risk from Oral Exposure

The quantitative cancer risk assessment is new to the IRIS file for 1,3-dichloropropene. The carcinogenicity assessment placed on-line on 10/01/1993 did not include quantitative risk estimates.

II.B.1. Summary of Risk Estimates

In the absence of a single best study, both the NTP (1985) and Stott et al. (1995) studies have been evaluated separately and used for the quantitative oral cancer assessment. Given that both studies have limitations for quantitative risk assessment, the most conservative slope factor, 1E-1 $(mg/kg/day)^{-1}$ for urinary bladder tumors in mice (NTP, 1985), is recommended because there is less uncertainty in the delivered dose in that study.

II.B.1.1. Oral Slope Factor

- 1E-1 per (mg/kg)/day (NTP, 1985; urinary bladder tumors)
- 5E-2 per (mg/kg)/day (NTP, 1985; liver tumors)
- 5E-2 per (mg/kg)/day (Stott et al., 1995; liver tumors)

II.B.1.2. Drinking Water Unit Risk

- 3E-6 per (µg/L) (NTP, 1985; urinary bladder tumors)
- 2E-6 per (µg/L) (NTP, 1985; liver tumors)
- 1E-6 per (µg/L) (Stott et al., 1995; liver tumors)

II.B.1.3. Extrapolation Method — linearized multistage model, extra risk

Drinking Water Concentrations at Specified Risk Levels (NTP, 1985; urinary bladder tumors):

Risk Level	Concentration
E-4 (1 in 10,000)	4E+1 µg/L
E-5 (1 in 100,000)	4E+0 µg/L
E-6 (1 in 1,000,000)	4E-1 µg/L

Drinking Water Concentrations at Specified Risk Levels (NTP, 1985; liver tumors):

Risk Level	Concentration
E-4 (1 in 10,000)	7E+1 µg/L
E-5 (1 in 100,000)	7E+0 µg/L
E-6 (1 in 1,000,000)	7E-1 µg/L

Drinking Water Concentrations at Specified Risk Levels (Stott et al., 1995; liver tumors):

Risk Level	Concentration
E-4 (1 in 10,000)	8E+1 µg/L
E-5 (1 in 100,000)	8E+0 µg/L
E-6 (1 in 1,000,000)	8E-1 µg/L

II.B.2. Dose-Response Data (Carcinogenicity, Oral Exposure)

Tumor Type: urinary bladder carcinoma
Test animals: female mouse
Route: oral, gavage
Source: NTP, 1985

Administered Dose (mg/kg/event)	Human Equivalent Dose (mg/kg/day)	Tumor Incidence
0	0	0/50
50	2.88	8/50
100	5.81	21/47

Tumor type -- hepatocellular adenoma/carcinoma
Test animals — male rat
Route — oral, gavage
Source -- NTP, 1985

Administered Dose (mg/kg/event)	Human Equivalent Dose (mg/kg/day)	Tumor Incidence
0	0	1/49
25	2.75	6/48
50	5.4	8/50

Tumor type -- hepatocellular adenoma/carcinoma
Test animals — male rat

Route — oral, dietary
Source -- Stott et al., 1995

Administered Dose (mg/kg/event)	Human Equivalent Dose (mg/kg/day)	Tumor Incidence
0	0	2/49
2.5	0.65	1/50
12.5	3.22	6/50
25	6.31	10/49

II.B.3. Additional Comments (Carcinogenicity, Oral Exposure)

Because there was concordance in rat liver tumors in both the gavage (NTP, 1985) and feeding studies (Stott et al., 1995), these tumors were chosen for quantitative assessment. The forestomach tumor data in rats and mice in the NTP (1985) study were not chosen because of the confounding effects of epichlorohydrin in the formulation and because the tumors did not appear in the feeding studies (Stott et al., 1995; Redmond et al., 1995). The male mouse tumor data in the NTP study (bronchioalveolar adenoma/carcinoma) are unacceptable for quantitative assessment; the control group survival was inadequate because of early deaths attributed to myocarditis. Although the urinary bladder tumors in female mice in the gavage study (NTP, 1985) were not observed in the feeding study (Redmond et al., 1995), these data were chosen for quantitative assessment because transitional cell carcinoma of the bladder is a rare tumor and because the dosing for mice in the feeding study may have been inadequate.

Administered doses for the gavage study (NTP, 1985) were averaged over 7 days/week. All doses were adjusted to human equivalent doses by multiplying by (animal body weight/human body weight)$^{1/4}$ with human body weight = 70 kg and animal body weight = final weight at the end of the study. Both the multistage model with extra risk (per proposed cancer risk assessment guidelines; U.S. EPA, 1996) and the linearized multistage model (per existing cancer risk assessment guidelines; U.S. EPA, 1987) were used to calculate the cancer slope factors. Although the cancer slope factors for both methods were similar (U.S. EPA, 2000, Appendix A, Section II.A-C), those from the linearized multistage model are reported here

because the proposed guidelines have not been finalized. The cancer slope factors are 1E-1 for urinary bladder tumors in mice, 5E-2 for rat liver adenoma/carcinoma (NTP, 1985), and 5E-2 for rat liver adenoma/carcinoma (Stott et al., 1995). The most conservative factor, 1E-1 per (mg/kg)/day, is recommended.

II.B.4. Discussion of Confidence (Carcinogenicity, Oral Exposure)

Confidence in the database is medium to high. Two chronic bioassays were available for both rats and mice. Limitations of the gavage studies included the bolus dosing and the thrice-weekly rate of administration, which are not relevant to human exposure. In addition, the 1,3-dichloropropene formulation contained epichlorohydrin, a known carcinogen. Inadequate dosing is suspected for the Redmond et al. (1995) study because of the lack of in-cage stability data for the microencapsulated 1,3-dichloropropene in feed and the lack of cancer (urinary bladder tumors) and noncancer effects (urinary bladder hyperplasia, forestomach hyperplasia, and hydronephrosis) seen in mice in the gavage study (NTP, 1985). In the absence of a single best study, both the NTP (1985) and Stott et al. (1995) studies were used for the quantitative cancer assessment. Major database uncertainties are the importance of 1,3 dichloropropene's mutagenic potential in a whole-animal system and the mechanism of tumorigenic action. The results from short-term mutagenicity assays for the parent compound are mixed, and although 1,3-dichloropropene is metabolized to mutagenic epoxides at ~LD_{50} doses, the extent of epoxide formation in vivo at the low doses characteristic of chronic exposure is unknown. In vitro assays indicated that the presence of glutathione decreases epoxide formation and abolishes or greatly reduces the mutagenic response, but evidence of protection against tumor formation is lacking. Thus, the linear quantitative assessment provides a conservative estimate of cancer potency.

II.C. Quantitative Estimate of Carcinogenic Risk from Inhalation Exposure

II.C.1. Summary of Risk Estimates

II.C.1.1. Inhalation Unit Risk — 4E-6 risk per µg/m^3

II.C.1.2. Extrapolation Method — linearized multistage model, extra risk

Air Concentrations at Specified Risk Levels:

Risk Level	Concentration
E-4 (1 in 10,000)	2E+1 μg/m^3
E-5 (1 in 100,000)	2E-0 μg/m^3
E-6 (1 in 1,000,000)	2E-1 μg/m^3

II.C.2. Dose-Response Data for Carcinogenicity, Inhalation Exposure

Tumor Type: bronchioalveolar adenoma
Test animals: male mouse
Route: inhalation
Source: Lomax et al., 1989

Administered Dose (mg/m^3)	Human Equivalent Concentration (mg/m^3) [1,2]	Tumor Incidence
0	0	9/50
22.7	3.7	6/40
90.8	15	13/50
272	45	22/50

[1] Correction for purity of formulation concentration (92%) and correction for intermittent exposure to continuous exposure: 22.7 mg/m^3 $\times$ 0.92 $\times$ 6/24 hrs $\times$ 5/7 days = 3.7 mg/m^3.
[2] Correction for thoracic effects using RGDR(TH) of 3.21 as described in II.C.3.

II.C.3. Additional Comments (Carcinogenicity, Inhalation Exposure)

The critical study for assessment of cancer inhalation potency is the study by Lomax et al. (1989) in which rats and mice were exposed to up to 272 mg/m^3 1,3-dichloropropene vapors for 6 hours/day, 5 days/week for 2 years. This is a well-designed and well-conducted bioassay that followed standard guidelines. Epoxidized soybean oil was the stabilizing agent in the formulation of 1,3-dichloropropene, which eliminated possible confounding effects of epichlorohydrin. Lomax et al. (1989) is the only available 2-year inhalation bioassay. Confidence in this study is supported by the results of a 90-day subchronic study (Stott et al., 1988), which are consistent with the Lomax et al. (1989) bioassay findings.

The only neoplastic response observed in any species or sex was an increased incidence of bronchioalveolar adenomas with late onset, in male mice in the highest dose group. The incidence in the high-dose group exceeded the range of historical control rates among mice in the same laboratory.

The administered dose was adjusted for purity and for continuous exposure as shown in the notes for Section II.C.2. Algorithms for the thoracic effects of Category 1 gases were used to adjust animal exposure concentrations of 1,3-dichloropropene to HECs (U.S. EPA, 1994). The HEC for a Category 1 gas is derived by multiplying the duration- and purity-adjusted exposure concentrations by an interspecies dosimetric adjustment for gas: respiratory effects in the tracheobronchial and pulmonary (i.e., thoracic) regions of the lung, according to the following calculation (U.S. EPA, 1994):

$$RGDR(TH) = (MV_a/S_a)/(MV_h/S_h)$$

RGDR(TH)= regional gas dose ratio for the thoracic (tracheobronchial and pulmonary) area of the lung

MV_a = animal minute volume (mouse = 0.041 L/min)

MV_h = human minute volume (13.8 L/min)

S_a = surface area of the thoracic region of the animal lung (mouse = 503.5 cm^2), and

S_h = surface area of the thoracic region of the human lung (543,200 cm^2).

Using default values, the RGDR(TH) = (0.041/503.5)/(13.8/543,200) = 3.21.

Using the duration-adjusted HECs and tumor incidences, both the multistage model with extra risk (per proposed cancer risk assessment guidelines; U.S. EPA, 1996) and the linearized multistage model (per existing cancer risk assessment guidelines; U.S. EPA, 1987) were used to calculate unit risk. Although the unit risk from both methods was similar (U.S. EPA, 2000, Appendix A, Section II.D), those from the linearized multistage model are reported here because the proposed guidelines have not been finalized. The unit risk (i.e., risk at $1 \, \mu g/m^3$) is 4E-6 risk per $\mu g/m^3$.

II.C.4. Discussion of Confidence (Carcinogenicity, Inhalation Exposure)

Confidence in the database is medium. One well-conducted study was available for rodent exposure via inhalation. Confidence in the study is increased by site concordance with mouse tumors in the NTP (1985) gavage study. Major database uncertainties are the importance of the mutagenic potential of 1,3-dichloropropene in a whole-animal system and the precise mechanism of tumorigenic action. The results from short-term mutagenicity assays for the parent compound are mixed, and although 1,3-dichloropropene is metabolized to mutagenic epoxides at ~LD_{50} doses, the extent of epoxide formation in vivo at the low doses characteristic of chronic exposure is unknown. In vitro assays indicated that the presence of glutathione decreases epoxide formation and abolishes or greatly reduces the mutagenic response, but evidence of protection against tumor formation is lacking. Thus, the linear quantitative assessment provides a very conservative estimate of cancer potency.

II.D. EPA Documentation, Review, and Contacts (Carcinogenicity Assessment)

II.D.1. EPA Documentation

Source Document — U.S. EPA, 2000

This assessment was peer reviewed by external scientists. Their comments have been evaluated carefully and incorporated in finalization of this IRIS Summary. A record of these comments is included as an appendix to the Toxicological Review for 1,3-Dichloropropene. *To review this appendix, exit to the toxicological review, Appendix B, Summary of and Response to External Peer Review Comments (PDF)*.

II.D.2. EPA Review (Carcinogenicity Assessment)

Agency Consensus Date — 04/20/00

Screening-Level Literature Review Findings — A screening-level review conducted by an EPA contractor of the more recent toxicology literature pertinent to the cancer assessment for 1,3-Dichloropropene (DCP) conducted in August 2003 did not identify any critical new studies. IRIS users who know of important new studies may provide that information to the IRIS Hotline at hotline.iris@epa.gov or 202-566-1676.

II.D.3. EPA Contacts (Carcinogenicity Assessment)

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202)566-1676 (phone), (202)566-1749 (fax), or hotline.iris@epa.gov (Internet address).

III. [reserved]
IV. [reserved]
V. [reserved]

VI. Bibliography

Substance Name — 1,3-Dichloropropene (DCP)
CASRN — 542-75-6

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VII. Revision History

Substance Name — 1,3-Dichloropropene (DCP)
CASRN — 542-75-6

Date	Section	Description
09/26/1988	II.	Carcinogen summary on-line
10/01/1989	II.B.	Oral quantitative risk estimate has been withdrawn
01/01/1991	I.B.	Inhalation RfC summary on-line
05/25/2000	I.A	Revised RfD, RFC and carcinogen summary; Oral cancer potency and inhalation cancer potency added
10/28/2003	I.A.6., I.B.6., II.D.2.	Screening-Level Literature Review Findings message has been added.

VIII. Synonyms

Substance Name — 1,3-Dichloropropene (DCP)
CASRN — 542-75-6
Last Revised — 05/25/2000

- 542-75-6
- 3-CHLOROALLYL CHLORIDE
- alpha-CHLOROALLYL CHLORIDE
- gamma-CHLOROALLYL CHLORIDE
- 3-CHLOROPROPENYL CHLORIDE
- DCP
- DICHLOROPROPENE
- 1,3-DICHLOROPROPENE-1
- 1,3-Dichloropropene
- 1,3-DICHLORO-2-PROPENE
- Dichloropropene, 1,3-
- 1,3-DICHLOROPROPYLENE
- alpha,gamma-DICHLOROPROPYLENE
- NCI-C03985
- PROPENE, 1,3-DICHLORO-
- RCRA WASTE NUMBER U084
- Telone II