Residue Reviews

Reviews of Environmental Contamination and Toxicology

Volume 97

Springer-Verlag
New York Berlin Heidelberg Tokyo

1,3-Dichloropropene

By

RAYMOND S. H. YANG*

Contents

I. Introduction

1,3-Dichloropropene, the main ingredient of Telone II®[1], was introduced as a commercial fumigant in 1955 (Berry et al. 1980). A preparation containing 1,3-dichloropropene and 1,2-dichloropropane was subsequently marketed under the name D-D®[1] (Maddy et al. 1982, Parker et al. 1982). According to Parker et al. (1982) and Thompson (1983), there are presently at least seven commercial preparations of fumigant containing 1,3-dichloropropene (Table I).

*National Institute of Environmental Health Sciences, National Toxicology Program, P.O. Box 12233, Research Triangle Park, NC 27709.

[1]Telone II® is manufactured by Dow Chemical Company which also produced Vidden-D®, Telone®, Telone-C®, Telone-C17® at different times in the last 27 years. All of these preparations contained 1,3-dichloropropene at varying concentrations (Personal communication, Dow Chemical Company, 1985). D-D® is a product of Shell Oil Company.

Residue Reviews, Volume 97.

Table I. *Commercial fumigant preparations containing 1,3-dichloropropene*[a]

Fumigant	Composition	Synonyms
Telone II®	92% 1,3-dichloropropene 2% 1,2-dichloropropane 1% epichlorohydrin 5% mixture of chlorinated propenes and hexenes	
Telone-C17	74% Telone 16.5% chloropicrin	
D-D®	52% 1,3-dichloropropene 29% 1,2-dichloropropane minor components: 3,3-dichloropropene 2,2-dichloropropene other related chlorinated hydrocarbons	NEMAFENE
Terr-O-Cide 15-D	85% D-D® 15% chloropicrin	
Terr-O-Cide 30-D	70% D-D® 30% chloropicrin	
Terr-O-Gas 57/43T	43% D-D® 57% chloropicrin	
Vorlex	20% methylisothiocyanate 80% mixture of dichloropropenes dichloropropanes and other related compounds	TRAPEX DI-TRAPEX MENCS MIC MITC

[a] From Parker et al. (1982) and Thompson (1983).

1,3-Dichloropropene, a mixture of *cis* and *trans* isomers, is a clear, light straw-colored liquid with a penetrating, irritating, chloroform-like odor. The physical properties of a *cis/trans* mixture depend on the ratio of the isomers. For comparison, the chemical and physical properties of three major fumigants, 1,3-dichloropropene, ethylene dibromide (EDB), and methyl bromide are given in Table II.

Following the suspension of use of EDB as a soil fumigant by the Environmental Protection Agency in September 1983 (Chemical Regulator Reporter), the major replacements for EDB are methyl bromide and Telone II®. The object of this presentation is to consolidate the available information on 1,3-dichloropropene.

Table II. *Chemical and physical properties of three major fumigants*[a]

Property	EDB	1,3-DCP	Methyl bromide
Molecular formula	$BrCH_2CH_2Br$	$CHCl{=}CHCH_2Cl$	CH_3Br
Molecular weight	187.88	110.97	94.95
Physical state	Colorless liquid	Clear light-straw color liquid	Colorless gas
Boiling point (°C)	131.6	*cis*- 104.3 *trans*- 112	4.6
Vapor pressure (mm Hg, 25 °C)	12	*cis*- 43 *trans*- 34	1,380 (20 °C)
Specific gravity	2.170 (25 °C/4 °C	*cis*- 1.224 *trans*- 1.217 (20 °C/4 °C)	1.732 (20 °C/4°C)
Water solubility	0.43%	*cis*- 0.27% *trans*- 0.28%	0.09%

[a] References: (1) The Merck Index, 10th Ed., 1983; (2) Handbook of Environmental Data on Organic Chemicals, 2nd Ed., 1983; (3) Patty's Industrial Hygiene and Toxicology, 3rd, Rev. Ed., 1981.

II. Production and use

Telone II® is widely used in agriculture as a soil fumigant for parasitic plant nematodes (De Lorenzo et al. 1977, Maddy et al. 1982). Before 1978, about 25 million kg of 1,3-dichloropropene were produced annually in the United States (Flessel et al. 1978). In California, over one million kg of pesticides containing 1,3-dichloropropene were used in 1971 (De Lorenzo et al. 1977). Current production data, though in existence, are proprietary information and are, therefore, not available to the public. In Italy, over 2 million kg were produced in 1972.

1,3-Dichloropropene formulations are usually applied undiluted to the soil around vegetable and tobacco crops to control nematodes (Flessel et al. 1978). 1,3-Dichloropropene is believed to act by chemically combining with a nucleophilic center (e.g., sulfhydryl, amine, or hydroxy groups) in an essential enzyme in the nematode (Metcalf 1978). As with other fumigants, the performance of 1,3-dichloropropene as a nematocide is dependent on the vapor pressure, diffusion coefficient, the distribution of the fumigant through air, water, and solid phases of the soil, and the temperature and moisture content of the soil.

III. Fate in soil

1,3-Dichloropropene was reported to have a half-life in soil of about ten days (Laskowski et al. 1982). In another study (Van Dijk 1974), however, the estimated rates of disappearance of 1,3-dichloropropene isomers under various soil, temperature, and pH conditions differed widely depending on the methods of analysis. When the disappearances of the parent compounds were followed by gas chromatography, the estimated half-lives for *cis*- and *trans*-1,3-dichloropropene ranged from three to 37 days. When Cl^- release resulting from the degradation of 1,3-dichloropropene was followed by potentiometric titration, the estimated half-life for *cis*- and *trans*-1,3-dichloropropene was as long as 23 wk. The *cis*- and *trans*-3-chloroallyl alcohols, assumed degradation products of the corresponding 1,3-dichloropropenes, are more rapidly biodegraded in soil. At 15 °C in clay-containing soils, the average half-lives for the 3-chloroallyl alcohols were one to two days.

Since 1,3-dichloropropene is volatile and insoluble in water, losses are more likely to occur from volatilization than from leaching. The decomposition rate of 1,3-dichloropropene in loam soil was determined to be about 3.5%/day, whereas the decomposition rate in sandy and peat soils was less than 1%/day (Leistra 1970). *cis*- and *trans*-1,3-Dichloropropene are hydrolyzed in wet soil to *cis*- and *trans*-3-chloroallyl alcohol (Castro and Belser 1966). Studies under laboratory and outdoor conditions (Roberts and Stoydin 1976) confirmed that 3-chloroallyl alcohols were the major degradation products and showed that *cis*- and *trans*-3-chloroacrylic acids were minor products.

Despite the volatility and degradability of 1,3-dichloropropene, both the *cis* and *trans* isomers were detected several mon after being applied to soils (Leistra 1970, Williams 1968). Twelve wk after labeled *cis*- or *trans*-1,3-dichloropropene was applied to soils and stored in sealed containers, 19% of the *cis* isomer and 18% of the *trans* isomer remained in sandy loam and 10% of the *cis* isomer and 22% of the *trans* isomer remained in medium loam (Roberts and Stoydin 1976). After 20 wk, 5% of the *cis* isomer and 4% of the *trans* isomer remained in sandy loam and 3% of the *cis* isomer and 14% of the *trans* isomer remained in medium loam. Eight mon after D-D® soil fumigant was applied to a muck soil and to a sandy loam, *cis*- and *trans*-1,3-dichloropropene were detected in both soils (Williams 1968).

IV. Residue analysis of well water

Fifty-four wells, primarily municipal supply system for urban and residential use in 30 communities in California near where Telone II® or D-D® had been applied for several yr, were selected for residue analysis of 1,3-dichloropropene and other pesticides (Maddy et al. 1982). No samples had measurable amounts of 1,3-dichloropropene at a minimum detectable level of 0.1 ppb. A similar study

III. Fate in soil

1,3-Dichloropropene was reported to have a half-life in soil of about ten days (Laskowski et al. 1982). In another study (Van Dijk 1974), however, the estimated rates of disappearance of 1,3-dichloropropene isomers under various soil, temperature, and pH conditions differed widely depending on the methods of analysis. When the disappearances of the parent compounds were followed by gas chromatography, the estimated half-lives for *cis*- and *trans*-1,3-dichloropropene ranged from three to 37 days. When Cl^- release resulting from the degradation of 1,3-dichloropropene was followed by potentiometric titration, the estimated half-life for *cis*- and *trans*-1,3-dichloropropene was as long as 23 wk. The *cis*- and *trans*-3-chloroallyl alcohols, assumed degradation products of the corresponding 1,3-dichloropropenes, are more rapidly biodegraded in soil. At 15 °C in clay-containing soils, the average half-lives for the 3-chloroallyl alcohols were one to two days.

Since 1,3-dichloropropene is volatile and insoluble in water, losses are more likely to occur from volatilization than from leaching. The decomposition rate of 1,3-dichloropropene in loam soil was determined to be about 3.5%/day, whereas the decomposition rate in sandy and peat soils was less than 1%/day (Leistra 1970). *cis*- and *trans*-1,3-Dichloropropene are hydrolyzed in wet soil to *cis*- and *trans*-3-chloroallyl alcohol (Castro and Belser 1966). Studies under laboratory and outdoor conditions (Roberts and Stoydin 1976) confirmed that 3-chloroallyl alcohols were the major degradation products and showed that *cis*- and *trans*-3-chloroacrylic acids were minor products.

Despite the volatility and degradability of 1,3-dichloropropene, both the *cis* and *trans* isomers were detected several mon after being applied to soils (Leistra 1970, Williams 1968). Twelve wk after labeled *cis*- or *trans*-1,3-dichloropropene was applied to soils and stored in sealed containers, 19% of the *cis* isomer and 18% of the *trans* isomer remained in sandy loam and 10% of the *cis* isomer and 22% of the *trans* isomer remained in medium loam (Roberts and Stoydin 1976). After 20 wk, 5% of the *cis* isomer and 4% of the *trans* isomer remained in sandy loam and 3% of the *cis* isomer and 14% of the *trans* isomer remained in medium loam. Eight mon after D-D® soil fumigant was applied to a muck soil and to a sandy loam, *cis*- and *trans*-1,3-dichloropropene were detected in both soils (Williams 1968).

IV. Residue analysis of well water

Fifty-four wells, primarily municipal supply system for urban and residential use in 30 communities in California near where Telone II® or D-D® had been applied for several yr, were selected for residue analysis of 1,3-dichloropropene and other pesticides (Maddy et al. 1982). No samples had measurable amounts of 1,3-dichloropropene at a minimum detectable level of 0.1 ppb. A similar study

was conducted in which well water samples were taken from areas where 1,2-dibromo-3-chloropropane (DBCP) had been applied. The samples were analyzed for DBCP, 1,3-dichloropropene, 1,2-dibromoethane (EDB), and other pesticides (Peoples et al. 1980). Although DBCP was found in 94 of 262 wells at concentrations ranging from 0.1 to 39 ppb, no detectable levels of 1,3-dichloropropene or EDB were found in the 72 well water samples analyzed. However, no data were given to indicate that either 1,3-dichloropropene or EDB was used near the wells.

V. Metabolism and disposition

When 2.53 to 2.70 mg of *cis*- or *trans*-1,3-dichloro(2-^{14}C)propene was administered orally to Carworth Farm E rats, 80% to 90% of the radiolabel was eliminated in the feces, urine, or expired air during the first 24 hr of the experiment (Hutson et al. 1971). Within 24 hr, 80.7% of the administered *cis* isomer and 56.5% of the administered *trans* isomer were eliminated in the urine. About 3.9% of the *cis* isomer and 23.6% of the *trans* isomer were recovered as (^{14}C)carbon dioxide. A small amount (1 to 4%) of 1,3-dichloropropene was exhaled directly. Rats apparently retain little ingested 1,3-dichloropropene. After four days, about 1% of the administered dose of either isomer was found in the carcass.

A glutathione-dependent reaction is on the major metabolic pathway of *cis*-1,3-dichloro(^{14}C)propene (Climie et al. 1979). A hepatic glutathione transferase catalyzes the conjugation of *cis*-1,3-dichloropropene with glutathione. The conjugate is further metabolized to a mercapturic acid and is excreted in the urine as *N*-acetyl-*S*-[(*cis*)-3-chloroprop-2-enyl]cysteine. This metabolite accounted for 92% of the zero to 24-hr cumulative urinary radioactivity. In vitro metabolic studies using rat liver 10,000g supernatant or cytosol preparations (Climie et al. 1979) revealed that the *cis* isomer of 1,3-dichloropropene was degraded four to five times faster than the *trans* isomer.

The metabolic fate of 1,3-dichloropropene was studied in plants by using uniformly labeled ^{14}C-1,3-dichloropropene (60% *trans* isomer, 40% *cis* isomer) (Berry et al. 1980). 1,3-Dichloropropene was absorbed by the bush bean, tomato, or carrot from the solution culture (vermiculite and sand), rapidly translocated in the plants, and metabolized to 3-chloroallyl alcohol, 3-chloro-1-propanol, and 3-chloroacrylic acid. The dichloropropene isomers and chloroallyl alcohol had short half-lives in the plant and were not detectable 120 hr after the administration of 1,3-dichloropropene.

With the exception of 3-chloro-1-propanol, metabolites similar to those present in the plant were also found in soil treated with 1,3-dichloropropene. Microbial metabolism by soil *Pseudomonas* sp. was responsible for this biotransformation (Castro and Belser 1966, Belser and Castro 1971).

In a series of three recent abstracts (Dietz et al. 1984 a and b, Stott et al. 1985 a), the pharmacokinetics of 1,3-dichloropropene in rats and/or mice via oral

dosing and inhalation exposure and the macromolecular binding of 1,3-dichloropropene and its effects on nonprotein sulfhydryl content in the tissues were reported.

When oral doses of 1 or 50 mg/kg ^{14}C-*cis*-, *trans*-1,3-dichloropropene (62%:38% mixture) were administered to male F344 rats and 1 or 100 mg/kg to male B6C3F$_1$ mice, urinary excretion was the predominant route of elimination in 48 hr, accounting for 51% to 61% in rats and 63% to 79% in mice. Feces and expired carbon dioxide contained approximately 18% and 6% of the administered dose in rats and 15% and 14% of the administered dose in mice, respectively. Only 2 to 6% of the original dose remained in the carcasses at the end of 48 hr. The predominant metabolite was identified as *N*-acetyl-*S*-(3-chloroprop-2-enyl) cysteine, confirming the earlier findings of Climie et al. (1979). The sulfoxide or sulfone derivative of the above metabolite was tentatively identified as another major metabolite.

When rats were exposed to 30, 90, 300, or 900 ppm of Telone II® (91% 1,3-dichloropropene) vapors for three hr (Stott et al. 1985 a), the absorption of 1,3-dichloropropene at the higher dose levels did not increase proportionally with increasing exposure level. A 40 to 50% depression of respiratory minute volume (RMV) in the rats of the higher two levels was suggested to be partially responsible for the low rates of absorption in the high doses. The authors claimed that the body burden of 1,3-dichloropropene in rats is determined by the chemically induced changes in respiratory physiology and isomeric-specific, saturable, elimination mechanism(s).

In the second study by Dietz et al. (1984 b), the amount of nonprotein sulfhydryl (NPS) and covalent binding to macromolecules was measured in the forestomach, glandular stomach, liver, kidney, and urinary bladder in male F344 rats and male B6C3F$_1$ mice two hr following administration of a single oral dose of ^{14}C-1,3-dichloropropene (*cis*:*trans* = 62%:38%). The doses given were 0, 1, 5, 25, 50, and 100 mg/kg for NPS studies and 0, 1, 50, or 100 mg/kg for binding studies. Significant depletion of NPS levels was noted in the forestomach of rats and mice dosed with 25 mg/kg or above; the depletion ranged between 17% and 51% of the control values. Effects on NPS in the glandular stomach and liver were also dose dependent but less severe. Macromolecular covalent binding in the forestomach and glandular stomach was greatest at doses that caused the most depletion of tissue NPS. Limited binding was also noted in the liver, kidneys, or urinary bladders.

The overall metabolic pathway of 1,3-dichloropropene is illustrated in Figure 1.

VI. Toxicity of Telone II® and 1,3-dichloropropene in animals

The acute oral LD_{50} value for Telone II® was 713 mg/kg body wt in male rats and 470 mg/kg in female rats (strain unspecified) (Torkelson and Oyen 1977). The liver and kidneys were the primary sites of acute toxicity. Telone II® formulations irritated the skin, causing edema, redness, and necrosis. When a 12.5%

50 ppm for seven hr/day, five days/wk for one mon, produced kidney and liver injury (Torkelson and Oyen 1977). In another experiment, rats, guinea pigs, rabbits, and dogs received 7-hr inhalation exposures to 1,3-dichloropropene at either 1 or 3 ppm, five days/wk for six mon. The only effect attributable to exposure was a cloudy swelling of the renal tubular epithelium in male rats exposed at 3 ppm. Female rats exposed at 3 ppm had marginal increases in the ratio of liver wt to body wt.

In a recent abstract (Stott et al. 1985 b), the results of a 13-wk inhalation study in Fischer 344 rats and B6C3F$_1$ mice were reported. After exposure to 0, 10, 30, 90, or 150 ppm Telone II® vapors (corresponding to 0, 9.1, 27.3, 81.8, and 136 ppm 1,3-dichloropropene), 6 hr/day, five days/wk for 13 wk, a number of dose-related effects were seen. Body wt gain depression (10 to 20%) was seen in both sexes and both species of the two higher exposure levels. In all animals of the 90 or 150 ppm groups and two of the ten male rats in the 30 ppm group, degeneration of the nasal olfactory epithelium and/or hyperplasia of the respiratory epithelium were diagnosed. Lesions of the olfactory epithelium in the 150 ppm mice were occasionally accompanied by some focal areas of respiratory metaplasia. In female mice of the 90 and 150 ppm groups, a diffused, moderate hyperplasia of the transitional epithelium of the urinary bladder was observed. Submucosal aggregates of lymphoid cells, which had been associated with some areas of bladder epithelial hyperplasia in the exposed mice, were seen in the bladders of female mice of the 30 ppm group. The author proposed that a no-observable-effect-level was between 10 and 30 ppm Telone II® vapors.

VII. Toxicity of D-D® in animals

D-D®, a commercial preparation containing 25% *cis*-dichloropropene, 27% *trans*-dichloropropene, 29% 1,2-dichloropropane, and other related chlorinated hydrocarbons, was studied to examine inhalation toxicity in CD-1 mice and F344 rats (Parker et al. 1982). Exposure concentrations were 0, 5, 14, and 54-ppm, six hr/day, five days/wk for 6 or 12 wk. Body wt, organ wt, hematologic values, serum chemistry, urinalysis, and gross pathologic and histopathologic findings were evaluated. The only exposure-related effects observed were increased liver-to-body wt ratios (male rats), increased kidney-to-body wt ratios (female rats), and slight-to-moderate diffuse hapatocyte enlargement (male mice), all at the 54-ppm level.

VIII. Toxicity and exposure in humans

The most likely routes of human exposure to 1,3-dichloropropene are through inhalation and the skin. Irritation of eyes and upper respiratory mucosa, accompanied by lacrimation, appears promptly after exposure to vapors (Gosselin et al. 1976). Inhalation by human beings of air containing concentrations greater than

1,500 ppm produces headaches, mucous membrane irritation, dizziness, nausea, vomiting, gasping, coughing, substernal pain, and respiratory distress. Slightly elevated levels of serum glutamic oxaloacetic transaminase, serum glutamic pyruvic transaminase, or both were reported (Flessel et al. 1978, Gosselin et al. 1976). The chemical at vapor concentrations lower than 1,500 ppm produces central nervous system depression and moderate irritation of the respiratory system. Dermal exposure (no doses given) causes severe skin irritation with marked inflammatory response. Ingestion (no doses given) produces acute gastrointestinal distress, pulmonary congestion and edema, and central nervous system depression. The only known human acute fatality occurred a few hr after the accidental ingestion of a D-D® mixture (Gosselin et al. 1976). The victim experienced abdominal pain and vomiting. He became semicomatose and exhibited muscle twitching. Death occurred in spite of gastric lavage and therapy for pulmonary edema.

1,3-Dichloropropene was speculatively implicated in three cases of human hematologic malignancies (Markovitz and Crosby 1984). Two firemen and a farmer, all in good health prior to exposure to 1,3-dichloropropene, died of cancer within one to seven yr. The two firemen were among a group of nine exposed to the spilled 1,3-dichloropropene from a tank truck accident in a cleanup operation. Immediately after the exposure, symptoms that included headache, neck pain, nausea, and breathing difficulty developed in these nine firemen. Six years later, two of them developed histiocytic lymphoma. Despite chemo- and radiation therapy the patients died a yr later at the ages of 40 and 33, respectively. The cause of death was given as "malignant lymphoma" and "histiocytic lymphoma," respectively. No such malignancies were observed in the other seven firemen at the time of the publication of the article (Markovitz and Crosby 1984). The farmer was exposed to 1,3-dichloropropene repeatedly over a one mon period because of a leaky hose in his pressure-injected soil fumigation operation. Within one yr, he developed myelomonocytic leukemia and died of the secondary complication of pneumonia. A causal association with exposure to 1,3-dichloropropene has not been established for these three cases. Epidemiologic studies on manufacturing or user groups have not been reported.

IX. Mutagenicity studies

Neudecker et al. (1977) found that the *cis* and *trans* isomers of 1,3-dichloropropene were mutagenic in strain TA1535 of *Salmonella typhimurium* and that the addition of rat liver S9 reduced the mutagenicity and cytotoxicity of both isomers. De Lorenzo et al. (1977) also found that *cis*- and *trans*-1,3-dichloropropene as well as Telone II® and D-D® soil fumigants were mutagenic in strains TA1535, TA1978, and TA100 in the presence or absence of S9. Stolzenberg and Hine (1980) confirmed that 1,3-dichloropropene was a direct-acting mutagen in strain TA100 and that S9 reduced the mutagenicity. A mixture of the *cis* and *trans*

isomers of 1,3-dichloropropene was mutagenic in strain TA1535 and TA100, was weakly mutagenic in strain TA98, and was not mutagenic in strain TA1537. S9 reduced the mutagenicity of the isomer mixture, confirming the previous reports. These results suggest that 1,3-dichloropropene is a base-pair substitution mutagen that can be enzymatically detoxified by S9. In vitro studies by Climie et al. (1979) demonstrated that the glutathione-dependent detoxification of the *trans* isomer is four- to fivefold less rapid than that of the *cis* isomer. In addition, a mixture of the two isomers induced sex-linked recessive lethal mutations in *Drosophila* but gave negative results when tested for its ability to induce reciprocal translocations in *Drosophila*.

Recently Talcott and King (1984) demonstrated that purification of four separate preparations of 1,3-dichloropropene by silicic acid chromatography, which removes polar impurities, eliminated the mutagenicity of the preparations in *S. typhimurium* strain TA100. Thus, the mutagenicity of 1,3-dichloropropene preparations observed in other studies may have been due to mutagenic polar impurities and not to 1,3-dichloropropene itself. Subsequent studies at NIEHS by Dr. E. Zeiger (unpub. data) using purified (99.9%) and unpurified samples of 1,3-dichloropropene confirmed that the purified 1,3-dichloropropene was not mutagenic in *Salmonella* TA100. These findings are intriguing because the *cis*- and *trans*-1,3-dichloropropene samples used in the Neudecker et al. (1977) studies were 99.97% and 97.46% pure with the impurities characterized as 3,3-dichloropropene and 1,2-dichloropropane. Furthermore, 1,3-dichloropropene has an allylic carbon which should be very reactive. It also has a carbon-carbon double bond which theoretically could form an epoxide via the cytochrome P-450 system. The formation of an epoxide has indeed been demonstrated in vitro with both the S9 fraction and washed microsomes/NADPH from rat liver (Brooks et al. 1985). Therefore, 1,3-dichloropropene would be expected to be both a direct- and an indirect-acting (i.e., requiring metabolic activation) mutagen. The recent report by Creedy et al. (1984) on the dramatic reduction of microbial mutagenicity of 1,3-dichloropropene by glutathione shed some light on the controversial findings of mutagenicity of 1,3-dichloropropene in the *Salmonella* assay system. Whether there may be a rapid biodegradation of the reactive species of 1,3-dichloropropene in these cell systems remains to be investigated.

X. A teratogenicity study

In an internal report of Dow Chemical Company (personal communication, Dr. Fran O'Melia, 1985), an inhalation teratology study in Fischer 344 rats and New Zealand white rabbits was summarized. Exposure to Telone II® at 0, 20, 60, or 120 ppm during gestation days 6 to 15 (rats) or 6 to 18 (rabbits) was found not to be embryotoxic or teratogenic in these two species. Treatment related-maternal toxicity (decreases in body wt, body wt gain, and food consumption) was observed in the rats. While single occurrences of some malformations

were seen among litters of exposed rabbits, they were within the range of historical controls.

XI. Carcinogenicity studies

cis-1,3-Dichloropropene has been tested for carcinogenicity in mice by dermal and subcutaneous routes and in a mouse-skin initiation-promotion experiment (Van Duuren et al. 1979). The only chemical-related positive findings came from the subcutaneous injection experiment. Weekly injections of 3 mg of *cis*-1,3-dichloropropene in 0.05 ml of trioctanoin for 538 days produced fibrosarcomas at the injection site (left flank) in 6/30 female HA:ICR Swiss mice. Neither the trioctanoin vehicle controls nor the untreated controls had any fibrosarcomas.

Because of the lack of conclusive carcinogenicity studies, its widespread agricultural use, and the structural similarity of 1,3-dichloropropene to vinyl chloride (a known human and animal carcinogen), Telone II® was tested for chronic toxicity/carcinogenicity by the National Cancer Institute (NCI) and the National Toxicity Program (NTP) (NTP 1985, Yang et al. 1985). Commercial-grade Telone II® (containing approximately 89% *cis*- and *trans*-1,3-dichloropropene, 2.5% 1,2-dichloropropane, 1.5% of a trichloropropene isomer, and 1.0% epichlorohydrin) was administered in corn oil by gavage to groups of 52 male and 52 female F344/N rats at doses of 0, 25, or 50 mg/kg and to groups of 50 male and 50 female B6C3F$_1$ mice at doses of 0, 50, and 100 mg/kg. Doses were administered three times/wk for 104 wk. Ancillary studies were conducted in which dose groups containing five male and five female rats were killed after receiving Telone II® for 9, 16, 21, 24, or 27 mon. The histopathology on the animals of the ancillary studies was not carried out until the availability of the findings of the main chronic toxicity/carcinogenicity studies. Only seven target tissues (stomach, urinary bladder, liver, kidney, adrenal gland, thyroid gland, and mammary gland) were evaluated microscopically in these ancillary studies.

The primary organs affected were the forestomach (rats and mice), urinary bladder (mice), lung (mice), and liver (rats). Compound-related nonneoplastic lesions included basal cell or epithelial hyperplasia of the forestomach (rats and mice), epithelial hyperplasia of the urinary bladder (mice), and hydronephrosis (mice). Neoplastic lesions associated with administration of Telone II® included squamous cell papillomas of the forestomach [incidence rates (no. of animals with lesion/no. of animals examined) for male rats: Control: 1/52; low dose: 1/52; high dose: 9/52; female rats: 0/52; 2/52; 3/52; female mice: 0/50; 1/50; 2/50)], squamous cell carcinoma of the forestomach (male rats: 0/52; 0/52; 4/52; female mice: 0/50; 0/50; 2/50), transitional cell carcinomas of the urinary bladder (female mice: 0/50; 8/50; 21/48), alveolar/bronchiolar adenomas (female mice: 0/50; 3/50; 8/50), and neoplastic nodules of the liver (male rats: 1/52; 6/52; 7/52).

Although the study in male mice was considered inadequate due to high mortality in the vehicle control group (8/50 survived to the terminal sacrifice), 2/50 of the high dose males had transitional cell carcinomas of the urinary bladder, a very rare tumor in this experimental animal (NTP historical incidence rates for $B6C3F_1$ male mice: 0/1033). Furthermore, a positive trend was seen in the incidences of alveolar/bronchiolar neoplasms of the lung (1/50; 13/50; 12/50) and of squamous cell papillomas of the forestomach (0/50; 2/50; 3/50). These findings plus the nonneoplastic lesions in two of these organs (basal cell or epithelial hyperplasia of the forestomach: 0/50; 0/50; 4/50; epithelial hyperplasia of the urinary bladder: 0/50; 9/50; 18/50) suggest that Telone II® may have been responsible for the development of these lesions in male mice.

In the NCI-NTP studies, two additional points were stressed by the authors (NTP 1985, Yang et al. 1985). The first area involved the contribution of the ancillary studies to the main chronic toxicity/carcinogenicity studies. The development of forestomach lesions (basal cell hyperplasia and squamous cell papilloma) in rats in the ancillary studies followed a time-dependent trend in the high dose males and females. Basal cell hyperplasia of the forestomach was seen as early as 9 to 16 mon after dosing began. The neoplasms of the forestomach and liver, on the other hand, were not seen until 24 mon after dosing began. In the case of the forestomach neoplasms, the results of the ancillary studies strengthened the statistical evidence of the findings of the carcinogenesis studies. The second area involved the potential toxic effects of 1,2-dichloropropane and epichlorohydrin in the Telone II® preparation. A lengthy discussion was given and the final conclusion was that *cis*- and *trans*-1,3-dichloropropene are the principal components (89%) in Telone II®, but the 1.0% epichlorohydrin, a direct-acting mutagen and carcinogen added as a stabilizer, may have influenced the development of the forestomach lesions.

The NTP concluded that, under the conditions of these gavage studies, there was clear[2] evidence of carcinogenicity for male F344/N rats, as indicated by Telone II®-related increased incidences of squamous cell papillomas and carcinomas of the forestomach, as well as an increased incidence of neoplastic nodules of the liver. In female F344/N rats, there was some[2] evidence of carcinogenicity because Telone II® caused an increased incidence of squamous cell papillomas of the forestomach. The experiment in male $B6C3F_1$ mice was an inadequate[2] study of carcinogenicity because of reduced survival in the vehicle control group. However, 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. There was clear[2] evidence of carcinogenicity for female $B6C3F_1$ mice, since Telone II® caused increased incidences of transitional cell carcinomas of the urinary bladder; Telone II® also increased the incidences

[2]See NTP Technical Report No. 269 for the definitions of these classifications.

of alveolar/bronchiolar adenomas of the lung and of squamous cell papillomas or carcinomas of the forestomach in the female mice (NTP 1985).

XII. Structure/activity relationship

Chu and Milman (1981) reviewed the carcinogenesis data on vinyl chloride (a structural analog to 1,3-dichloropropene), vinylidine chloride, trichloroethylene, 1,2-dichloroethane, 1,2-dibromoethane (EDB), tetrachloroethylene, and epichlorohydrin. The molecular structures of these compounds and that of 1,3-dichloropropene are given in Figure 2. These compounds have been shown to be carcinogenic in at least one study, although controversy regarding carcinogenicity for some of these compounds may still exist.

These chemicals have two common features: they are all small molecules with a short carbon chain, and they are all chlorinated or brominated. Chu and Milman (1981) summarized the bioassay results on vinyl chloride analogs and related compounds specifically in regard to tumor sites. There appeared to be a pattern that some direct-acting compounds (1,2-dibromoethane and 1,2-dichloroethane) produced tumors at the sites of application (e.g., stomach, nasal cavity) as well as in organs distant from the sites of application. On the other hand, epichlorohydrin, also a direct-acting compound, has been shown to produce tumors only

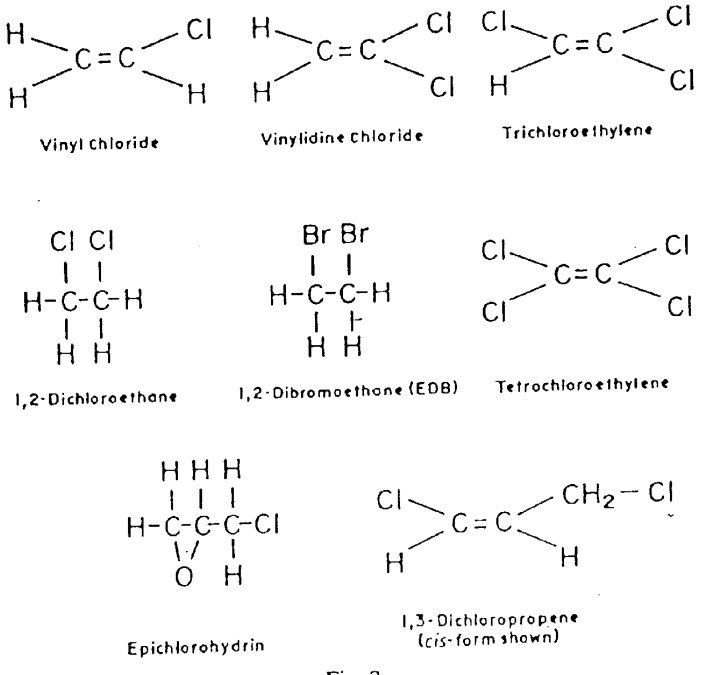

Fig. 2.

at the sites of application (Van Duuren et al. 1974, Konishi et al. 1980, Laskin et al. 1980). Other compounds reviewed by Chu and Milman (1981), which require metabolic activation for alkylation, produced tumors in organs distant from the site of application. Presumably, these differences were related to the variations in the intrinsic chemical reactivity, molecular structure, absorption, distribution, biotransformation, and excretion of the parent compound and the metabolites in the experimental animals. In the case of 1,3-dichloropropene, it has an allylic carbon that should be reactive and could account for the induction of tumors of the forestomach in the NCI-NTP study (NTP 1985). In addition, metabolic activation is possible at the carbon-carbon double bond. The development of tumors at locations (i.e., liver, urinary bladder, lung) distant from the site of application may be related to the formation of reactive intermediates within the body.

Summary

1,3-Dichloropropene is the principal ingredient of some of the leading soil fumigant preparations being used today. A great deal of attention has been focused on 1,3-dichloropropene recently following the wide publicity of the food residue problems of ethylene dibromide. In this review, some basic information regarding the fate of 1,3-dichloropropene in animals, plants, soil, and water as well as various aspects of toxicology of this chemical are consolidated.

Microbial degradation of 1,3-dichloropropene appeared to be active; however, soil residues may be detected several mon after the application of 1,3-dichloropropene. On the other hand, according to a study in California, there is no residue problem in well water in communities where 1,3-dichloropropene has been applied. The major metabolic pathway of 1,3-dichloropropene in the animals appeared to be a GSH dependent conjugation reaction whereas the principal biotransformation in the plants and microorganisms seemed to involve oxidation reactions.

There is moderate acute and subchronic toxicity of 1,3-dichloropropene and the related commercial preparations, Telone II® and D-D®. The primary target organs are liver and kidneys; depending on the routes of administration, the port of entry (i.e., nasal cavity, lung, skin, etc.) may be affected. Chronic dosing (gavage) of Telone II® to the rats and mice, however, induced tumors in the stomach (rats and mice), urinary bladder (mice), liver (rats), and the lung (mice).

Some uncertainties exist as to whether or not the mutagenicity from 1,3-dichloropropene samples tested were actually the results from extremely reactive breakdown products. The ongoing research effort in this area should shed further light on this issue.

Acknowledgment

This review is derived from the NCI-NTP toxicity and carcinogenicity studies on Telone II®. Numerous colleagues at NCI-NTP have participated in these

studies. Their contribution is gratefully acknowledged. I thank Drs. W. M. Kluwe, E. E. McConnell, R. L. Melnick, and B. A. Schwetz, NIEHS/NTP, for reviewing this manuscript.

References

Belser N, Castro C (1971) Biodehalogenation—the metabolism of the nematocides *cis*- and *trans*-3-chloroallyl alcohol by a bacterium isolated from soil. J. Agr. Food Chem. 19:23–26

Berry D, Campbell W, Strrt J, Salunkhe D (1980) Uptake and metabolism of 1,3-dichloropropene in plants. J. Food Safety 4:247–255

Brooks T, Huckle K, Hutson D, Lang K, Logan C, Watson W, Wright A (1985) Investigation of the potential genotoxicity of *cis*(Z)-1,3-dichloropropene (Z-DCP). The Toxicologist 5:77 (Abstract No. 307)

Castro C, Belser N (1966) Hydrolysis of *cis*- and *trans*-1,3-dichloropropene in wet soil. J. Agr. Food Chem. 14:69–70

Chemical Regulation Reporter (1983) 7:859, Sept. 30, 1983

Chu K, Milman H (1981) Review of experimental carcinogenesis by compounds related to vinyl chloride. Environ. Health Perspect. 41:211–220

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

Creedy C, Brooks T, Dean B, Hutson D, Wright A (1984) The protective action of glutathione on the microbial mutagenicity of the Z- and E-isomers of 1,3-dichloropropene. Chem.-Biol. Interactions 50:39–48

De Lorenzo F, Degl'Innocenti S, Ruocco A, Silengo L, Cotese R (1977) Mutagenicity of pesticides containing 1,3-dichloropropene. Cancer Res. 37:1915–1917

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

_____, Dittenber D, Kirk H, Ramsey J (1984 b) Non-protein sulfhydryl content and macromolecular binding in rats and mice following administration of 1,3-dichloropropene. The Toxicologist 4:147 (Abst. No. 586)

Flessel P, Goldsmith J, Kahn E, Wesolowski J, Maddy K, Peoples S (1978) Acute and possible long-term effects of 1,3-dichloropropene—California. Morbidity and Mortality Weekly Report 27:50, 55

Gosselin R, Hodge H, Smith R, Gleason M (1976) Clinical Toxicology of Commercial Products, 4th ed. Baltimore, Wilkins-Williams, pp. 119–121

Hutson D, Moss J, Pickering B (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

Konishi Y, Kawabata A, Denda A, Ikeda T, Katada H, Maruyama H, Higashiguchi R (1980) Forestomach tumors induced by orally administered epichlorohydrin in male Wistar rats. Gann 71:922–923

Laskin S, Sellakumar A, Kuschner M, Nelson N, La Mendola S, Rusch G, Katz G, Dulak N, Albert R (1980) Inhalation carcinogenicity of epichlorohydrin in noninbred Sprague-Dawley rats. J. Nat. Cancer Inst. 65:751–757

Laskowski D, Goring C, McCall P, Swann R (1982) Terrestrial environment. Environ. Risk Anal. Chem. 25:198–240

Leistra M (1970) Distribution of 1,3-dichloropropene over the phases in soil. J. Agr. Food Chem. 18:1124–1126

Maddy K, Fong H, Lowe J, Conrad D, Fredrickson A (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. 144:1409–1411

Metcalf R (1978) Fumigants. In: White-Stevens J (ed) Pesticides in the environment. Marcel Dekker, New York, pp. 120–130

Neudecker T, Stefani A, Henschler D (1977) In vitro mutagenicity of soil nematocide 1,3-dichloropropene. Experientia 33:1084–1085

NTP (1985) Toxicology and carcinogenesis studies of Telone II® in F344/N rats and B6C3F$_1$ mice (gavage studies). NTP Tech. Report No. 269

Parker C, Coate W, Voelker R (1982) Subchronic inhalation toxicity of 1,3-dichloropropene/1,2-dichloropropane (D-D®) in mice and rats. J. Toxicol. Environ. Health 9:899–910

Peoples S, Maddy K, Cusick W, Jackson T, Cooper C, Frederickson A (1980) A study of samples of well water collected from selected areas in California to determine the presence of DBCP and certain other pesticide residues. Bull. Environ. Contam. Toxicol. 24:611–618

Roberts T, Stoydin G (1976) The degradation of (Z)- and (E)-1,3-dichloropropene and 1,2-dichloropropane in soil. Pest. Sci. 7:325–335

Stolzenberg S, Hine C (1980) Mutagenicity of 2- and 3-carbon halogenated compounds in the *Salmonella*/mammalian-microsome test. Environ. Mutagenesis. 2:59–66

Stott W, Kastl P, McKenna M (1985 a) Inhalation pharmacokinetics of *cis*- and *trans*-1,3-dichloropropene in rats exposed to Telone II® vapors. The Toxicologist 5:110 (Abst. No. 440)

———, Young J, Calhoun L, Battjes J (1985 b) Telone II® soil fumigant: A 13-week inhalation study in rats and mice. The Toxicologist 5:220 (Abst. No. 877)

Talcott R, King J (1984) Mutagenic impurities in 1,3-dichloropropene preparations. J. Natl. Cancer Inst. 72:1113–1116

Thomson WT (1983) Agricultural chemicals—Book III. Miscellaneous chemicals. Thomson Publications, Fresno, CA

Torkelson T, Oyen F (1977) The toxicity of 1,2-dichloropropene as determined by repeated exposure of laboratory animals. Amer. Ind. Hyg. Assoc. J. 38:217–223

Van Dijk H (1974) Degradation of 1,3-dichloropropenes in the soil. Agro-Ecosystems 1:177–184

Van Duuren B, Goldschmidt B, Katz C, Seidman I, Paul J (1974) Carcinogenic activity of alkylating agents. J. Natl. Cancer Inst. 53:695–700

———, Goldschmidt BM, Loewengart G, Smith AC, Melchionne S, Seldman I, Roth D (1979) Carcinogenicity of halogenated olefinic and aliphatic hydrocarbons in mice. J. Natl. Cancer Inst. 63:1433–1439