Public Health Goal for 1,3-Dichloropropene In Drinking Water

Prepared by

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PREFACE

Drinking Water Public Health Goals

Pesticide and Environmental Toxicology Section

Office of Environmental Health Hazard Assessment

California Environmental Protection Agency

This Public Health Goal (PHG) technical support document provides information on health effects from contaminants in drinking water. PHGs are developed for chemical contaminants based on the best available toxicological data in the scientific literature. These documents and the analyses contained in them provide estimates of the levels of contaminants in drinking water that would pose no significant health risk to individuals consuming the water on a daily basis over a lifetime.

The California Safe Drinking Water Act of 1996 (amended Health and Safety Code, Section 116365) requires the Office of Environmental Health Hazard Assessment (OEHHA) to perform risk assessments and adopt PHGs for contaminants in drinking water based exclusively on public health considerations. The Act requires that PHGs be set in accordance with the following criteria:

1. PHGs for acutely toxic substances shall be set at levels at which no known or anticipated adverse effects on health will occur, with an adequate margin of safety.
2. PHGs for carcinogens or other substances which can cause chronic disease shall be based solely on health effects without regard to cost impacts and shall be set at levels which OEHHA has determined do not pose any significant risk to health.
3. To the extent the information is available, OEHHA shall consider possible synergistic effects resulting from exposure to two or more contaminants.
4. OEHHA shall consider the existence of groups in the population that are more susceptible to adverse effects of the contaminants than a normal healthy adult.
5. OEHHA shall consider the contaminant exposure and body burden levels that alter physiological function or structure in a manner that may significantly increase the risk of illness.
6. In cases of insufficient data to determine a level of no anticipated risk, OEHHA shall set the PHG at a level that is protective of public health with an adequate margin of safety.
7. In cases where scientific evidence demonstrates that a safe dose-response threshold for a contaminant exists, then the PHG should be set at that threshold.
8. The PHG may be set at zero if necessary to satisfy the requirements listed above.
9. OEHHA shall consider exposure to contaminants in media other than drinking water, including food and air and the resulting body burden.
10. PHGs adopted by OEHHA shall be reviewed every five years and revised as necessary based on the availability of new scientific data.

PHGs adopted by OEHHA are for use by the California Department of Health Services (DHS) in establishing primary drinking water standards (State Maximum Contaminant Levels, or MCLs). Whereas PHGs are to be based solely on scientific and public health considerations without regard

to economic cost considerations, drinking water standards adopted by DHS are to consider economic factors and technical feasibility. Each standard adopted shall be set at a level that is as close as feasible to the corresponding PHG, placing emphasis on the protection of public health. PHGs established by OEHHA are not regulatory in nature and represent only non-mandatory goals. By federal law, MCLs established by DHS must be at least as stringent as the federal MCL if one exists.

PHG documents are used to provide technical assistance to DHS, and they are also informative reference materials for federal, state and local public health officials and the public. While the PHGs are calculated for single chemicals only, they may, if the information is available, address hazards associated with the interactions of contaminants in mixtures. Further, PHGs are derived for drinking water only and are not to be utilized as target levels for the contamination of other environmental media.

Additional information on PHGs can be obtained at the OEHHA web site at www.oehha.ca.gov.

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PUBLIC HEALTH GOAL FOR 1,3-DICHLOROPROPENE IN DRINKING WATER

SUMMARY

OEHHA has developed a Public Health Goal (PHG) of 0.2 μg/L (0.2 ppb) for 1,3-dichloropropene (1,3-DCP) in drinking water, based on carcinogenic effects observed in mice. A 1985 National Toxicology Program (NTP) two-year gavage study provided evidence of increased incidence of urinary bladder transitional cell carcinomas in female mice administered 50 or 100 mg Telone® II (92% 1,3-DCP) per kg body weight per day. OEHHA followed the recommended practices of the 1996 United States Environmental Protection Agency (U.S. EPA) proposed draft guidelines for carcinogen risk assessment. Cancer potency estimates were made by fitting the linearized multistage model to the experimental data to establish the lower 95% confidence bound on the dose associated with a 10% increased risk of cancer (LED_{10}). The PHG was calculated based on a *de minimis* theoretical excess individual cancer risk level of 10^{-6} from exposure to 1,3-DCP. Based on these considerations, OEHHA has developed a PHG of 0.2 μg/L (0.2 ppb) for 1,3-DCP in drinking water. The health-protective concentration of 1,3-DCP in drinking water for a non-cancer endpoint is 90 ppb. This is calculated from a NOAEL of 2.5 mg/kg-day, based on body weight depression and hyperplasia of the non-glandular stomach mucosa of rats administered 12.5 (LOAEL) or 25 mg/kg-day of Telone® II (96% 1,3-DCP) in the diet for two years. An uncertainty factor of 100 was applied to account for interspecies extrapolation and potentially sensitive human subpopulations.

INTRODUCTION

The purpose of this document is to develop a PHG for 1,3-DCP. A Maximum Contaminant Level (MCL) of 0.5 μg/L (0.0005 mg/L, or 0.5 ppb) was established by the California Department of Health Services (DHS) in 1988 (DHS, 1988b). A federal Maximum Contaminant Level Goal (MCLG) of zero mg/L for 1,3-DCP is tentative (not officially proposed) (U.S. EPA, 1996b).

Under the Safe Drinking Water and Toxic Enforcement Act of 1986 (Proposition 65), 1,3-DCP is listed as a chemical known to the state to cause cancer. The International Agency for Research on Cancer (IARC) has classified 1,3-DCP as a Group 2B chemical, possibly carcinogenic to humans (IARC, 1987). 1,3-DCP also is listed in the NTP's seventh annual report on carcinogens as a compound "reasonably anticipated" to be a carcinogen (NTP, 1994). U.S. EPA has classified 1,3-DCP as a B2 chemical, a probable human carcinogen (U.S. EPA, 1998).

In this document, we evaluated the available data on the toxicity of 1,3-DCP, primarily by the oral route, and included information made available since the previous assessment done by OEHHA (formerly in DHS) (DHS, 1988a). To determine a public health-protective level of 1,3-DCP in drinking water, we identified and considered sensitive human subpopulations.

CHEMICAL PROFILE

Chemical Identity

1,3-DCP, a chlorinated hydrocarbon, is a mixture of approximately equal amounts of cis- and trans-isomers. The chemical formula, structure, synonyms and CAS Registry numbers are listed in Table 1.

Table 1. Chemical Identity of 1,3-Dichloropropene

Chemical name	1,3-dichloropropene
Synonyms	3-chloroallyl chloride; 1,3-dichloro-1-propene; 1,3-dichloropropylene; 1,3-D; 1,3-DCP
Registered trade names	Telone®; Telone® II; DD®
Chemical formula	$C_3H_4Cl_2$
Chemical structure	$Cl\text{-}CH_2\text{-}CH{=}CH\text{-}Cl$
CAS Registry numbers	542-75-6 (cis- and trans- isomers); cis-isomer: 10061-01-5; trans-isomer: 10061-02-6

From: ATSDR, 1992; HSDB, 1997

Physical and Chemical Properties

Important physical and chemical properties of 1,3-DCP are given in Table 2. 1,3-DCP is miscible in several solvents and is highly volatile.

Production and Uses

1,3-DCP, the active ingredient in Telone® II, was introduced in 1945 as a commercial pre-plant soil fumigant for the control of nematodes in various food and nonfood crops (Hayes and Laws, 1991).

1,3-DCP is produced either by high-temperature chlorination of propylene or more typically from 1,3-dichloro-2-propanol by dehydration with phosphorus oxychloride ($POCl_3$) or with phosphorus pentaoxide (P_2O_5) in benzene (Budavari, 1989; HSDB, 1997).

Amounts of 1,3-DCP in formulations or preparations have changed over the years with the introduction of newer formulations (78% in Telone, 92 % to 98% in Telone® II) (Osterloh et al., 1984). Telone® II originally was formulated with epichlorohydrin as a stabilizer; this has been replaced with epoxidized soybean oil. 1,3-DCP also is combined with 1,2-dichloropropane (DD® mixtures) and with chloropicrin (Telone C-17) (ATSDR, 1992).

Other ingredients that may be found in Telone® II formulations include mixtures of chlorinated hexenes, hexanes, and hexadienes, cis-1,3,3-trichloropropene-1, and propylene dichloride (1,2-dichloropropane) (DowElanco, 1991).

Table 2. Physical and Chemical Properties of 1,3-Dichloropropene

Property	Value or Information
Molecular weight	110.98 g/mol
Color	Colorless to straw-colored
Physical state	Liquid; exists as mixture of cis- and trans- isomers
Odor	Sharp, sweet, irritating; chloroform-like odor
Odor threshold	1 ppm
Boiling point	104°C (cis); 112°C (trans)
Freezing point	-84.5°C
Flash point	28°C
Flammability limits	5.3% to 14.5% (80°C)
Autoignition temperature	>500°C
Solubility	
Water (at 25°C);	cis: 2.18 g/L; trans: 2.32 g/L
Organic solvents	Miscible in acetone, benzene, ethanol, methanol, carbon tetrachloride, chloroform, octane, toluene
Specific Gravity	cis: 1.214 (20°C); trans: 1.209 (25°C)
Density	cis: 1.217 g/mL; trans: 1.224 g/mL
Partition coefficients	
K_{ow}, Octanol-water	cis: 116 (25°C); trans: 107 (25°C)
Log K_{ow}	cis: 1.82 (20°C); trans: 2.22 (25°C)
	1.4-2.0 (1,3-dichloropropene)
K_{oc}, Organic matter (soil)-water	cis: 14; trans: 15
Log K_{oc}	cis: 1.36; trans: 1.41
Vapor pressure (mm Hg at 25°C)	cis: 34.4; trans: 23.0
Henry's law constant (atm-m^3/gmol)	cis: 1.8 x 10^{-3}; trans: 1.05 x 10^{-3}
Conversion factor (91.2% 1,3-DCP)	1 ppm = 4.54 mg/m^3 (25°C)

From: ATSDR (1992); DowElanco (1991); HSDB (1997); NIOSH (1994); WHO (1993)

Recent U.S. production information was not found, but U.S. EPA estimated that 38 to 43 million pounds of dichloropropene were used in U.S. agriculture in 1995 (Aspelin, 1997). Nearly 410,000 pounds of 1,3-DCP were used in California in 1995 (DPR, 1996a). Telone® II may be used in any county in California with a use permit. Currently, no more than 5,000 gallons of Telone® II may be applied per township (36 square mile area) (DPR, 1996b).

ENVIRONMENTAL OCCURRENCE AND HUMAN EXPOSURE

1,3-DCP is released into the air and in wastewater during its production and use as a soil fumigant and chemical intermediate (WHO, 1993). When used as a soil fumigant, 1,3-DCP is injected into the soil, and the soil surface is compacted to seal in the fumigant. Volatilization occurs from the soil surface and decreases to negligible amounts after approximately four weeks. Factors such as soil type, temperature, and moisture content, and application depth influence the volatilization of 1,3-DCP from soil. Dichloropropenes can enter aquatic sources as discharges from industrial and municipal effluents and through run-off from agricultural land, but they tend to disappear rapidly due to a relatively low water solubility and high volatility.

Based on its vapor pressure and occupational use, the inhalation of 1,3-DCP vapors represents the primary potential route of human exposure to 1,3-DCP. Other possible exposure scenarios are ingestion of contaminated foodstuffs or drinking water, accidental ingestion during field application or manufacture of 1,3-DCP and its products, or dermal contact.

Air

Ambient air monitoring for Telone® II (1,3-DCP) was conducted in Merced County, California, during March and April 1995, the months during which the fumigant was applied (ARB, 1995). The 24-hour concentrations taken at five different sites ranged from 0.11 $\mu g/m^3$ to 7.4 $\mu g/m^3$. Similar monitoring was conducted in Kern County from May to December 1995 (ARB, 1996). The 24-hour concentrations ranged from 0.10 $\mu g/m^3$ (the minimum detection limit) to 27.0 $\mu g/m^3$. No Telone® II applications were made from August 10 through November 10, 1995.

Houtman (1993) evaluated worker exposures to 1,3-DCP during Telone® II loading, application, and re-entry activities in eastern Washington using biological and air monitoring. Biological monitoring results indicated exposures ranging from 26.52 $\mu g/m^3$ to 5,078.75 $\mu g/m^3$, whereas air monitoring results indicated potential exposures ranging from 81.84 $\mu g/m^3$ to 3,487.68 $\mu g/m^3$ 1,3-DCP.

Environmental and biological monitoring of voluntary bystanders exposed to 1,3-DCP via inhalation was performed by van Welie et al. (1991) during field application of 1,3-DCP in the Dutch flower-bulb culture. The use of bystanders simulated non-occupational or residential exposure to the fumigant. The volunteers were located downwind along the edges of treated fields from the start until the end of pesticide application. Exposures to cis- and trans-1,3-DCP ranged from non-detectable levels (0.09 mg/m^3 8-hour TWA) to 1.12 mg/m^3 8-hour TWA for cis-1,3-DCP. Maximal urinary concentrations of the mercapturic acid metabolite were 16.86 mg/L for the cis-isomer and 7.28 mg/L for the trans-isomer. Excretion of the mercapturic acid metabolites of 1,3-DCP was strongly correlated with air exposure levels ($r = 0.92$ and 0.94 for cis- and trans-1,3-DCP, respectively).

Soil

The mean concentration of 1,3-DCP in soil for 341 observations was 5.44 ppb (dry weight basis), and the maximum level was 500 ppb (HSDB, 1997 citing Smith et al., 1985).

Water

From July 1, 1995 to June 30, 1996, 1,435 wells in 35 counties were monitored for 1,2-dichloropropane plus 1,3-DCP plus C-3 compounds and 248 wells in three counties were monitored for 1,3-DCP alone (DPR, 1997). 1,3-DCP was not detected in any of the wells (minimum detection limit not provided). In areas of California where soil fumigants containing 1,3-DCP had been applied for over 15 years, 1,3-DCP was not detected in any of the 54 municipal wells examined (limit of detection = 0.1 µg/L) (Maddy et al., 1982).

Concentrations of 1,3-DCP up to 18 µg/L were detected in groundwater contaminated by leachates from municipal landfills in New York, Minnesota, and Wisconsin (ATSDR, 1992 citing Sabel and Clark, 1984).

Some production of 1,3-DCP (<1 µg/L) is thought to occur via the chlorination of organic matter during the disinfecting of drinking water and wastewater (HSDB, 1997 and WHO, 1993, citing Krijgsheld and Van der Gen, 1986).

Food

Since 1,3-DCP is used as a pre-plant soil fumigant, it is not expected to be taken up into food crops. Residues of 1,3-DCP in edible crop commodities treated with "MIX D/D" (not less than 50% 1,3-DCP) were generally below the limit of detection (<0.01 mg/kg) (WHO, 1993). Uptake of radioactivity was measured in potato tubers planted six months after treating sandy loam soil with cis- and trans-[^{14}C]-1,3-DCP and [^{14}C]-1,2-dichloropropane (Roberts and Stoydin, 1976). The total radioactivity in the tubers, expressed as 1,3-DCP equivalents, was 7 µg/kg. However, the authors did not determine if the radioactivity was from the 1,3-DCP, 1,2-dichloropropane, or various metabolites of these compounds. Berry et al. (1980) found that [^{14}C]-1,3-DCP applied to vermiculite or sand was absorbed by tomato plants, bush beans, and carrots, rapidly translocated, and metabolized to 3-chloroacrylic acid. [^{14}C]-label from the parent compound or metabolites was rapidly metabolized in the plants to normal plant products. The half-life of 1,3-DCP in the plants was 1.5 hours.

METABOLISM AND PHARMACOKINETICS

Absorption

Hutson et al. (1971) reported that 80% to 90% of cis- or trans-1,3-dichloro[2-^{14}C]propene administered orally by gavage to rats was eliminated in the urine, feces and expired air within 24 hours.

Rats absorbed about 50% of inhaled vapors with nose-only exposure to 90 or 150 ppm 1,3-DCP (Stott and Kastl, 1986). Approximately 50% of the inhaled dose was absorbed in the lungs, with a small amount via the nasal mucosa (11% to 16%). The absorption of 1,3-DCP by rats exposed via inhalation to 30, 90, 300, or 900 ppm did not increase proportionately with increasing exposure level. A decrease in the respiratory rate at exposures ≥90 ppm and a decrease in the respiratory minute volume at 300 and 900 ppm was partially responsible for the lack of proportional absorption (Stott and Kastl, 1986).

In human male volunteers exposed to 1 ppm 1,3-DCP (50.6% cis and 45.2% trans) via inhalation for six hours, the calculated percent of the inhaled dose that was absorbed was: cis-1,3-DCP, 72% to 80%, and trans-1,3-DCP, 77% to 82% (Waechter et al., 1992).

Five adult volunteers (one female and four male) were exposed only on the arm to 1,3-DCP vapor concentrations of 86±4 mg/m^3 for 45 minutes (Kezic et al., 1996). Absorption was estimated by analysis of urine for the presence of the mercapturic acid conjugate of 1,3-DCP. The authors estimated dermal absorption was approximately 2-5% of that from inhalation exposure.

Distribution

Less than 2% of the [^{14}C]-1,3-DCP dose administered orally to rats was found in the carcass, skin, and gut as ^{14}C (Hutson et al., 1971). Similar results (2% to 6% in carcasses) were reported for both rats and mice by Dietz et al. (1984a). After oral administration of 0, 1, 50, or 100 mg/kg of [^{14}C]-1,3-DCP to rats and mice, [^{14}C]-activity was greatest in the forestomach and glandular stomach, with limited binding in the liver, kidneys, or bladder (Dietz et al., 1984b).

Metabolism

1,3-DCP is metabolized predominantly by conjugation with reduced glutathione (GSH). The glutathione conjugate, *S*-[3-chloroprop-2-enyl]glutathione (GSCP), is further metabolized to the corresponding mercapturic acid, *N*-acetyl-*S*-[3-chloroprop-2-enyl]cysteine (3C-NAC), which is then excreted in the urine (Climie et al., 1979; Dietz et al., 1984a; Hutson et al., 1971; Osterloh et al., 1984). The mercapturic acid metabolite may undergo further biotransformation to the sulfoxide or sulfone (Dietz et al., 1984a). A proposed minor metabolic pathway is the mono-oxygenase-catalyzed oxygenation of cis-1,3-DCP, leading to the formation of cis-1,3-dichloropropene-oxide (WHO, 1993, citing Van Sittert, 1989). The oxide also may undergo hydrolysis to 2-chloroacrolein.

The cis-1,3-DCP isomer is metabolized more quickly than the trans-isomer, based on concentration of cis- or trans-1,3-DCP in human blood or urine, and accounting for the proportions of cis- and trans-isomers in the administered dose (Waechter et al., 1992).

GSH was decreased in a dose-dependent manner in tissues consistent with the portal of entry: with the oral route, GSH was decreased in the forestomach, and to a lesser extent, the glandular stomach and liver (Dietz, 1984b). With inhalation exposure, GSH was decreased in the nasal tissue, and to a lesser extent lung and liver (Fisher and Kilgore, 1988).

The elimination of the glutathione conjugate of 1,3-DCP from blood, following a one-hour, nose-only inhalation exposure of rats to 78 to 404 ppm 1,3-DCP, best fit a one-compartment model and appeared to be independent of the dose (Fisher and Kilgore, 1989). The elimination half-life of GSCP in blood was approximately 17 hours (Fisher and Kilgore, 1989).

Excretion

The major route of excretion of 1,3-DCP is urine. Generally, more than 80% of the administered dose to humans, rats or mice, whether via the inhalation or oral route, was excreted in urine within 24 hours after exposure (Climie et al., 1979; Hutson et al., 1971; Waechter et al., 1992). Other routes of excretion in rats or mice include feces and expired air (primarily as CO_2) (Dietz et al., 1984a; Hutson et al., 1971). More of the cis- than trans-1,3-DCP isomer was recovered in urine collected from humans (2.5 to 8 times more cis-3C-NAC) and rats (80.7% vs. 56.5% of administered dose as [^{14}C]-1,3-DCP derived radioactivity, respectively) (Waechter et al., 1992; Hutson et al., 1971). However, rats administered 1,3-DCP orally had less cis-isomer as [^{14}C]CO_2 in expired air than trans-isomer (3.9% vs. 23.6%, respectively) (Hutson et al., 1971).

The amount of cis-3C-NAC excreted in urine over a 24-hour period by workers exposed to 1,3-DCP was highly correlated (correlation coefficient = 0.83) with the time-weighted exposure product (exposure duration [hours] $\times$ air concentration of 1,3-DCP [mg/m^3]) (Osterloh et al., 1984).

Waechter et al. (1992) proposed a biphasic model for the elimination of 1,3-DCP from human subjects. The model has a well-perfused compartment and a poorly perfused compartment (adipose) because of a slower second elimination phase. The urinary half-life of cis-3C-NAC was 4.2 hours and 12.3 hours for the first and second phases, respectively, and of trans-3-C-NAC was 3.2 hours and 17.1 hours for the first and second phases, respectively (Waechter et al., 1992).

TOXICOLOGY

Toxicological Effects in Animals

Acute Toxicity

The acute oral LD_{50} of 1,3-DCP in rats ranged from 57 mg/kg to 726 mg/kg and in mice from 215 mg/kg to 749 mg/kg, depending on the purity of 1,3-DCP, and the rodent sex and strain used (WHO, 1993). Signs of toxicity following oral administration included: hunched posture, lethargy, pilo-erection, decreased respiratory rate, ptosis, diarrhea, diuresis, ataxia, tip-toe gait, red/brown staining around the snout, tremors, emaciation, and pallor of extremities. The lungs and gastrointestinal tract showed signs of hemorrhage and congestion, and the liver showed patchy areas of pallor (WHO, 1993).

The acute four-hour inhalation LC_{50} value for 1,3-DCP vapor in rats ranged from 2,700 mg/m^3 to 5,403 mg/m^3 and varied with the chemical purity and animal sex and strain (WHO, 1993). The following signs of toxicity were observed during the exposure and observation periods: pilo-erection, salivation, lacrimation and partial closing of eyes, lethargy, diarrhea, reduced and irregular respiratory rate, hunched posture, brown staining of fur, reddening of ears, tail, and feet. Pathological examination revealed signs of cardiopulmonary failure, acute renal tubular necrosis, and local respiratory tract effects.

The acute dermal LD_{50} was >1,211 mg/kg in mice (JCL:ICR) and 504 mg/kg in rabbits (strain not specified) (WHO, 1993). For rats, the dermal LD_{50} ranged from 423 to 2,000 mg/kg, depending on the sex and strain and the purity of the 1,3-DCP testing solution. The signs of acute toxicity for dermal exposure were similar to those listed above for the oral and inhalation routes, but also included edema, eschar formation, or subcutaneous hemorrhage (WHO, 1993).

Slight to moderate erythema and moderate to severe edema was observed following application of 0.5 mL of Telone® II to the shaved skin of New Zealand White rabbits for four hours (WHO, 1993, citing Jeffrey, 1987a). The dermal irritation was still present in some of the animals after 14 days. Instillation of 0.1 mL of Telone® II into one eye of New Zealand White rabbits caused marked conjunctival redness and chemosis, which was reversible in 14 days (WHO, 1993, citing Jeffrey, 1987b).

Subchronic Toxicity

The subchronic toxicity of 1,3-DCP via ingestion and inhalation has been studied in rats and mice. Haut et al. (1996) administered 1,3-DCP (95.8% purity, microencapsulated in a starch/sucrose mixture) via the diet to groups of Fischer 344 rats and B6C3F1 mice (ten each/sex/dose) for 13 weeks. Dose levels were 0, 5, 15, 50, or 100 mg/kg-day for rats and 0, 15, 50, 100, or 175 mg/kg-day for mice. Additional rats (ten/sex at 0 and 100 mg/kg-day) were fed control rodent chow for four weeks after the 13-week dosing period to allow for recovery and to examine the reversibility of any adverse effects from exposure to 1,3-DCP. Mean body weights of male rats ingesting ≥5 mg/kg-day and females ingesting ≥15 mg/kg-day were significantly lower than controls, and the decrease was dose-related. Mean body weights of male and female mice ingesting ≥15 mg/kg-day also were decreased in a dose-related manner compared to controls. Basal cell hyperplasia of the nonglandular stomach mucosa was observed in male and female rats at dose levels ≥15 mg/kg-day. Hyperkeratosis of the nonglandular stomach mucosa was observed in male and female rats treated at ≥50 mg/kg-day and in one male at 15 mg/kg-day. The major histopathological effect in mice was a slight decrease in hepatocyte size in males receiving ≥15 mg/kg-day 1,3-DCP. The authors stated that this effect was consistent with decreased cytoplasmic glycogen, which could result from the body weight depression in mice at the same doses.

Fischer 344 rats and B6C3F1 mice (ten/sex/exposure level) were administered 1,3-DCP (90.9% purity, stabilized with 1.2% epichlorohydrin) via inhalation at exposure levels of 0, 10, 30, 90, and 150 ppm (0, 45.4, 136, 409, and 681 mg/m^3, respectively) for six hours/day, five days/week for 13 weeks (Stott et al., 1988). The body weights of male and female rats exposed to 90 or 150 ppm were significantly decreased in a dose-related manner compared to control rats. A treatment-related depression in body weights of male and female mice exposed to 90 and 150 ppm 1,3-DCP also was observed. Statistically significant differences occurred in the 150 ppm group only, beginning at the third week of exposure to study

termination. Slight hyperplasia of the respiratory epithelium was present in male and female rats and mice exposed to 90 or 150 ppm 1,3-DCP and in 2/10 male rats exposed to 30 ppm. Slight degeneration of olfactory epithelium was observed in male and female rats exposed to 150 ppm and male and female mice exposed to 90 or 150 ppm 1,3-DCP. Male and female mice exposed to 150 ppm also had slight multifocal respiratory metaplasia of the olfactory epithelium. Moderate hyperplasia of the urinary bladder epithelial cells was present only in female mice at the 90 and 150 ppm exposure levels. Submucosal lymphoid cells were observed in some of these mice (6/9 and 4/9, respectively), but were present in the control (2/10), 10 ppm (3/10), and 30 ppm groups (9/10) as well.

Genetic Toxicity

Salmonella Reversion Assay

Telone® II, D-D®, cis- and trans-1,3-dichloropropene were found to be mutagenic in *Salmonella* strains TA1535 and TA100 both with and without metabolic activation and weakly mutagenic in strain TA1978 (De Lorenzo et al., 1977). The cis- and trans-isomers of 1,3-DCP (99.75% and 97.46% pure, respectively, with 3,3-dichloropropene and 1,2-dichloropropane as impurities) were found to be mutagenic in *Salmonella typhimurium* strains TA1535, TA1537, and TA1538 (Neudecker et al., 1977). In this study it was noted that mutagenicity and cytotoxicity were reduced by the addition of rat liver S9 homogenate. In another testing, 1,3-DCP (purity not specified) was found to be positive for mutagenicity when tested in *Salmonella* strains TA100 and TA1535, but not TA1537 and only slightly in TA98 (Haworth et al., 1983; NTP, 1985b). Using preparations of >99.5% purity by distillation *in vacuo*, the isomers of 1,3-DCP were also found to be mutagenic in *Salmonella typhimurium* strain TA100 (Neudecker and Henschler, 1986). The addition of S9 liver homogenate enhanced the mutagenicity. In an earlier testing, 1,3-DCP was also found to be a direct-acting mutagen in strain TA100 and this effect was reduced by the addition of S9 liver homogenate; the purity of the test compound was not specified (Stolzenberg and Hine, 1980).

1,3-DCP (49.8% cis-form, 46.3% trans-form) was tested in the *Salmonella typhimurium* reverse mutation assay (Sudo et al., 1987a; Sudo et al., 1987b). The compound tested weakly positive in strains G46, TA1537, TA1538, and T98, and strongly positive in strains TA1535 and TA100. A host-mediated assay was determined to be negative in strain G46.

The cis- and trans-isomers of 1,3-DCP were shown to be mutagenic in *Salmonella typhimurium* strain TA100, both with and without metabolic activation (Creedy et al., 1984). Both isomers were stated to be 98% pure. The addition of 5 mM glutathione reduced the level of mutagenicity of both isomers substantially.

Cis- and trans-1,3-DCP were evaluated in a standard 4-(*p*-nitrobenzyl)pyridine alkylating procedure and for mutagenicity in *Salmonella typhimurium* strain TA100 (Eder et al., 1982). Both compounds showed alkylating effects and were positive for mutagenicity both with and without a S9 metabolic activation. The purity of the test compounds following distillation was stated to be 100% by gas-liquid chromatography. Twelve compounds evaluated showed good correlation between alkylating activity and mutagenicity.

Four commercial preparations of 1,3-DCP were compared in terms of mutagenicity with 1,3-DCP purified by silicic acid chromatography using *Salmonella typhimurium* strain TA100. The removal of impurities by this method resulted in the elimination of mutagenic activity of the commercial preparations (Talcott and King, 1984; Talcott, 1981 [abstract]). The purified preparations negative mutagenicity suggested that the polar contaminants of the preparation were responsible for the mutagenic activity. A re-testing produced the same results (E. Zeiger, NIEHS, unpublished, reported in NTP, 1985b). The mutagenicity of the compound could be restored by 'refluxing' which suggested to the author that oxygenated 1,3-DCP derivatives may be responsible for its mutagenicity. Among the polar impurities identified were epichlorohydrin and 1,3-dichloro-2-propanol, two known mutagens.

Another group of investigators examined the possibility that contaminants were responsible for the mutagenicity of cis-1,3-DCP (Watson et al., 1987). Again, 99.7% cis-1,3-DCP was purified by silicic acid adsorption chromatography, producing a purified product with no mutagenicity to *Salmonella typhimurium* strain TA100. Autooxidation of 1,3-DCP was shown to produce cis- and trans-2-chloro-3-(chloromethyl)oxiranes (DCP oxides). The metabolic activating systems were shown to mediate the conversion of cis-1,3-DCP to bacterial mutagens, although this activity may be protected by the addition of physiological levels of glutathione.

1,3-DCP enhanced the mutagenicity of *Salmonella typhimurium* strain TA98 for both histidine reversion and rifampicin resistance (Vithayathil et al., 1983). The purity of the test compound was not stated.

The mutagenicity of the urine of mice treated with technical grade 1,3-DCP was investigated (Stott et al., 1989). Mutagenicity in *Salmonella* strains TA98 and TA100 was not observed. Synthetic metabolites of 1,3-DCP including N-acetylcysteine, sulfoxide, and thioglycolic acid conjugates produced a three-fold increase in revertants in strain TA100. A weaker response was observed in strain TA98.

Genotoxicity Assays in Other Bacteria

Telone® II was found to be negative in a reversion test in *Escherichia coli* and in a rec assay in *Bacillus subtilis* (Sudo et al., 1987b).

1,3-DCP was shown to be mutagenic to the *Escherichia coli* strain PQ37 in a test using the β-galactosidase gene under the control of the SOS-gene *sfiA* (SOS chromotest; von der Hude et al., 1988). The purity of the test compound was not stated.

Micronucleus Test

Female NMRI mice treated with 187 mg 1,3-DCP/kg body weight (95.0% purity) showed a significantly increased incidence in the frequency of micronucleated polychromatic erythrocytes (Kevekordes et al., 1996). No increase in frequency of polychromatic erythrocytes was produced in response to treatment of mice with Telone® II in the mouse micronucleus assay (Bhaskar Gollapudi et al., 1985). The micronucleus assay also showed no indication for the genotoxicity of 1,3-DCP isomers (98% pure) in the bone marrow, spleen, or liver cells of partially hepatectomized rats (Ghia et al., 1993).

CHO/HPGRT Assay

Technical grade 1,3-DCP of proprietary composition was reported to be negative in a Chinese hamster ovary cell/hypoxanthine (guanine) phosphoribosyl transferase (CHO/HPGRT) forward mutation assay, both with and without metabolic activation (Mendrala, 1986). In one of three tests without activation, an increase in activity was observed, although cellular toxicity was also observed at these doses.

Mouse Lymphoma

1,3-DCP was found to be positive in the mouse lymphoma assay both with and without metabolic activation (U.S. EPA, 1990; citing Tennant et al., 1987; Myhr and Caspary, 1991).

Mouse Spot Test

Pregnant C57BL/6 mice were injected on the tenth day of pregnancy with 150 mg 1,3-DCP/kg body weight (Imanishi et al., 1987 [abstract]). Recessive color spots were observed in 2.2% of the offspring indicating in vivo somatic mutagenicity.

Drosophila

Treatment of *Drosophila melanogaster* with technical grade cis/trans-1,3-DCP (95.5% purity) by feeding (5,750 ppm in 10% ethanol) produced a significant increase in sex-linked recessive lethal mutations (Valencia et al., 1985; also reported in NTP, 1985b). No evidence of reciprocal translocations was observed for this compound following injection of 5,750 ppm of the same preparation.

Chromosome Aberrations / Sister Chromatid Exchange (SCE)

In the absence of metabolic activation, 1,3-DCP (98% pure) was found to be a potent inducer of SCE in Chinese hamster V79 cells (von der Hude et al., 1987). This activity was enhanced by the addition of S9 mix. Another study demonstrated that Telone® IIb induced SCE in Chinese hamster ovary cells both with and without metabolic activation, but not chromosomal aberrations (Loveday et al., 1989). Mitotic aberrations were reported both with and without metabolic activation in Chinese hamster lung cells exposed to cis- and trans-1,3-DCP (Sasaki et al., 1988; as described in ATSDR, 1992).

DNA damage / DNA Repair / Unscheduled DNA Synthesis

Dose-related increases in DNA fragmentation were observed in the liver and gastric mucosa of rats treated with single doses of 1,3-DCP (62.5 to 125 mg/kg body weight) by oral gavage (Ghia et al., 1993). The test compound was stated to be 98% pure mixed isomers. 1,3-DCP (98% pure mixed isomers) also was shown to induce a dose-dependent increase in single strand DNA breaks at sub-cytotoxic levels in Chinese hamster lung cells (Martelli et al., 1993). Primary cultures of rat and human hepatocytes also showed an increase in DNA

fragmentation and DNA repair synthesis upon exposure to 1,3-DCP. An increase in DNA breaks was observed when cells were depleted of glutathione. Telone® II was not found to induce unscheduled DNA synthesis in rat hepatocytes (Mendrala, 1987).

Developmental and Reproductive Toxicity

Telone® II has been tested for its effects on rat and rabbit embryonic and fetal development and on rat reproduction via the inhalation route of exposure. Groups of 30 bred Fischer 344 rats and 25 to 31 inseminated New Zealand White rabbits were exposed to 0, 20, 60, or 120 ppm Telone® II (90.1% 1,3-DCP; 47.7% cis/42.4% trans) via inhalation for six hours/day on days 6 to 15 (rats) or on days 6 to 18 (rabbits) (John et al., 1983; Hanley et al., 1987). No maternal rat deaths occurred, but mean body weights and body weight gains of the dams were significantly less than controls at all exposure levels, and the decreases were dose-related. Absolute liver weights were significantly decreased at all exposure levels, but relative liver weights were not different from controls. Relative kidney weights were increased significantly in rat dams exposed to 120 ppm Telone® II only. The only reproductive parameters of rats affected by Telone® II exposure were a significant decrease in percent pregnant at 60 ppm (70% versus 93% of controls) and a significant decrease in fetal body weight at 20 ppm (4.26 $\pm$ 0.14 grams versus 4.38 $\pm$ 0.17 grams for controls). Pregnancy rates were within the range of historical controls for F344 rats observed in this laboratory (70% to 97%), so the statistically identified difference at 60 ppm was not considered relevant. Also, the decrease in fetal body weight was not dose-related and only occurred at the low dose; therefore, this effect was not considered relevant. The only statistically significant increase in any external, soft tissue, or skeletal alterations in exposed litters compared to controls was delayed ossification of the vertebrae centra at 120 ppm (12/24 litters versus 6/27 control litters). This effect was not considered to be toxicologically significant, as there were no other malformations or fetal effects that could be attributed to Telone® II exposure. Therefore, Telone® II was not a developmental toxicant in rats at exposure levels up to 120 ppm (no-observed-adverse-effect level or NOAEL >120 ppm). The maternal NOAEL in rats was <20 ppm, based on body weight changes at all exposure levels.

There were three maternal deaths during the course of the rabbit study: two from pneumonia (one control and one 60 ppm group) and one from unknown causes on day 10 from the 120 ppm group. There was a significant decrease in body weight gain during days 6 to 8 for does exposed to 60 ppm Telone® II and during days 6 to 18 for does exposed to 60 and 120 ppm Telone® II compared to the control animals. Liver or kidney weights of treated rabbits were not different from controls. There were no adverse effects on reproductive parameters, or any increases in the incidence of external, soft tissue, or skeletal alterations that could be attributed to Telone® II exposure. Therefore, Telone® II was not a developmental toxicant in rabbits at exposure levels up to 120 ppm. The maternal NOAEL in rabbits was 20 ppm, based on body weight changes at 60 and 120 ppm.

A two-generation reproduction study was performed using Fischer 344 rats (Breslin et al., 1989). Groups of 30 male and 30 female rats were exposed via inhalation to 0, 10, 30, or 90 ppm technical-grade 1,3-DCP (92% purity) for six hours/day, five days/week for two generations. Mean body weights of f_0 and f_1 adult male and female rats exposed to 90 ppm 1,3-DCP were decreased throughout most of the treatment periods. The decrease was

statistically significant for the males throughout most of the treatment period, but was only occasionally significant for females during the pre-mating, gestation, and lactation periods. Mean body weights at 10 or 30 ppm 1,3-DCP were not significantly changed, compared to controls. There were no adverse treatment-related effects on the mating, conception, or gestation indices, cohabitation time required for mating, pup survival indices, pup body weights, or litter size at any exposure level in the f_{1a}, f_{1b}, f_{2a}, or f_{2b} litters. Adult male and female rats exposed to 90 ppm exhibited treatment-related effects on the nasal mucosa, such as slight hyperplasia of the respiratory epithelium and focal degenerative changes of the olfactory epithelium. Additionally, adult f_0 and f_1 females in the 90 ppm group had an increased incidence of stomach lesions. Technical grade 1,3-DCP did not produce any adverse treatment-related effects on reproductive parameters or neonatal growth or survival at any of the exposure levels. A NOAEL of 30 ppm for parental adults was based on treatment-related effects on nasal mucosa and body weights in male and female rats and stomach lesions in females exposed to 90 ppm 1,3-DCP via inhalation.

Chronic Toxicity

Several studies have been conducted to evaluate the chronic toxicity of 1,3-DCP using Telone® II. These include both oral (gavage and dietary) and inhalation studies. In the most recent oral studies, Telone® II was microencapsulated in a starch/sucrose matrix, rather than being stabilized with 1% epichlorohydrin or epoxidized soybean oil. These studies were conducted using Fischer 344 rats, B6C3F1 mice, and Beagle dogs.

Fischer 344 rats (50 animals/sex/dose for entire study; 10 animals/sex/dose for interim sacrifice at 12 months) were fed microencapsulated Telone® II (96% purity; 50.7% cis/45.1% trans 1,3-DCP) in the diet (0, 2.5, 12.5, or 25 mg/kg-day) up to 24 months (Stott et al., 1995). Body weights of male rats fed 12.5 and 25 mg/kg-day were significantly lower than controls from week 13 to study termination. Body weights of females fed 12.5 mg/kg-day were significantly lower than controls only during the last three to four months of dosing and at 25 mg/kg-day were significantly lower than controls from week 73 to study termination. Also, body weight gains for both sexes were lower at 12.5 and 25 mg/kg-day, but the difference was significant only with the high dose. Relative brain and kidney weights of male and female rats were significantly increased at 12.5 and 25 mg/kg-day. Slight basal cell hyperplasia of the non-glandular stomach mucosa was increased in male and female rats in a dose-related manner at 12 and 24 months of exposure. At 24 months, the increase was statistically significant for males and females at 12.5 and 25 mg/kg-day, but not at 2.5 mg/kg-day; the increase was not significant in male or female rats at 12 months (Stott et al., 1995). Hepatocellular eosinophilic foci appeared to increase in number and/or degree at all doses. The occurrence was significantly increased at all doses compared to controls for males with "slight" (6 to 15 foci per standard three sections of liver) and females with "any severity" of altered liver foci. Additionally, the occurrence of hepatocellular adenomas in male rats at 24 months was dose-related, but statistically different from controls only at 25 mg/kg-day. OEHHA identified a NOAEL of 2.5 mg/kg-day, based on a significant decrease in body weights and a dose-related increase in basal cell hyperplasia of the non-glandular stomach mucosa of male and female rats at 12.5 and 25 mg/kg-day. Hepatocellular eosinophilic foci, which were present at all dose levels, are considered to be precancerous lesions that may progress to hepatocellular carcinomas (Bannasch and Zerban, 1992; Pitot et al., 1996; Su et al., 1997). Therefore, this toxicological effect, although the most sensitive end point in this study, is more appropriate

as supporting data for carcinogenicity and was not used in the identification of a non-cancer NOAEL.

B6C3F1 mice (50 animals/sex/dose for entire study; 10 animals/sex/dose for interim sacrifice at 12 months) were fed microencapsulated Telone® II (95.8% purity; 50.7% cis/45.1% trans 1,3-DCP) in the diet (0, 2.5, 25, or 50 mg/kg-day) up to 24 months (Redmond et al., 1995). Body weights were significantly decreased at 25 and 50 mg/kg-day (males, 11% to 14% decrease relative to controls; females, 7% to 9% decrease relative to controls). Body weight gains also were significantly depressed at 25 and 50 mg/kg-day. The study did not report blood chemistry data, only hematological data, which were not different from controls. The only significant histological effect reported was decreased size of hepatocytes in high-dose males (6 of 10) at the 12-month interim sacrifice. This effect was attributed to a decrease in hepatocellular cytoplasmic area, compared to controls, and it was consistent with a decrease in hepatocellular glycogen content as a result of decreased absolute liver weight at 12 months. The NOAEL for this study was 2.5 mg/kg-day, based on decreased body weights and body weight gains in male and female mice fed 25 and 50 mg/kg-day of Telone® II.

Telone® II (1,3-DCP 95.8% purity) was administered in the diet (0, 0.5, 2.5, or 15 mg/kg-day) to Beagle dogs (four animals/sex/dose group) for 12 months (Stott et al., 1992). Clinical observations included paleness of mucous membranes, bilateral alopecia, roughened skin, and occasional generalized redness of the skin. Body weights of high-dose males and females were decreased, but the difference was statistically significant only in males. Relative liver weights were statistically elevated at the 15 mg/kg-day dose for both sexes combined; there were no histopathological changes that could account for the changes in liver weight. Although the increased liver weights could be due to biological variability, the values were outside of the range of historical controls typically seen in Beagle dogs in the conducting laboratory, so this effect was considered treatment-related.

The major effect of dietary Telone® II in dogs was a treatment-related increase in hematopoiesis in bone marrow and extramedullary hematopoiesis in spleen, consistent with a regenerative response to hypochromic, microcytic anemia. This effect was observed in male and female dogs given 15 mg/kg-day Telone® II. No treatment-related histopathological changes were found at 0.5 or 2.5 mg/kg-day. The NOAEL in this study was 2.5 mg/kg-day, based on the histopathological changes in bone marrow and spleen and the body weight and liver weight changes in male and female dogs at 15 mg/kg-day.

The National Toxicology Program conducted an earlier study of the oral chronic toxicity of Telone® II (NTP, 1985b; Yang et al., 1986). Male and female Fischer 344 rats and B6C3F1 mice were administered Telone® II (0, 25, or 50 mg/kg to rats and 0, 50, or 100 mg/kg to mice) in corn oil by gavage three times/week for 104 weeks. Interim sacrifices (five rats/sex/dose) were performed at 9, 16, 21, 24, and 27 months. The Telone® II formulation was composed of 88% to 90% 1,3-DCP, 2.5% 1,2-dichloropropane, 1.0% epichlorohydrin, and about 9% of other chlorinated propenes and hexenes. The primary adverse effects observed were basal cell hyperplasia of the forestomach (equivalent to non-glandular portion of the stomach) of male and female rats (significantly increased at 50 mg/kg compared to controls, but apparent in both sexes at 25 and 50 mg/kg at 16 months); epithelial hyperplasia of the urinary bladder of male and female mice (statistically increased compared to controls at 50 and 100 mg/kg); and epithelial hyperplasia of the forestomach of male and female mice (significantly different from controls at 100 mg/kg; females only).

The presence of 1% epichlorohydrin, a known carcinogen that also produces forestomach hyperplasia in rats (Konishi et al., 1980, cited in Yang et al., 1986), in the Telone® II formulation may have confounded the toxicity of 1,3-DCP. However, that appears unlikely since adverse effects similar to those observed in the NTP study were observed in rats fed microencapsulated Telone® II that contained 96% 1,3-DCP and no epichlorohydrin (Stott et al., 1995).

The chronic toxicity of inhaled Telone® II was evaluated in Fischer 344 rats and B6C3F1 mice (Lomax et al., 1989; Lomax et al., 1987; Stott et al., 1987). Fifty animals per species per sex per exposure level were exposed to 0, 5, 20, or 60 ppm Telone® II (92.1% 1,3-DCP, 49.5% cis and 42.6% trans) for six hours per day, five days per week, for up to 24 months. Two groups (10 animals/species/sex/exposure) also were exposed to Telone® II for interim sacrifice at 6 and 12 months. Total exposure days over the two-year period were 509 days and 510 days for rats and mice, respectively. Body weights of male and female rats exposed to 60 ppm and males exposed to 20 ppm Telone® II were significantly depressed compared to controls at various times during the first 60 weeks of the study, but were not different from controls during the remainder of the study. Exposure to 5 ppm Telone® II had no effect on body weights for either sex. In both male and female rats exposed to 60 ppm Telone® II, there was decreased thickness and erosion in the olfactory epithelium of nasal tissues; this change was statistically significant compared to controls (Lomax et al., 1987; Lomax et al., 1989). In addition, males exposed to 60 ppm had statistically more submucosal fibrosis compared to controls. The NOAEL for rats was 20 ppm, based on decreased body weights and effects on the nasal tissue at 60 ppm.

Body weights of male and female mice exposed to 60 ppm were sporadically decreased during the first weeks of the study, but were decreased significantly compared to controls from the 4th or 5th month to the end of the study (Stott et al., 1987; Lomax et al., 1989). Relative kidney weights of male mice exposed to 60 ppm were significantly decreased compared to controls after 6, 12, and 24 months of exposure. Likewise, relative liver weights were decreased at all times, but the difference was only significant at 6 and 12 months. The following histopathological changes were statistically identified in mice after 24 months of exposure to Telone® II: decreased vacuolation of renal proximal tubular epithelial cells (males, 60 ppm), slight degeneration of nasal olfactory epithelium (males and females, 60 ppm), slight hyperplasia and hypertrophy of respiratory epithelium (females, 20 ppm; males and females, 60 ppm), hyperplasia with chronic inflammation of the non-glandular portion of the stomach mucosa (males, 60 ppm), slight to moderate hyperplasia of urinary bladder mucosa (females, 20 ppm; males and females, 60 ppm), and chronic inflammation of the urinary bladder (females, 20 and 60 ppm). Hypertrophy/hyperplasia of the respiratory epithelium also was evident after 6 and 12 months exposure to 20 ppm (males) or 60 ppm Telone® II (males and females). The NOAEL in mice was 5 ppm based on body weight changes and histopathological changes in nasal and urinary bladder tissues at 20 and 60 ppm Telone® II.

Carcinogenicity

Oral Studies

F344/N rats (52/sex/dose) were administered Telone® II by gavage at doses of 0, 25, or 50 mg/kg-day in corn oil for three days/week for 104 weeks (NTP, 1985b; also described in Yang et al., 1986). Interim-kill studies with five rats per dose group were also conducted at 9, 16, 21, 24, and 27 months to help evaluate the development of tumors with respect to time. In all studies the test agent was reported by the manufacturer to contain 92% 1,3-DCP (45% cis-isomer and 47% trans-isomer), 2% 1,2-dichloropropane, and 1% epichlorohydrin. After 13 months of storage, re-analysis indicated a composition of 88% to 90% 1,3-DCP (41.6% cis-isomer and 45.9% trans-isomer), 2.5% 1,2-dichloropropane, 1.5% trichloropropene isomer, 1.0% epichlorohydrin, and 7.5% other impurities (nine). Survival, weight gain, hematological and clinical chemistry parameters showed no indication of toxicologically significant effects during the course of the study.

Significantly increased tumor incidences are presented below (Table 3). Among male rats, significant increases in squamous cell papillomas and combined squamous cell papillomas and carcinomas of the forestomach were observed among high-dose male rats using incidences from both the two-year study alone and the combined results of the two-year plus ancillary studies. Among female rats, an increase in squamous cell papilloma incidence was observed, but only when the results of the two-year study were combined with the ancillary studies. The ancillary studies showed an increased hyperplastic response as early as 9 to 16 months, although neoplasms did not appear until 24 months. The reported incidences were well above the reported NTP historical incidences for both male (0.5%) and female (0.4%) rats.

Among male rats, the incidence of combined neoplastic nodules and carcinomas of the liver was increased in both the treated groups and both the two-year and combined two-year/ancillary studies. Nodules were described as “lesions causing only minimal compression, with little or no cytologic atypia in livers or with toxic or anoxic hepatic change (such as occurs with mononuclear cell leukemia)” (NTP, 1985b). The ancillary studies did not show the development of neoplastic nodules in the liver until the 24th month.

Female rats showed positive trends for adenomas and fibromas of the mammary glands, although the increases were not statistically significant.

Significantly increased incidences of tumors of the forestomach and liver led NTP to conclude that there was clear evidence of carcinogenicity of Telone® II in male F344/N rats. Tumors of the forestomach led NTP to conclude that there was some evidence of carcinogenicity in female rats.

Table 3. Tumors in Rats Receiving 0, 25, or 50 mg/kg-day Telone® II by Gavage for 104 Weeks[a] (NTP, 1985b).

Tumor Site and Type		Dose (mg/kg-day)					
		0		25		50	
Males		2 yr	2 yr+	2 yr	2 yr+	2 yr	2 yr+
Forestomach	squamous cell papilloma	1/52	1/77	1/52	1/77	9/52[b]	13/77[b]
	squamous cell carcinoma	0/52	0/77	0/52	0/77	4/52	4/77
	papilloma or carcinoma	1/52	1/77	1/52	1/77	13/52[b]	17/77[b]
Liver	neoplastic nodule	1/52	1/77	6/52[b]	6/76[b]	7/52[b]	8/77[b]
	neoplastic nodule or carcinoma	1/52	1/77	6/52[b]	6/76[b]	8/52[b]	9/77[b]
Adrenal gland	pheochromocytoma	2/52		8/52[b]		6/52	
Females		2 yr	2 yr+	2 yr	2 yr+	2 yr	2 yr+
Forestomach	squamous cell papilloma	0/52	0/75	2/52	2/77	3/52	8/77[b]

[a] Results presented include incidences from the two-year study alone (2 yr) as well as the two-year study plus the ancillary/interim-kill studies (2 yr+). Incidences are overall rates unadjusted for survival or animals at risk.

[b] Statistically increased incidence over control animals by Fisher's exact test ($p \leq 0.05$).

B6C3F1 mice (50/sex/dose) were administered Telone® II by gavage at doses of 0, 50, or 100 mg/kg, as described for the rat study. No ancillary studies were conducted for the mice. An initial difference in body weights between dosed and control groups was attributed to a "failure to fully randomize the distribution of the animals," although this short-coming in the way the study was conducted was not thought to compromise the significance of the study's findings (NTP, 1985). A significant decrease in the survival of male mice was observed, particularly in the control group in which 39 mice died. The cause of death was identified as suppurative inflammation of the heart (myocarditis) although the origin of the condition was unknown. Because of this reduced survival, the portion of the study concerning the male mice was deemed inadequate and "only analyses that account for differences in survival…[were] considered."

Among female mice, the incidences of transitional cell carcinomas of the urinary bladder were increased in both high and low-dose groups and a significant positive trend was observed (Table 4). These tumors were characterized as "solid or glandular growth that extended downward from the transitional epithelium into the submucosa and muscle layer" (Yang et al., 1986). Epithelial hyperplasia of the urinary bladder was also significantly increased in both treatment groups relative to controls (2/50, 15/50, 19/48; $p<<0.05$ by Fisher's exact test). Among male mice in the high-dose group, two transitional cell carcinomas were observed. Epithelial hyperplasia was reported in 0/50 control, 9/50 low-

dose, and 18/50 high-dose male mice. Tumors of the urinary bladder are extremely rare in B6C3F1 mice; an historical incidence in NTP studies of zero in more than one thousand control mice (male or female) was reported. No evidence of calculi was found in mice of either sex. Chronic inflammation of the urinary bladder was observed in 15/50 control, 15/50 low-dose, and 1/48 high-dose female mice, and only 1/50 high-dose male mice. The absence of calculi and the lack of correlation of chronic inflammation to tumors or hyperplasia incidence suggest that this effect is not the result of a chronic inflammatory response to Telone® II. The NTP report also noted that Telone® II preparations do not contain compounds of a similar nature to those that have been shown to produce bladder calculi and tumors (aromatic amines).

High-dose female mice also showed significantly increased incidences of alveolar/bronchiolar adenomas, combined alveolar/bronchiolar adenomas and carcinomas, and combined squamous cell papillomas and carcinomas of the forestomach (see Table 4). For female mice, the NTP historical control incidence is 5 ± 3% (52/1,103) for alveolar/bronchiolar adenomas or carcinomas and 0.4% (4/1,077) for combined squamous cell papillomas or carcinomas of the forestomach (NTP, 1985b).

Table 4. Tumors in B6C3F$_1$ Mice Receiving 0, 50, or 100 mg/kg-day Telone® II by Gavage for 104 Weeks[a] (NTP, 1985b).

Tumor Site and Type		Dose (mg/kg-day)		
		0	50	100
Males				
Lung	alveolar/bronchiolar adenoma	1/50	11/50	9/50
	alveolar/bronchiolar adenoma or carcinoma	1/50	13/50[b]	12/50[b]
Forestomach	squamous cell papilloma	0/50	2/50	3/50
Females				
Bladder	transitional cell carcinoma	0/50	8/50[b]	21/48[b]
Lung	alveolar/bronchiolar adenoma	0/50	3/50	8/50[b]
	alveolar/bronchiolar adenoma or carcinoma	2/50	4/50	8/50[b]
Forestomach	squamous cell papilloma or carcinoma	0/50	1/50	4/50
Liver	hepatocellular adenoma	0/50	5/50[b]	3/50
	hepatocellular adenoma or carcinoma	1/50	8/50[b]	3/50

[a] Incidences are overall rates unadjusted for survival or animals at risk.

[b] Statistically increased incidence over control animals by Fisher's exact test ($p \leq 0.05$).

Low-dose female mice showed an increased incidence of hepatocellular adenomas and combined adenomas and carcinomas. The reported NTP historical incidence for hepatocellular adenoma or carcinoma is 7 ± 3% (80/1,176).

The development of urinary bladder, lung, and forestomach tumors led NTP to conclude that there was clear evidence of carcinogenicity for female B6C3F1 mice. While the findings of the male mouse portion of the study were compromised by the reduced survival of the control group, there was "some indication in the male mice of Telone® II-related increases of transitional cell carcinomas of the urinary bladder, squamous cell papillomas of the forestomach, and alveolar/bronchiolar adenomas and carcinomas of the lung" (NTP, 1985b).

Beagle dogs (four/sex/dose) were fed diet containing microencapsulated Telone® II for one year at doses of 0, 0.5, 2.5, or 15 mg/kg-day (Stott et al., 1992). The test compound was a racemic mixture of 96% 1,3-DCP. No evidence of tumor formation was reported, although the study duration was only one year and the primary focus of the study was non-carcinogenic toxicological end points.

Fischer 344 rats (50/sex/dose) were fed diet containing microencapsulated Telone® II for two years at doses of 0, 2.5, 12.5, or 25 mg/kg-day (Stott et al., 1995). The test compound was reported to consist of 95.8% 1,3-DCP (50.7% cis-isomer, 45.1% trans-isomer). An auxiliary group of ten rats/sex/dose was sacrificed at one year. The incidence of hepatocellular adenoma was significantly increased among male rats in the high dose group (see Table 5). Additionally, hepatocellular eosinophilic foci appeared to increase in number and/or degree at all doses. The occurrence was significantly increased at all doses compared to controls for males with "slight" (6 to 15 foci per standard three sections of liver) and females with "any severity" of altered liver foci. Among female rats in the high dose group, the incidence of endometrial stromal polyps was significantly increased (see Table 5). Among male and female rats in the two highest dose groups, stomach lesions described as mucosal basal cell hyperplasia were observed, both at the end of the two year study and at the interim one year sacrifice. There was no evidence of progression in the severity of the lesions.

Table 5. Tumors and Lesions in Fischer 344 Rats Receiving 0, 2.5, 12.5, or 25 mg/kg-day Telone® II in the Diet for Two Years (Stott et al., 1995).

Tumor Site and Type		**Dose (mg/kg-day)**			
		0	2.5	12.5	25
Males					
Liver	hepatocellular adenoma	2/50	1/50	6/50	9/50[a]
Females					
Liver	hepatocellular adenoma	0/50	0/50	0/50	4/50[b]
Uterus	endometrial stromal polyps	12/50	13/50	10/50	24/50

[a] Statistically increased incidence over control animals by Fisher's exact test ($p \leq 0.05$) with a positive trend test. One hepatocellular carcinoma was also observed in this dose group.
[b] Positive trend test.

B6C3F1 mice (50/sex/dose) were fed diet containing microencapsulated Telone® II for two years at doses of 0, 2.5, 25, or 50 mg/kg-day (Redmond et al., 1995). The test compound was reported to consist of 95.8% 1,3-DCP (50.7% cis-isomer; 45.1% trans-isomer) with an 80:20 starch:sucrose vehicle. An auxiliary group of ten mice/sex/dose was sacrificed at one year. Stromal cell tumors (originating at any site - cervix or uterus) were noted to be increased among female mice, although the increase was not statistically significant (1/50, controls; 0/50, low-dose; 0/50, mid-dose; 4/50, high-dose).

Inhalation Studies

Fischer 344 rats (50/sex/dose) were exposed by inhalation to concentrations of 0, 5, 20 or 60 ppm technical grade 1,3-DCP for six hours/day, five days/wk, for up to two years (Lomax et al., 1987; part of Lomax et al., 1989). Ancillary groups of 10 rats and mice of each sex and dose were exposed for 6 and 12 months. Gas chromatographic analysis of the test compound showed a composition of 92.1% 1,3-DCP (49.5% cis-isomer and 42.6% trans-isomer) with 0.7% 1,2-dichloropropane plus several unidentified hexanes and hexadienes. Survival was not significantly affected by 1,3-DCP treatment nor were there clinical or hematological indications of toxicity during the course of the study. No statistically significant increase in tumor incidence was observed among male or female rats.

B6C3F1 mice (70/sex/group) were exposed by inhalation to 0, 5, 20, or 60 ppm Telone® II for six hours/day, five days/week for two years (Stott et al., 1987b; as described in U.S. EPA, 1990; part of Lomax et al., 1989). Additional groups of 10 mice/sex were exposed for 6 or 12 months. The test compound was stated to consist of 49.5% cis-isomer, 42.6% trans-isomer with 0.7% 1,2-dichloropropane, 1.8% 1,3-dichloropropane, 4.3% mixed isomers of chlorohexene, chlorohexane, and trichloropropene, stabilized by approximately 2% epoxidized soybean oil. Among male mice, a significant increase in incidence of bronchioloalveolar adenomas of the lung was observed in the high-dose group relative to the control group (9/57, control; 6/51, low-dose; 13/49, mid-dose; 22/60, high-dose, whereas Lomax et al., 1989, describes 22/50 high dose versus 9/50 controls; $p = 0.004$, Fisher's exact test; $\alpha = 0.05$ by Yate's χ^2 pairwise test). A dose-related trend was also observed. The incidence in the high-dose group is also outside of the range of historical controls reported for the laboratory conducting the experiment (seven previous chronic studies). Lacrimal gland cystadenomas were increased among males in the mid-dose group relative to the control group (1/57, control; 6/60, low-dose; 10/58, mid-dose; 5/60, high-dose). These significantly elevated incidences were just beyond the range of historical controls reported by Dow Chemical Company. Among female mice, the incidence of mesenteric lymph node lymphosarcomas was increased in the low-dose group relative to the control group (3/57, control; 11/49, low-dose; 5/47, mid-dose; 6/55, high-dose). The incidence of epithelial hyperplasia of the urinary bladder was significantly increased among male mice in the high-dose group and female mice in both the mid- and high-dose groups. This effect was more pronounced among female mice than male. The lesions were described as "diffuse, uniform thickening of the transitional epithelium" and were found to increase in frequency and severity with dose. Hyperplasia of the epithelium of the urinary bladder was stated to be "occasionally accompanied by inflammation, primarily in female mice" (Lomax et al., 1989). The highest incidence of inflammation observed was 8/50 high-dose female mice, whereas hyperplasia was observed in 44/50 high-dose female mice.

This suggests that the hyperplasia was not the result of a chronic inflammatory response. Two carcinomas and one adenoma of the urinary bladder were observed in female mice in the mid-dose group.

Studies by Other Routes

Weekly subcutaneous injection of 3 mg cis-1,3-DCP in 0.05 mL trioctanoin for 77 weeks produced injection site fibrosarcomas in female Ha:ICR Swiss mice (6/30 treated versus 0/30 controls; Van Duuren et al., 1979). In an initiation/promotion study, a single dermal application of 122 mg 1,3-DCP per mouse followed by repeated treatment with phorbol myristic acid did not lead to skin papilloma formation after 58 weeks. Similarly, dermal application of 122 mg 1,3-DCP per mouse three times weekly did not induce skin papillomas after 74 weeks.

Toxicological Effects in Humans

Acute, Subchronic, or Chronic Toxicity

Hernandez et al. (1994) described a case of fatal 1,3-DCP intoxication. A previously healthy 27-year-old male was hospitalized two hours after accidentally drinking a solution containing 1,3-DCP. Initial symptoms were acute gastrointestinal distress, sweating, tachypnea, tachycardia, hypovolemic disturbance, and lividity on both legs. The gastric lavage had a garlic-like odor. Chest X-ray revealed diffuse, extensive bilateral interstitial and alveolar infiltrates consistent with adult respiratory distress syndrome. The patient was infused with 135 units of insulin over a 36-hour period for hyperglycemia. He developed respiratory arrest, metabolic acidosis, elevation of serum peritoneal fluid amylase, and gastrointestinal disturbances, as well as liver and kidney failure, and died 38 hours after admission. Analysis of biological fluids showed a mixture of cis- and trans-isomers of 1,3-DCP (Telone) with 0.33 µmol/L in blood (1.13 µmol/L upon hospital admission) and 0.20 µmol/L in urine. The authors noted that the insulin-resistant hyperglycemia and the elevation of peritoneal fluid amylase levels in the patient are consistent with acute pancreatitis, which may have been caused by 1,3-DCP directly or as a result of multiorgan failure.

Approximately 80 persons were exposed to 1,3-DCP vapors in Sutter County, California, on October 21, 1975, when a truck hauling an estimated 1,200 gallons of the fumigant, Telone® II (92% 1,3-DCP; 8% other short-chain chlorinated hydrocarbons), spilled a large portion of its contents onto the highway during a traffic accident (Flessel et al., 1978). Forty-six persons were examined at a local hospital; 24 with the greatest exposure were hospitalized overnight. The most common signs and symptoms were headache (six persons), mucous membrane irritation (five), dizziness (five), chest discomfort (four), and nausea and vomiting (four). Three persons reportedly lost consciousness. Other clinical findings were slightly elevated serum glutamic-oxaloacetic transaminase (SGOT), serum glutamic-pyruvic transaminase (SGPT), or both in 11 of 41 persons. Eight of the 11 were re-tested within 48 to 72 hours, and five still had a slightly elevated SGOT. Seven to 14 days after the accident, some of the patients still reported symptoms including headache (12

persons), abdominal discomfort (six), chest discomfort (five), and malaise (five). Persons with the greatest exposure were significantly ($p<0.01$) more likely to report persistent symptoms.

Follow-up interviews of 21 patients were held in August and September 1977, approximately two years after exposure to 1,3-DCP (Flessel et al., 1978). Ten of the 21 complained of severe or unusual headaches, 10 complained of chest pain or discomfort, and 13 complained of personality changes, such as fatigue, irritability, difficulty concentrating, or decreased libido. The frequency of the chronic symptoms was not significantly associated with the degree of Telone® II exposure. Although the symptoms reported by these patients raise the question of possible long-term effects from 1,3-DCP exposure, they are very subjective and do not appear to be dose-related.

Genetic Toxicology

Primary cultures of rat and human hepatocytes showed a similar increase in DNA fragmentation and DNA repair synthesis upon exposure to 1,3-DCP (Martelli et al., 1993). The test compound was stated to be 98% pure mixed isomers. 1,3-DCP has also been tested for its ability to induce unscheduled DNA synthesis (UDS) in human HeLa cells. 1,3-DCP was found to be a relatively potent inducer of UDS compared to other tested allylic compounds (cis- > trans-1,3-DCP) (Schiffmann et al., 1983).

1,3-DCP exposure led to the induction of sister chromatid exchange in vitro in human lymphocytes with and without the addition of a metabolic activation system (Kevekordes et al., 1996). The test compound was reported to be 95% pure.

Carcinogenicity

Three case reports described hematological malignancies that arose in individuals exposed to 1,3-DCP (Markovitz and Crosby, 1984). Two of the cases involved exposure from a single incident in which a tanker truck carrying 1,3-DCP overturned and spilled its contents. Nine responding firemen at the scene were exposed to toxic levels of 1,3-DCP, with symptoms including headache, neck pain, nausea, and dyspnea. Among them, two developed what was termed histiocytic (non-Hodgkin's) lymphoma 6.5 years following the incident. In spite of treatment efforts, both patients died within eight years of the exposure. A third case report involved a farmer exposed to 1,3-DCP during the course of application from a leaky hose in close proximity to his face. Within a month he presented with hyperemia and ulceration of the nasal mucosa, redness/tenderness of the external right ear, and pharyngeal inflammation. At one point the patient was given a transfusion and treated briefly with mercaptopurine and chlorambucil, although the patient ultimately declined further treatment. After returning to work a year following the first exposure, the patient was again exposed during the course of application and shortly thereafter presented with similar, but more severe, symptoms. His hematological profile was reported to be consistent with a diagnosis of acute myelomonocytic leukemia. Within five weeks the patient died of pneumonia. In each of the cases, inadequate information is available for a quantitative evaluation of exposure levels.

Summary of Evidence for Carcinogenicity

In January 1, 1989, 1,3-DCP was listed under California's Safe Drinking Water and Toxic Enforcement Act of 1986 (Proposition 65) as a chemical known to the State to cause cancer (OEHHA, 1998). Supporting data for carcinogenicity come from several bioassays in experimental animals which have shown positive evidence of tumor development by several different routes of exposure. Oral studies have shown Telone® II induced squamous cell papilloma and carcinoma of the forestomach and neoplastic nodule or carcinoma of the liver in rats and transitional cell carcinoma of the urinary bladder, squamous cell papilloma and carcinoma of the forestomach, and alveolar/bronchiolar adenoma and carcinoma of the lung in mice. Inhalation studies have shown Telone® II-induced bronchioloalveolar adenomas of the lung in mice. The available animal studies also tend to support each other in terms of the spectrum of lesions produced upon exposure to Telone® II: alveolar/bronchiolar adenoma and carcinoma were produced by both oral and inhalation routes, a hyperplastic response and/or adenoma and carcinoma in the urinary bladder were produced in mice exposed by both oral and inhalation routes, and liver adenoma and carcinoma development was observed in mice in two oral studies (feed and gavage studies).

The oral gavage studies in rats and mice by NTP (1985b) identified numerous significant sites of tumor development including the forestomach and liver in rats and the urinary bladder and lung in mice. The more recent feed studies identified only liver adenomas in rats (Stott et al., 1995; Redmond et al., 1995). The studies differed from each other in several respects:

- Dosing regimen -- NTP used Telone® II administered by oral gavage three times per week versus the continuous administration of microencapsulated Telone® II in feed in the Dow Chemical studies. The overall time-weighted dose administered for each of the species in the different studies was approximately equal (42.9 and 21.4 mg/kg-day for gavaged mice and rats, respectively, in the NTP studies and 50 and 25 mg/kg-day for Telone® II fed mice and rats, respectively, in the Dow Chemical studies). It is unclear what impact the bolus vs. 'continuous' administration may have on the development of tumors. The locally and temporarily high doses achieved in the forestomachs of gavaged animals have been speculated to result in concentrations of epichlorohydrin near levels which have resulted in tumor development in other studies of epichlorohydrin alone (NTP, 1985b) (see below).
- Test compound -- The Telone® II preparation used in the NTP study contained 88% to 92% 1,3-DCP isomers with epichlorohydrin (2%) as a stabilizer and minor contamination by a number of other compounds including 1,2-dichloropropane. The Dow Chemical studies used a preparation of mixed isomers of 1,3-DCP (95.2%) also with a number of compounds constituting ~5.2% of the preparation.

Human epidemiological evidence of carcinogenicity currently is inadequate to add to the body of evidence supporting the carcinogenicity of 1,3-DCP.

The weight of evidence for carcinogenicity of Telone® II or 1,3-DCP preparations is supported by the observation of mutagenicity in numerous short-term tests including bacterial reversion assays in *Salmonella typhimurium* and *Escherichia coli*, and rodent cells

assays for SCE and DNA fragmentation. Human cells also have shown susceptibility to the genotoxic effects of 1,3-DCP, with positive findings in DNA damage/repair studies and SCE studies, with some indication that human cells are as sensitive to these effects as rats.

The weight of evidence for carcinogenicity is also supported by the chemical structural analogy of 1,3-DCP to other known carcinogens such as vinyl chloride (a lung carcinogen by inhalation), epichlorohydrin (a forestomach carcinogen by the oral route), and ethylene dibromide (various tumors by several routes). Like 1,3-DCP, these are short-carbon chain halogenated compounds.

Confounding Contaminants of Telone® II

There are potential artifactual results due to contaminants and oxidation by-products in both the mutagenicity and carcinogenicity assays of Telone II® and 1,3-DCP. Two compounds present in the Telone® II formulation used in the NTP (1985b) study, epichlorohydrin (1%) and 1,2-dichloropropane (2%), have been shown to produce tumors in experimental animals. Both are listed under Proposition 65 as chemicals known to the State of California to cause cancer. Forestomach lesions were observed in Wistar rats in a drinking water study of epichlorohydrin at levels several-fold above those in the present studies with Telone® II (Konishi et al., 1980; Wester et al., 1985). The NTP report on Telone® II noted that since the epichlorohydrin was administered by gavage, it is possible that concentrations at the site of application (the stomach) could be quite high, although briefly, and therefore epichlorohydrin may play a role in the carcinogenicity of orally administered Telone® II. Using the epichlorohydrin cancer potency provided by Konishi et al. (1980) and Wester et al. (1985) that was based on forestomach tumor incidence data for male rats and converting to a potency for mice, OEHHA (formerly in DHS) suggested that the epichlorohydrin content of the Telone® II preparation in the NTP bioassay may have contributed to the induction of forestomach tumors in rats and mice in the study, although the degree of the contribution is uncertain (DHS, 1988a). Epichlorohydrin is not known to induce tumors at sites other than that of initial contact, therefore, OEHHA (formerly in DHS) considered it unlikely that the epichlorohydrin in Telone® II was involved in the production of the other tumors observed in the NTP bioassay.

1,2-dichloropropane has been shown to produce hepatocellular adenomas in mice and mammary tumors in rats (NTP, 1985a). Since this is a different primary spectrum of tumors from those observed in the NTP Telone® II study and since the dose level of this component is considerably higher than that achieved through the administration of Telone® II, the NTP dismissed this compound as a probable contributor to the carcinogenic effect (NTP, 1985b).

There is some evidence that auto-oxidation of 1,3-DCP produces compounds which may account for the mutagenicity of several commercial 1,3-DCP preparations (Talcott and King, 1984; Watson et al., 1987). It is unclear whether such auto-oxidation products of 1,3-DCP also may be generated in vivo resulting in the production of a proximate carcinogen. This is a possibility given the likely reactivity of the allylic carbon. Also unclear is whether Telone® II preparations, if not in their formulation then through their use, generate such compounds which may be of mutagenic or carcinogenic concern.

DOSE-RESPONSE ASSESSMENT

Noncarcinogenic Effects

Several animal studies have described adverse noncarcinogenic effects resulting from exposure to 1,3-DCP. A few case reports of human exposures are available, but they are limited by inadequate estimation of exposure levels or by insufficient exposure duration for establishing effects that may result from long-term exposure.

The Stott et al. (1995) chronic dietary studies in Fischer 344 rats demonstrated several noncarcinogenic adverse effects, including a significant dose-related increase in basal cell hyperplasia of the non-glandular stomach mucosa, a significant decrease in body weights, and a significant increase in relative brain and kidney weights in both male and female rats at 12.5 and 25 mg/kg-day of Telone® II. From these studies, a NOAEL of 2.5 mg/kg-day was identified.

From a chronic dietary study using mice (Redmond et al., 1995), a NOAEL of 2.5 mg/kg-day was identified, based on significant dose-related decreases in body weights and body weight gains of male and female mice ingesting 25 and 50 mg/kg-day of Telone® II.

Beagle dogs fed 15 mg/kg-day Telone® II for one year developed treatment-related changes in erythroid parameters, consistent with hypochromic, microcytic anemia (increased hematopoiesis in bone marrow and increased extramedullary hematopoiesis in spleen in both males and females) (Stott et al., 1992). These effects were not observed in animals fed 0.5 or 2.5 mg/kg-day Telone® II in their diets. Other adverse effects included decreased body weights in male and female dogs at 15 mg/kg-day, but the change was statistically significant only in males. The authors identified a NOAEL in dogs of 2.5 mg/kg-day.

Although chronic inhalation studies are available, we did not consider them to identify NOAELs because of the availability of chronic oral studies and the additional uncertainty associated with route-to-route extrapolation. Likewise, we did not consider the subchronic toxicity studies because of the availability of chronic studies and the necessity to include an additional uncertainty factor in calculating the PHG to account for a less than lifetime exposure period.

From the toxicity studies described above, we identified a NOAEL and LOAEL for the chronic oral administration of 1,3-DCP of 2.5 and 12.5 mg/kg-day, respectively, based on the results of the chronic rat study (Stott et al., 1995). This is consistent with the recommendations of the Health Effects Division RfD/QA Peer Review Committee of the U.S. EPA that evaluated the existing or recently submitted toxicology data for Telone® II to reassess the reference dose (RfD) for this chemical (U.S. EPA, 1997). Based on the chronic study in rats (Stott et al., 1995), the committee established a no-observed-effect level (NOEL) of 2.5 mg/kg-day and a lowest-observed-effect level (LOEL) of 12.5 mg/kg-day, based on decreased body weight gain and increased incidence of basal cell hyperplasia of the nonglandular mucosa of the stomach.

Carcinogenic Effects

For the purpose of establishing the most sensitive site of tumor formation in the most sensitive sex and strain of experimental animals, cancer potencies and slope factors were calculated for the exposure-related tumor incidences reported as statistically significant increases in the oral studies by NTP (1985b) and Stott *et al.* (1995) (Table 6). The inhalation studies (Lomax et al., 1989), while supportive of the finding of carcinogenicity of Telone® II, were not used in the generation of cancer potencies because of the availability of oral studies and the additional uncertainty associated with route-to-route extrapolation. A recent evaluation by the inhalation route for use in an inhalation route risk assessment (DPR, 1994) identified a cancer potency of 0.055 $(mg/kg\text{-}day)^{-1}$, a value within the range of those identified in the present evaluation from oral exposures (see below).

Available evidence suggests that formulations of Telone® II are genotoxic. The chemical nature of its primary component, 1,3-DCP, also suggests that it is a highly reactive compound and there is evidence of alkylating activity. An assumption of linearity was chosen in the approach to the evaluation of the dose-response below the observable range because of the evidence of gene mutation and potential DNA reactivity. U.S. EPA's recent guidelines on carcinogenicity risk assessment suggest that "[a] default assumption of linearity is appropriate when the evidence supports a mode of action of gene mutation due to DNA reactivity or supports another mode of action that is anticipated to be linear" in part because "the former modeling procedure [estimates from the linearized multistage model] gave an appearance of specific knowledge and sophistication unwarranted for a default." (U.S. EPA, 1996a). There is not adequate evidence to support a non-linear approach to the dose-response evaluation for 1,3-DCP. The estimation of the dose-response relationship at low doses was determined to be most appropriately carried out using linear extrapolation from a point of departure from a polynomial fit to the observed data, in this case the lower bound on the dose associated with 10% extra risk (LED_{10}). According to U.S. EPA (1996a), "[t]he rationale supporting the use of the LED_{10} is that a 10% response is at or just below the limit of sensitivity of discerning a significant difference in most long-term rodent studies." In the case of the carcinogenicity data for 1,3-DCP, no data are available below the calculated LED_{10}s that would provide a more appropriate point of departure. The LED_{10} was used in generating a cancer slope factor (CSF) which described the linear relationship of extra cancer risk to dose below this point of departure.

For the generation of the potencies, the Tox_Risk (Version 3.5) program was used which fit the linearized multistage model to the data on tumor incidence (Tox_Risk, 1993). The results of these analyses are presented in Table 7 below. Estimates of the cancer potency were also made using the multistage model polynomial exclusively (q_1*), for comparative purposes. Interspecies scaling of cancer potencies from experimental animals (CSF_{animal} or q_{animal}) to human potencies (CSF_{human} or q_1*) were based on the following relationship:

$$CSF_{human} = CSF_{animal} \times \left(\frac{bw_h}{bw_a}\right)^{\frac{1}{4}}$$

where bw_h and bw_a are human and animal body weight defaults, respectively. The default body weights are 70 kg for humans, 0.03 kg for mice, and 0.35 kg for rats.

Table 6 identifies the data sets evaluated in establishing a cancer slope factor for Telone® II. The cancer slope factors generated from the same data sets are presented in Table 7. The calculated slope factors for all data sets fell within a three-fold range. Given the possible contribution of epichlorohydrin to the development of forestomach tumors in the NTP Telone® II bioassay, a cancer slope factor calculation using these tumor incidences was deemed inadequate for the estimation of the cancer risk from exposure to Telone® II. Based upon the cancer potency estimates from the various data sets, the most sensitive site, sex, and species for tumor development is transitional cell carcinomas in the urinary bladder observed in female mice in the NTP bioassay, with a CSF_{human} from this data set of $0.091(mg/kg\text{-}day)^{-1}$. We therefore selected this value as most appropriate for the calculation of the drinking water PHG for carcinogenic end points.

Table 6. Tumor Incidence Used for Estimation of Cancer Potency.

Data Set / Study		Dose	Time-Averaged Dose	Tumor Incidence
1	urinary bladder carcinoma - female mice (NTP, 1985b)	0, 50, 100 mg/kg-day 3 days/week gavage	0, 21.4, 42.9 mg/kg-day	0/50, 8/50, 21/45[a]
2	lung/combined adenoma or carcinoma - female mice (NTP, 1985b)	0, 50, 100 mg/kg-day 3 days/week gavage	0, 21.4, 42.9 mg/kg-day	2/50, 4/50, 8/47[a]
3	forestomach/combined papilloma or carcinoma - male rats (NTP, 1985b)	0, 25, 50 mg/kg-day 3 days/week gavage	0, 10.7, 21.4 mg/kg-day	1/49, 1/48, 13/50[a]
4	liver/combined neoplastic nodule or carcinoma - male rats (NTP, 1985b)	0, 25, 50 mg/kg-day 3 days/week gavage	0, 10.7, 21.4 mg/kg-day	1/49, 6/48, 8/50[a]
5	liver adenomas - male rats (Stott et al., 1995)	0, 2.5, 12.5, 25 mg/kg-day in feed	0, 2.5, 12.5, 25 mg/kg-day	2/50, 1/50, 6/50, 9/50[b]

[a] Incidence adjusted for animals at risk (excluding animals that died before week 52 or the time tumors were first detected or animals not examined microscopically at a specific site).

[b] Number of tumor-bearing animals/number of animals examined at the site.

Table 7. Cancer Potencies from Carcinogenicity Bioassays of Telone® II by the Oral Route (generated using Tox_Risk Version 3.5).

Data Set		q_{animal} (/mg/kg-d)	q_1* (/mg/kg-d)	χ^2	p	k	MLE_{10} (mg/kg-d)	LED_{10} (mg/kg-d)	CSF_{animal} (/mg/kg-d)	CSF_{human} (/mg/kg-d)
1	urinary bladder carcinoma - female mice[a]	1.37×10^{-2}	9.5×10^{-2}	~0	1.00	2	16.1	7.7	1.30×10^{-2}	9.1×10^{-2}
2	lung/combined adenoma or carcinoma - female mice[a]	5.44×10^{-3}	3.8×10^{-2}	~0	1.00	2	35.8	19.4	5.16×10^{-3}	3.6×10^{-2}
3	forestomach/ combined papilloma or carcinoma - male rats[a]	6.95×10^{-3}	2.6×10^{-2}	2.39	0.12	2	14.3	10.9	9.13×10^{-3}	3.4×10^{-2}
4	liver/combined neoplastic nodule or carcinoma - male rats[a]	1.33×10^{-2}	5.0×10^{-2}	0.36	0.55	2	1.3	7.9	1.26×10^{-2}	4.7×10^{-2}
5	liver adenomas - male rats[b]	1.11×10^{-2}	4.2×10^{-2}	1.03	0.31	3	16.3	9.5	1.06×10^{-2}	4.0×10^{-2}

[a] Data from NTP, 1985b
[b] Data from Stott et al., 1995

CALCULATION OF PHG

Calculations of concentrations of chemical contaminants in drinking water associated with negligible risks for carcinogens or noncarcinogens must take into account the toxicity of the chemical itself, as well as the potential exposure of individuals using the water. Tap water is used directly as drinking water, for preparing foods and beverages. It is also used for bathing or showering, and in washing, flushing toilets and other household uses resulting in potential dermal and inhalation exposures.

Noncarcinogenic Effects

Calculation of a public health-protective concentration (C, in mg/L) for 1,3-DCP in drinking water for noncarcinogenic end points follows the general equation:

$$C = \frac{NOAEL/LOAEL \times BW \times RSC}{UF \times L/day}$$

where,

NOAEL/LOAEL = No-observed-adverse-effect-level or lowest-observed-adverse-effect level

BW	=	Adult body weight (a default of 70 kg for male or 60 kg for female)
RSC	=	Relative source contribution (a default of 20% to 80%)
UF	=	Uncertainty factors (typical defaults of a 10 to account for inter-species extrapolation, a 10 for uncertainty from the subchronic nature of the principal study and a 10 for potentially sensitive human subpopulations)
L/day	=	Daily water consumption rate: 2 L/day for 60 to 70 kg adult, 1 L/day for 10 kg child, higher values of L equivalents (Leq/day) are used for volatile organic compounds to account for inhalation and dermal exposure through showering, flushing of toilets, and other household uses of tap water.

In the case of 1,3-DCP, the oral chronic study using rats identified an experimental NOAEL of 2.5 mg/kg-day and a LOAEL of 12.5 mg/kg-day, based on body weight depression and hyperplasia of the non-glandular mucosa of the stomach. A NOAEL of 2.5 mg/kg-day also was identified in the chronic mouse and dog studies. The adult human body weight (BW) default value is 70 kg. The RSC of 20% was used in the calculation in the absence of information suggesting this value is not appropriate. We applied a cumulative uncertainty factor of 100, which incorporates uncertainty contributions for interspecies extrapolation (10) and potentially sensitive human subpopulations (10). 1,3-DCP is a volatile organic compound (VOC); the OEHHA default value for adult human water consumption for VOCs is 4 Leq/day, with 2 L/day by ingestion and 2 Leq/day by inhalation. Thus:

$$C = \frac{2.5\ {}^{mg}/_{kg-day} \times 70\ kg \times 0.2}{100 \times 4\ {}^{Leq}/_{day}} = 0.0875\ mg/L$$

$$= 0.09\ mg/L\ (rounded)$$

$$= 90\ \mu g/L = 90\ ppb$$

Carcinogenic Effects

For carcinogens, the following general equation can be used to calculate the public health-protective concentration (C) for 1,3-DCP in drinking water (in mg/L):

$$C = \frac{BW \times R}{q_1^* \text{ or } CSF \times L/day} = mg/L$$

where,

BW	=	Adult body weight (a default of 70 kg)
R	=	*De minimis* level for lifetime excess individual cancer risk (a default of 10^{-6})
q_1* or CSF	=	Cancer slope factor, q_1* is the upper 95% confidence limit on the cancer potency slope calculated by the LMS model, and CSF is a potency derived from the lower 95% confidence limit on the 10% tumor dose (LED_{10}). CSF = 10% / LED_{10}. Both potency estimates are converted to human equivalent [in $(mg/kg\text{-}day)^{-1}$] using $BW^{3/4}$ scaling.
L/day	=	Daily water consumption rate: 2 L/day for 60 to 70 kg adult, 1 L/day for 10 kg child, higher values of L equivalents (Leq/day) are used for volatile organic compounds to account for inhalation and dermal exposure through showering, flushing of toilets, and other household uses of tap water.

The purpose of calculating two potency estimates for a carcinogen is based on the fact that our current experience-base is almost wholly with the LMS model whereas the new method by U.S. EPA (1996a) in its proposed guidelines for carcinogen risk assessment, is based on the LED_{10} which has little or no experience-base and may present problems. The LMS model focuses on the linear low dose extrapolation and analysts (e.g., U.S. EPA) have often accepted relatively poor fits to the observed tumor incidence data. The new method, however, places a higher premium on fitting the observed data to estimate the ED_{10} and the 95% lower bound (LED_{10}), the point from which the low dose extrapolation is made (U.S. EPA, 1996a). As shown in Table 7, the potency estimates for 1,3-DCP, which were calculated using the two methods, were consistent (0.095 $(mg/kg\text{-}day)^{-1}$ and 0.091 $(mg/kg\text{-}day)^{-1}$) for q_1*and CSF_{human}, respectively).

The cancer slope factor selected for calculating the PHG was derived using the LED_{10} method from the proposed U.S. EPA guidelines. For 1,3-DCP, the cancer slope factor (CSF_{human}) derived from the principal study is 0.091 $(mg/kg\text{-}day)^{-1}$ and the adult human body weight (BW) default value is 70 kg. 1,3-DCP is a VOC; the OEHHA default value for adult human water consumption for VOCs is 4 Leq/day, with 2 L/day by ingestion and 2 Leq/day by inhalation. A de minimis risk level of 10^{-6} is used for calculating the health protective level.

Therefore :

$$C = \frac{10^{-6} \times 70\ kg}{0.091\,(mg/kg\text{–}day)^{-1} \times 4\ {}^{Leq}\!/_{day}} = 0.00019\ mg/L$$

$$= 0.0002\ mg/L\ (rounded)$$

$$= 0.2\ \mu g/L = 0.2\ ppb$$

OEHHA has developed a PHG of 0.2 µg/L (0.2 ppb) for 1,3-DCP in drinking water based on its carcinogenic evidence in mice.

RISK CHARACTERIZATION

The primary sources of uncertainty in the development of the PHG for 1,3-DCP in drinking water are also the general issues of uncertainty in any risk assessment, particularly inter- and intra-species extrapolation and relative source contribution (RSC). Another source of uncertainty is to what extent epichlorohydrin may contribute to the carcinogenicity of Telone® II used in the NTP study upon which the PHG is based. However, epichlorohydrin is not known to induce tumors at sites other than that of initial contact; therefore, the urinary bladder tumors in female mice observed in the NTP bioassay were felt to be unaffected by the epichlorohydrin content of the Telone® II.

The PHG of 0.2 ppb was calculated based on the carcinogenic potency of 1,3-DCP. In calculating the PHG, a *de minimis* theoretical excess individual cancer risk level of 10^{-6} was used. The corresponding levels for cancer risk levels of 10^{-5} or 10^{-4} are 2 and 20 ppb, respectively.

For PHGs, our use of the RSC has, with a few exceptions, followed U.S. EPA drinking water risk assessment methods. U.S. EPA has treated carcinogens differently from noncarcinogens with respect to the use of RSCs. For noncarcinogens, RfDs (in mg/kg-day), drinking water equivalent levels (DWELs, in mg/L) and MCLGs (in mg/L) are calculated using uncertainty factors (UFs), body weights and water consumption rates (L/day) and the RSC, respectively. The RSC range is 20% to 80% (0.2 to 0.8) depending on the scientific evidence.

U.S. EPA follows a general procedure in promulgating MCLGs:

1. if Group A and B carcinogens (i.e., strong evidence of carcinogenicity) MCLGs are set to zero,
2. if Group C (i.e., limited evidence of carcinogenicity), either an RfD approach is used (as with a noncarcinogen) but an additional UF of 1 to 10 (usually 10) is applied to account for the limited evidence of carcinogenicity, or a quantitative method (potency and low-dose extrapolation) is used and the MCLG is set in the 10^{-5} to 10^{-6} cancer risk range,
3. if Group D (i.e., inadequate or no animal evidence) a RfD approach is used to promulgate the MCLG.

For approaches that use low-dose extrapolation based on quantitative risk assessment, U.S. EPA does not factor in an RSC. The use of low-dose extrapolation is considered by U.S. EPA to be adequately health-protective without the additional source contributions. In developing PHGs, we have adopted the assumption that RSCs should not be factored in for carcinogens grouped in U.S. EPA categories A and B, and for C carcinogens for which we have calculated a cancer potency based on low-dose extrapolation. This is an area of uncertainty and scientific debate and it is not clear how this assumption impacts the overall health risk assessment.

OTHER REGULATORY STANDARDS

The U.S. EPA maximum contaminant level goal (MCLG) for 1,3-DCP of zero mg/L is tentative (not officially proposed) (U.S. EPA, 1996b). A value of zero may be used for Group A or B carcinogens. U.S. EPA does not currently have an MCL for 1,3-DCP.

The California MCL for 1,3-DCP is 0.5 µg/L and is based on the chemical's carcinogenic potential (DHS, 1988a, b). OEHHA (formerly in DHS) calculated the MCL using a q_1* of 0.18 $(mg/kg\text{-}day)^{-1}$ derived by U.S. EPA. Like OEHHA, U.S. EPA also used the NTP bioassay as the principal study (NTP, 1985b), but based the cancer potency calculation on forestomach papillomas and carcinomas in rats, instead of urinary bladder tumors in mice. Using the default drinking water consumption rate of 2 L/day and the default body weight of 70 kg, a *de minimis* water concentration of 0.2 ppb was calculated (DHS, 1988a). However, because the detection limit of 1,3-DCP for purposes of reporting is 0.5 µg/L, the MCL is 0.5 µg/L (DHS, 1988b; California Code of Regulations, Title 22, Article 4, Section 64444).

Ambient water criteria for the protection of human health from the toxic properties of ingested dichloropropenes are: 87 µg/L (water and contaminated aquatic organisms) and 14.1 mg/L (contaminated aquatic organisms alone) (U.S. EPA, 1986)

A Threshold Limit Value (TLV) of 1 ppm is recommended for 1,3-DCP (ACGIH, 1989 as cited in ATSDR, 1992).

REFERENCES

ACGIH (1989). Threshold limit values and biological exposure indices for 1989-1990. American Conference of Governmental Industrial Hygientists, Cincinnati, OH.

ARB (1995). Ambient air monitoring in Merced County for Telone (1,3-dichloropropene) during DowElanco's commercial reintroduction, March-April, 1995. Test Report No. C94-071-M. California Air Resources Board, November 9, 1995.

ARB (1996). Ambient air monitoring in Kern County for Telone (1,3-dichloropropene) during DowElanco's commercial reintroduction, May-December, 1995. Test Report No. C94-071-K. California Air Resources Board. November 8, 1996.

Aspelin AL (1997). Pesticides industry sales and usage. 1994 and 1995 Market estimates. U.S. Environmental Protection Agency, Office of Prevention, Pesticides and Toxic Substances. Report 733-R-97-002. August 1997.

ATSDR (1992). Toxicological profile for 1,3-dichloropropene. TP-91/15. Agency for Toxic Substances and Disease Registry, U.S. Public Health Service, Atlanta, GA. September 1992.

Bannasch P, Zerban H (1992). Predictive value of hepatic preneoplastic lesions as indicators of carcinogenic response. In: Vainio H, Magee PN, McGregor DB, McMichael AJ, editors. Mechanisms of carcinogenesis in risk identification. Lyon: International Agency for Research on Cancer. pp. 389-427.

Berry DL, Campbell WF, Street JC, Salunkhe DK (1980). Uptake and metabolism of 1,3-dichloropropene in plants. J. Food Safety 2(4):247-255.

Bhaskar Gollapudi B, Bruce RJ, Hinze CA (1985). Evaluation of Telone® II soil fumigant in the mouse bone marrow micronucleus test. Testing at Lake Jackson Research Center, Dow Chemical Co. and submitted to US Environmental Protection Agency. EPA/OTS 86-870002289.

Breslin WJ, Kirk HD, Streeter CM, Quast JF, Szabo JR (1989). 1,3-Dichloropropene: two-generation inhalation reproduction study in Fischer 344 rats. Fund. Appl. Toxicol. 12:129-143.

Budavari S (ed.) (1989). The Merck Index - Encyclopedia of Chemicals, Drugs, and Biologicals. Rahway, NJ: Merck & Co., Inc.

Climie IJG, Hutson DH, Morrison BJ, Stoydin G (1979). Glutathione conjugation in the detoxication of (*Z*)-1,3-dichloropropene (a component of the nematocide D-D) in the rat. Xenobiotica 9(3):149-156.

Creedy CL, Brooks TM, Dean BJ, Hutson DH, Wright AS (1984). The protective effect of glutathione on the microbial mutagenicity of the *Z*- and *E*-isomers of 1,3-dichloropropene. Chem. Biol. Interact 50(1):39-48.

De Lorenzo F, Degl'Innocenti S, Ruocco A, Silengo L, Cortese R (1977). Mutagenicity of pesticides containing 1,3-dichloropropene. Cancer Res. 37(6):1915-7.

DHS (1988a). Proposed Maximum Contaminant Level (PMCL), 1,3-Dichloropropene. Hazard Evaluation Section, California Department of Health Services. Currently the Pesticide and Environmental Toxicology Section, Office of Environmental Health Hazard Assessment, California Environmental Protection Agency.

DHS (1988b). Maximum contaminant levels for xylenes, monochlorobenzene, ethylbenzene, 1,3-dichloropropene and 1,1,2,2-tetrachloroethane in drinking water (R-5-88). Notice of proposed rulemaking. California Department of Health Services.

Dietz FK, Hermann EA, Ramsey JC (1984a). The pharmacokinetics of ^{14}C-1,3-dichloropropene in rats and mice following oral administration. Toxicologist 4(1):147 (Abstr. No. 585).

Dietz FK, Dittenber DA, Kirk HD, Ramsey JC (1984b). Non-protein sulfhydryl content and macromolecular binding in rats and mice following oral administration of 1,3-dichloropropene. Toxicologist 4(1):147 (Abstr. No. 586).

DowElanco (1991). Telone ® II Soil Fumigant. Material Safety Data Sheet. Effective 4/29/93. DowElanco, Indianapolis, IN.

DPR (1994). Interim risk assessment of 1,3-dichloropropene for the proposed use of Telone® II(1994-95). NR Reed, Health Assessment Section, Medical Toxicology Branch, California Department of Pesticide Regulation. November, 1994.

DPR (1996a). 1995 Annual pesticide use report indexed by chemical. California Environmental Protection Agency, Department of Pesticide Regulation, Sacramento, CA. December 1996.

DPR (1996b). Stewardship program and suggested permit conditions for the statewide use of Telone® II (1,3-dichloropropene). ENF 96-009. February 15, 1996.

DPR (1997). Sampling for pesticide residues in California well water. 1996 Update of the well inventory database for sampling results reported from July 1, 1995 through June 30, 1996. California Environmental Protection Agency, Department of Pesticide Regulation, Sacramento, California. EH96-06. March 1997.

Eder E, Neudecker T, Lutz D, Henschler D (1982). Correlation of alkylating and mutagenic activities of allyl and allylic compounds: standard alkylation test vs. kinetic investigation. Chem. Biol. Interact 38(3):303-15.

Fisher GD, Kilgore WW (1988). Tissue levels of glutathione following acute inhalation of 1,3-dichloropropene. J. Toxicol. Environ. Health 23:171-182.

Fisher GD, Kilgore WW (1989). Pharmacokinetics of S-[3-chloroprop -2-enyl]glutathione in rats following acute inhalation exposure to 1,3-dichloropropene. Xenobiotica 19(3):269-278.

Flessel P, Goldsmith JR, Kahn E, Wesolowski JJ, Maddy K, Peoples SA (1978). Acute and possible long-term effects of 1,3-dichloropropene -- California. Morbid. Mortal. Wkly. Rep. 271:50, 55.

Ghia M, Robbiano L, Allavena A, Martelli A, Brambilla G (1993). Genotoxic activity of 1,3-dichloropropene in a battery of in vivo short-term tests. Toxicol. Appl. Pharmacol. 120(1):120-5.

Hanley TR Jr, John-Green JA, Young JT, Calhoun LL, Rao KS (1987). Evaluation of the effects of inhalation exposure to 1,3-dichloropropene on fetal development in rats and rabbits. Fund. Appl. Toxicol. 8:562-570.

Haut KT, Stebbins KE, Johnson KA, Shabrang SN, Stott WT (1996). Subchronic toxicity of ingested 1,3-dichloropropene in rats and mice. Fund. Appl. Toxicol. 32:224-232.

Haworth S, Lawlor T, Mortelmans K, Speck W, Zeiger E (1983). *Salmonella* mutagenicity test results for 250 chemicals. Environ. Mutagen 5(Suppl 1):3-142.

Hayes WJ Jr, Laws ER Jr (1991). Handbook of Pesticide Toxicology. Vol. 2. Classes of Pesticides. San Diego: Academic Press, Inc.

Hernandez AF, Martin-Rubi JC, Ballesteros JL, Oliver M, Pla A, Villanueva E (1994). Clinical and pathological findings in fatal 1,3-dichloropropene intoxication. Hum. Experiment. Toxicol. 13:303-306.

Houtman BA (1993). An evaluation of 1,3-dichloropropene worker exposures associated with TELONE* II soil fumigant loading, application and re-entry-Phase I. Interim report. North American Environmental Chemistry Laboratory, DowElanco, Indianapolis, IN. Study ID. ECL92095. March 15, 1993.

HSDB (1997). 1,3-Dichloropropene (CASRN 542-75-6). Hazardous Substances Databank. Last revised 10/20/97.

Hutson DH, Moss JA, Pickering BA (1971). The excretion and retention of components of the soil fumigant D-D and their metabolites in the rat. Food Cosmet. Toxicol. 9:677-680.

IARC (1987). 1,3-Dichloropropene (technical-grade) (Group 2B). International Agency for Research on Cancer, Monographs on the Evaluation of Carcinogenic Risks to Humans. Suppl. 7:195-196.

Imanishi H, Sasaki YF, Watanabe M, Moriya M, Shirasu Y, Tutikawa K (1987). Mutagenicity evaluation of pesticides in the mouse spot test [Abstract]. Mutat. Res. 182:361.

Jeffrey MM (1987a). Telone® II soil fumigant: Primary dermal irritation study in New Zealand White rabbits. Study No. M-003993-017B. Dow Chemical Co., Midland, MI.

Jeffrey MM (1987b). Telone® II soil fumigant: Primary eye irritation study in New Zealand White rabbits. Study No. M-003993-017C. Dow Chemical Co., Midland, MI.

John JA, Kloes PM, Calhoun LL, Young JT (1983). Telone* II: inhalation teratology study in Fischer 344 rats and New Zealand White rabbits. Dow Chemical USA, Midland, MI. October 31, 1983.

Kezic S, Monster AC, Verplanke AJW, de Wolff FA (1996). Dermal absorption of cis-1,3-dichloropropene vapour: human experimental exposure. Hum Exp Toxicol 15:396-9.

Kevekordes S, Gebel T, Pav K, Edenharder R, Dunkelberg H (1996). Genotoxicity of selected pesticides in the mouse bone-marrow micronucleus test and in the sister-chromatid exchange test with human lymphocytes in vitro. Toxicol. Lett. 89(1):35-42.

Konishi Y, Kawabata A, Denda A, Ikeda T, Katada H, Maruyama H, et al. (1980). Forestomach tumors induced by orally administered epichlorohydrin in male Wistar rats. Gann 71:922-3.

Krijgsheld KR, Van der Gen A (1986). Assessment of the impact of the emission of certain organochlorine compounds on the aquatic environment. Part II: Allylychloride, 1,3- and 2,3-dichloropropene. Chemosphere 15(7):861-880.

Lomax LG, Calhoun LL, Stott WT, Frauson LE (1987). Telone® II soil fumigant: 2-year inhalation chronic toxicity-oncogenicity study in rats. Study ID: M-003993-009R (US EPA MRID No. 403122-01). The Dow Chemical Co., Midland, MI. July 13, 1987.

Lomax LG, Stott WT, Johnson KA, Calhoun LL, Yano BL, Quast JF (1989). The chronic toxicity and oncogenicity of inhaled technical-grade 1,3-dichloropropene in rats and mice. Fund. Appl. Toxicol. 12(3):418-431.

Loveday KS, Lugo MH, Resnick MA, Anderson BE, Zeiger E (1989). Chromosome aberration and sister chromatid exchange tests in Chinese hamster ovary cells in vitro: II. Results with 20 chemicals. Environ. Mol. Mutagen. 13(1):60-94.

Maddy KT, Fong HR, Lowe JA, Conrad, DW, Fredrickson AS (1982). A study of well water in selected California communities for residues of 1,3-dichloropropene, chloroallyl alcohol and 49 organophosphate or chlorinated hydrocarbon pesticides. Bull. Environ. Contam. Toxicol. 29:354-359.

Markovitz A, Crosby WH (1984). Chemical carcinogenesis. A soil fumigant, 1,3-dichloropropene, as possible cause of hematologic malignancies. Arch. Intern. Med. 144(7):1409-1411.

Martelli A, Allavena A, Ghia M, Robbiano L, Brambilla G (1993). Cytotoxic and genotoxic activity of 1,3-dichloropropene in cultured mammalian cells. Toxicol. Appl. Pharmacol. 120(1):114-9.

Mendrala AL (1986). The evaluation of Telone® II soil fumigant in the Chinese hamster ovary cell/hypoxanthine (guanine) phosphoribosyl transferase (CHO/HPGRT) forward mutation assay (sanitized). Testing by Dow Chemical Co. and submitted to U.S. Environmental Protection Agency. EPA/OTS 86-870002293.

Mendrala AL (1987). Evaluation of Telone® II soil fumigant in the rat hepatocyte unscheduled DNA synthesis assay. EPA/OTS 86-870002287.

Myhr BC, Caspary WJ (1991). Chemical mutagenesis at the thymidine kinase locus in L5178Y mouse lymphoma cells: results for 31 coded compounds in the National Toxicology Program. Environ. Mol. Mutagen. 18(1):51-83.

Neudecker T, Henschler D (1986). Mutagenicity of chloroolefins in the *Salmonella*/mammalian microsome test. III. Metabolic activation of the allylic chloropropenes allyl chloride, 1,3-dichloropropene, 2,3-dichloro-1-propene, 1,2,3-trichloropropene, 1,1,2,3-tetrachloro-2-propene and hexachloropropene by S9 mix via two different metabolic pathways. Mutat. Res. 170(1-2):1-9.

Neudecker T, Stefani A, Henschler D (1977). In vitro mutagenicity of the soil nematicide 1,3-dichloropropene. Experientia 33(8):1084-5.

NIOSH (1994). NIOSH Pocket Guide to Chemical Hazards. National Institute for Occupational Safety and Health. pp. 100-101. June 1994.

NTP (1985a). Carcinogenesis studies of 1,2-dichloropropane (propylene dichloride) (CAS No. 78-87-5) in F344/N rats and B6C3F_1 mice (gavage studies). NTP TR 263. National Toxicology, Research Triangle Park, NC.

NTP (1985b). Toxicology and carcinogenesis studies of Telone® II(technical-grade 1,3-dichloropropene [CAS No. 542-75-6] containing 1% epichlorohydrin as a stabilizer) in F344/N rats and B6C3F1 mice (gavage studies). NTP TR 269. National Toxicology Program, Research Triangle Park, NC. May 1985.

NTP (1994). Seventh Annual Report on Carcinogens. National Toxicology Program, Research Triangle Park, NC.

OEHHA (1998). Safe drinking water and toxic enforcement act of 1986. Chemicals known to the state to cause cancer or reproductive toxicity. Office of Environmental Health Hazard Assessment, California Environmental Protection Agency. May 15, 1998.

Osterloh JD, Cohen B, Popendorf W, Pond SM (1984). Urinary excretion of the *N*-acetyl cysteine conjugate of the cis-1,3-dichloropropene by exposed individuals. Arch. Environ. Health 39(4):271-275.

Pitot HC, Dragan YP, Teeguarden J, Hsia S, Campbell H (1996). Quantitation of multistage carcinogenesis in rat liver. Toxicol. Pathol. 24(1):119-128.

Redmond JM, Stebbins KE, Stott WT (1995). Telone® II soil fumigant: Two-year dietary chronic toxicity/oncogenicity study in B6C3F1 mice - final report. Study ID: M-003993-032. The Dow Chemical Co., Midland, MI. August 9, 1995.

Roberts TR, Stoydin G (1976). The degradation of (Z)- and (E)-1,3-dichloropropenes and 1,2-dichloropropane in soil. Pesticide Sci. 7:325-335.

Sabel GV, Clark TP (1984). Volatile organic compounds as indicators of municipal solid waste leach contamination. Waste Manage. Res. 2:119-130.

Sasaki YFX, Imanishi H, Matsumoto K, et al. (1988). 1,3-Dichloropropene: In vitro cytogenetics test. IET 88-0038. Prepared by Dow Chemical Japan Limited and Shell Kagaku K.K., by the Institute of Environmental Toxicology, Tokyo, Japan. [Unpublished study to be peer reviewed.]

Schiffmann D, Eder E, Neudecker T, Henschler D (1983). Induction of unscheduled DNA synthesis in HeLa cells by allylic compounds. Cancer Lett. 20(3):263-9.

Smith JW et al. (1985). Health and Environmental Effects Profile on 1,3-Dichloropropene. Final Draft, SRC-TR-85-090.

Stolzenberg SJ, Hine CH (1980). Mutagenicity of 2- and 3-carbon halogenated compounds in the *Salmonella*/mammalian-microsome test. Environ. Mutagen. 2(1):59-66.

Stott W, Johnson K, Calhoun L, Weiss S, Frauson L (1987). Telone® II soil fumigant: 2-year inhalation chronic toxicity/oncogenicity study in mice. Study ID: M-003993-009. US EPA MRID No. 403123-00 (reviewed in Doc. No. 006573). Dow Chemical Co., Midland MI. July 13, 1987.

Stott WT, Johnson KA, Jeffries TK, Haut KT, Shabrang SN (1995). Telone®II soil fumigant: Two-year chronic toxicity/oncogenicity study in Fischer 344 rats. Study ID: M-003993-031. Toxicology Research Laboratory, The Dow Chemical Co., Midland MI. August 15, 1995.

Stott WT, Kastl PE (1986). Inhalation pharmacokinetics of technical grade 1,3-dichloropropene in rats. Toxicol. Appl. Pharmacol. 85:332-341.

Stott WT, Mendrala AL, Kastl PE (1989). Investigation of urinary excretion products of 1,3-dichloropropene using the Ames' bacterial mutagenicity assay (Final Report) with cover letter dated 060989. EPA/OTS 86-890000410.

Stott WT, Stebbins KE, Haut KT, Quast JF, Shabrang SN (1992). Telone®II soil fumigant: One-year dietary toxicity study in beagle dogs. Dow Chemical Co., Midland MI. July 22, 1992. Study ID: M-003993-024.

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

Su Q, Benner A, Hofmann WJ, Otto G, Pichlmayr R, Bannasch P (1997). Human hepatic preneoplasia: phenotypes and proliferation kinetics of foci and nodules of altered hepatocytes and their relationship to liver cell dysplasia. Virchows. Arch. 431(6):391-406. [Abstract.]

Sudo S, Kimura Y, Yamamoto K, Ichihara S (1987a). Mutagenicity test on 1,3-dichloropropene in bacteria test system. EPA/OTS 86-870002311. (Dow Chemical Japan study submitted to U.S. Environmental Protection Agency for Japanese registration purposes.)

Sudo S, Kimura Y, Yamamoto K, Ichihara S (1987b). Mutagenicity test on 1,3-dichloropropene in bacteria. EPA/OTS 86-870002298. (Dow Chemical Japan study submitted to U.S. Environmental Protection Agency for Japanese registration purposes.)

Talcott RE (1981). Mutagenic impurities associated with 1,3-dichloropropene. Toxicologist 1:41. [Abstract.]

Talcott RE, King J (1984). Mutagenic impurities in 1,3-dichloropropene preparations. J. Natl. Cancer Inst. 72(5):1113-6.

Tennant RW, Margolin BH, Shelby MD, Zeiger E, Haseman JK, Spalding J, et al. (1987). Prediction of chemical carcinogenicity in rodents from in vitro genetic toxicity assays. Science 236(4804):933-41.

Tox_Risk (1993). Toxicology Risk Assessment Program. Version 3.5. TXV01467. Copyright EPRI 1986-1993. Developed by ICF Kaiser International, Ruston, LA.

U.S. EPA (1986). US EPA Quality Criteria for Water, 1986: Dichloropropanes/Dichloropropenes. EPA 440/5-86-001. May 1, 1986.

U.S. EPA (1990). Memorandum from HM Pettigrew of the Science Support Section, Science Analysis and Coordination Branch, Health Effects Division, to A Levy of Review Section I, Toxicology Branch II, Health Effects Division regarding Telone® II - Quantitative Risk Assessment, Mouse ($B6C3F_1$) Inhalation Study. U.S. Environmental Protection Agency. April, 1990.

U.S. EPA (1996a). Proposed guidelines for carcinogen risk assessment. Office of Research and Development, Washington, D.C. EPA/600/P-92/003C.

U.S. EPA (1996b). Drinking water regulations and health advisories. U.S. EPA Office of Water. EPA 822-B-96-002. October 1996.

U.S. EPA (1997). RfD/peer review report of Telone II [1,3-Dichloropropene]. Memorandum from GA Ghali, Health Effects Division, to C Giles-Parker, Registration Division, U.S. Environmental Protection Agency, dated October 15, 1997.

U.S. EPA (1998). IRIS substance file for 1,3-dichloropropene. Carcinogenicity assessment for lifetime exposure (Last revised 10/01/93). Integrated Risk Information System, U.S. EPA. 05/28/98.

Valencia R, Mason JM, Woodruff RC, Zimmering S (1985). Chemical mutagenesis testing in *Drosophila*. III. Results of 48 coded compounds tested for the National Toxicology Program. Environ. Mutagen. 7(3):325-48.

Van Duuren BI, Goldschmidt BM, Loewengart G, Smith AC, Melchionne S, Seldman I, et al. (1979). Carcinogenicity of halogenated olefinic and aliphatic hydrocarbons in mice. J. Natl. Cancer Inst. 63(6):1433-9.

Van Sittert NJ (1989). Individual exposure monitoring from plasma or urinary metabolite determination. Arch. Toxicol. 13(Suppl.):91-100.

van Welie RTH, van Duyn P, Vermeulen NPE (1991). Environmental and biological monitoring of non-occupational exposure to 1,3-dichloropropene. Int. Arch. Occup. Environ. Health 63:169-173.

Vithayathil AJ, McClure C, Myers JW (1983). *Salmonella*/microsome multiple indicator mutagenicity test. Mutat. Res. 121(1):33-7.

von der Hude W, Behm C, Gürtler R, Basler A (1988). Evaluation of the SOS Chromotest. Mutat. Res. 203:81-94.

von der Hude W, Scheutwinkel M, Gramlich U, Fißler B, Basler A (1987). Genotoxicity of three-carbon compounds evaluated in the SCE test in vitro. Environ. Mutagen. 9:401-10.

Waechter JM Jr, Brzak KA, McCarty LP, LaPack MA, Brownson PJ (1992). 1,3-Dichloropropene (Telone® II soil fumigant): inhalation pharmacokinetics and metabolism in human volunteers. Internal report, Dow Chemical Co., Midland, MI.

Watson WP, Brooks TM, Huckle KR, Hutson DH, Lang KL, Smith RJ, et al. (1987). Microbial mutagenicity studies with (Z)-1,3-dichloropropene. Chem. Biol. Interact. 61(1):17-30.

Wester PW, Van der Heijden CA, Bisschop A, Van Esch GJ (1985). Carcinogenicity study with epichlorohydrin (CEP) by gavage in rats. Toxicology 36(4):325-9.

WHO (1993). 1,3-Dichloropropene, 1,2-dichloropropane and mixtures. Environ. Health Crit. 146. Geneva: World Health Organization.

Yang RSH, Huff JE, Boorman GA, Haseman JK, Kornreich M, Stookey JL (1986). Chronic toxicology and carcinogenesis studies of Telone® II by gavage in Fischer-344 rats and B6C3F_1 mice. J. Toxicol. Environ. Health 18 (3):377-392.

Responses to Major Comments on Technical Support Document

Public Health Goal
For
1,3-Dichloropropene
In Drinking Water

Prepared by

Pesticide and Environmental Toxicology Section
Office of Environmental Health Hazard Assessment
California Environmental Protection Agency

February 1999

TABLE OF CONTENTS

INTRODUCTION

The following are responses to major comments received by the Office of Environmental Health Hazard Assessment (OEHHA) on the proposed public health goal (PHG) technical support document for 1,3-dichloropropene as discussed at the PHG workshop held on October 6, 1998, or as revised following the workshop. Some commenters provided comments on both the first and second drafts. For the sake of brevity, we have selected the more important or representative comments for responses. Comments appear in quotation marks where they are directly quoted from the submission; paraphrased comments are in italics.

These comments and responses are provided in the spirit of the open dialogue among scientists that is part of the process under Health and Safety Code Section 57003. For further information about the PHG process or to obtain copies of PHG documents, visit the OEHHA web site at www.oehha.org. OEHHA may also be contacted at:

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RESPONSES TO MAJOR COMMENTS RECEIVED

Dow AgroSciences LLC

Comment 1: "Dow AgroSciences has reviewed the 'draft' document on the 'Public Health Goal for 1,3-D in Drinking Water.' We have identified many key studies and assessments that need to be added to your document and used in your PHG calculation. These scientific studies and assessments are critical to arriving at an appropriate PHG for 1,3-D. This letter will give you a list of these studies and assessments and an analysis of their importance to the overall PHG number."

Regarding the toxicology and carcinogenicity of 1,3-D, the commenter states: "Reviewing the PHG document it has been noted that several critical studies were not reviewed. Most of these studies are relatively new and have only recently been submitted to the EPA or made public. These studies are particularly critical because the data indicates increased margins of safety associated with the agricultural use of 1,3-D over that in previous regulatory assessments of 1,3-D. This is especially the case with the new carcinogenicity study results."

"We believe for the purpose of this drinking water assessment, the 23 studies listed must be considered."

Response 1: We thank you for your submission of the names of studies not cited in the PHG document (and your subsequent submission of a number of the recent studies from Dow Chemical Company Reports). A review of the subjects covered in the studies indicates that some provide useful supplemental information. Where appropriate, additional text has been added to the PHG document. Specifically, a summary of the Kezic *et al.* (1996) study examining the dermal absorption and metabolism of 1,3-DCP in human volunteers has been added to the Metabolism and Pharmacokinetics section. Aspects of some of the other studies, however, are already presented in the PHG document, and their inclusion is beyond the scope of the PHG review. Given the brief time available for review of these materials, emphasis has been placed on those studies which appear in the peer-reviewed literature. None affects the dose-response evaluation or the calculation of the PHG value at this time.

Comment 2: *Regarding the environmental fate of 1,3-D, the commenter states:* "In addition, there are also 16 environmental fate studies focusing on water, air, and soil that are also not included in your document. Again these are very recent studies. Each of these studies were evaluated as part of the USEPA's reregistration and Special Review evaluation. Again, if OEHHA is going to conduct a comprehensive assessment, it should take into account exposures from sources including, air, water, and soil and these studies will be critical for such an assessment."

"A complete list of studies is provided in the appendix."

Response 2: Thank you for identifying these materials relevant to the exposure assessment of 1,3-dichloropropene. Such materials would be relevant for a comprehensive assessment and may be useful for establishing or modifying the relative source contribution (RSC) for the non-cancer dose-response evaluation. The PHG value for 1,3-DCP is based on a cancer endpoint, so this information would not be expected to have an impact on the currently recommended number. Since these materials are not as yet available in their entirety, their review will need to occur when the PHG for 1,3-DCP is reconsidered.

Comment 3: *Regarding unpublished risk assessments not presented in the PHG document:* "As a result of the new scientific findings in the most recent toxicology and carcinogenicity studies on 1,3-D (see Appendix), Dow AgroSciences undertook the task of getting the scientific opinions of an independent group of scientists about these studies. We had an independent organization, Toxicology Excellence for Risk Assessment (TERA), establish a panel of expert scientists to review these new results and interpret and summarize the meaning of the results. I have enclosed in this package the 'Final Draft Document' for review by the TERA panel of experts. This is an up to date assessment which also contains the deliberations of the expert TERA panel. The final report of the TERA panel on 1,3-D will be published soon."

Response 3: We thank you for your submission of the draft TERA report and look forward to a review of the final published version. This document will become a part of the available materials when the PHG for 1,3-dichloropropene is reconsidered (within five years, by statute).

Comment 4: "In Summary, we request that rather than establishing a separate drinking water criterion for 1,3-D, OEHHA accept temporarily the values identified in the EPA RED document until the USEPA Cancer Peer Review panel carries out their reclassification review of 1,3-D in 1999."

Response 4: We believe the evaluation presented in the PHG document presents the most appropriate public health-protective assessment of 1,3-dichloropropene at the present time. Products of activities such as those carried out by U.S. EPA will certainly be a part of future OEHHA analyses of the health effects of 1,3-dichloropropene for purposes of establishing a drinking water standard. In support of the PHG document, U.S. EPA's recent Ambient Water Quality Criteria document (EPA/822/R-98/005; July 1998) identifies 1,3-DCP "likely to be carcinogenic to humans by all routes of exposure," with a mutagenic mode of action. Furthermore, under the Safe Drinking Water and Toxic Enforcement Act of 1986, 1,3-DCP is listed as a chemical known to the State to cause cancer. The International Agency for Research on Cancer has classified 1,3-DCP as a Group 2B carcinogen. 1,3-DCP is listed in the National Toxicology Program's seventh annual report on carcinogens as a compound "reasonably anticipated" to be a carcinogen. Consequently, there appears to be a substantial agreement in the scientific community that 1,3-DCP should be treated as a potential human carcinogen.