

**1,3-Dichloro-2-propanol**  
**[CAS No. 96-23-1]**

**Review of Toxicological Literature**

**January 2005**

# **1,3-Dichloro-2-propanol**

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*Prepared for*

National Toxicology Program (NTP)  
National Institute of Environmental Health Sciences (NIEHS)  
National Institutes of Health  
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## Abstract

1,3-Dichloro-2-propanol (1,3-DCP) is a semi-volatile organic liquid that is soluble in water and most organic solvents. It is used in high volume as an intermediate in epichlorohydrin production and the production of 1,3-dichloropropene and 1,2,3-trichloropropane. Therefore, workers may be exposed to 1,3-DCP during the manufacture and use of these chemical agents. Exposure to 1,3-DCP may also occur from ingestion of food to which hydrochloric acid-hydrolyzed vegetable protein has been added or drinking water in which epichlorohydrin polyamine polyelectrolytes are used as flocculents and coagulants for water purification. 1,3-DCP is "moderately toxic" via inhalation, ingestion, or skin contact. Following oral administration of 1,3-DCP to rats,  $\beta$ -chlorolactate, *N,N'*-bis(acetyl)-*S,S'*-(1,3-bis(cysteinyl))propan-2-ol, and *N*-acetyl-*S*-(2,3-dihydroxypropyl)cysteine were detected in 24-hour urine samples. Ethyl acetate-extractable metabolites 3-monochloro-1,2-propanediol and 1,2-propanediol were also recovered following subcutaneous exposure. Acute exposure of rats to 1,3-DCP produced liver injury, erosion of the kidneys and the gastrointestinal tract mucosa, diuresis, decreased white blood cell and platelet counts, and increased blood clotting time. Deaths occurred at  $\geq 50$  mg/kg bw. In rabbits, 1,3-DCP was a mild skin irritant, as well as an eye irritant. In subchronic studies, 1,3-DCP caused decreased body weights, increased liver and kidney weights, alterations in serum chemistry and urinary and hematological parameters, gross pathological changes in the stomach, and histopathological changes in the stomach, kidney, liver, and nasal tissue of rats. The no-observable adverse effect level was 1 mg/kg/day. Statistically significant decreases in mean body weight gain and dose-related increases in the relative weights of the liver, kidney, and brain were reported for rats treated 104 weeks. Some female rats exhibited hepatotoxicity and nephrotoxicity. 1,3-DCP reduced the sperm count in rat epididymis. Treatment-related non-neoplastic lesions also occurred in the liver, kidney, and thyroid. Statistically significant dose-related increases in the combined incidences of the following tumors were observed in male and female rats: in the liver, hepatocellular adenoma and carcinoma; in the tongue/oral cavity, squamous cell papilloma and carcinoma; and in the thyroid, follicular cell adenoma and carcinoma. In the kidney, the combined numbers of renal tubular adenoma and carcinoma were increased in males only. In numerous *in vitro* assays, 1,3-DCP was genotoxic. The role of 1,3-DCP metabolism in mutagenicity studies *in vitro* remains unclear and appears to be of no significant genotoxic potential *in vivo*.

## Executive Summary

### **Nomination**

1,3-Dichloro-2-propanol (herein abbreviated as 1,3-DCP) was nominated by the National Institute of Environmental Health Sciences for toxicological characterization, including metabolism and disposition, reproductive toxicity, and carcinogenicity studies. The nomination is based on high volume production and use, potential for human exposure in the workplace and through the diet, and suspicion of toxicity based on existing data as well as structural similarity to known rodent reproductive toxicants and carcinogens. Further studies are necessary to adequately characterize the potential human reproductive and carcinogenic hazard resulting from exposure to this substance.

### **Nontoxicological Data**

#### Chemical Identification

1,3-DCP (CASRN 96-23-1) is also called (glycerol)  $\alpha,\gamma$ -dichlorohydrin. It is a semi-volatile organic liquid (boiling point 174.3 °C) soluble in water and most organic solvents. It may be determined in foods, environmental media, wastes, and products by gas chromatographic (GC) methods with various detectors. Detection limits for 1,3-DCP using capillary GC/mass spectrometric methods are as low as 5 µg/kg.

#### Commercial Availability, Production, and Production Processes

Most suppliers of 1,3-DCP offer it in limited quantities. High-volume production is as an intermediate in the production of epichlorohydrin, 1,3-dichloropropene, and, possibly, 1,2,3-trichloropropane. The two high-volume producers of these products are Dow Chemical in Freeport, Texas, and Resolution Performance Products (RPP LLC), which recently took over the Shell Chemicals operation in Norco, Louisiana, where crude epichlorohydrin is produced. 1,3-DCP and 2,3-dichloro-1-propanol (2,3-DCP) are produced by treating allyl chloride with chlorine and water (which forms hypochlorous acid). Treating the reaction mixture (30% 1,3-DCP and 70% 2,3-DCP) with base yields epichlorohydrin, sodium chloride, and water.

#### Uses

1,3-DCP is used in high volume as an intermediate in epichlorohydrin production. Dehydration of 1,3-DCP with phosphoryl chloride forms 1,3-dichloropropene, a soil fumigant. Chlorination of 1,3-DCP (or 2,3-DCP) with phosphorus pentachloride gives 1,2,3-trichloropropane. Hydrolysis of dichlorohydrins has been used in the production of synthetic glycerol (glycerin). Use to manufacture lacquers, use as a solvent for nitrocellulose and hard resins, and other uses listed in secondary references such as *The Merck Index* were not confirmed. Use as a dye fixative/anti-fading agent in detergent formulations appears to be historical based on a limited patent survey.

#### Environmental Occurrence and Persistence

Epichlorohydrin manufacturing wastes and other wastes containing dichloropropanols are regulated under RCRA. The millions of pounds of epichlorohydrin wastes are apparently well managed by industry by biodegradation, high-pH, and high-temperature treatments. Most epichlorohydrin environmental releases are apparently fugitive emissions to air, which may form 1,3-DCP by hydrolysis. According to U.S. Environmental Protection Agency (EPA) reports, 1,3-DCP has not been found at centralized industrial waste management facilities in influent wastes from the oils, metals, and organics subcategories; in landfill leachates; or in emissions from hazardous waste incinerators. 1,3-DCP has been found in pulp mill effluents and spent kraft paper bleaching liquors. 1,3-DCP may be biodegraded by acclimated sewage and soil microorganisms. Volatilization from soils and water surfaces is not expected. Soil mobility is high. The hydrolysis rate at neutral pH corresponds to a half-life of 1.4 years. The half-life in the atmosphere for 1,3-DCP based on its rate of reaction with hydroxyl radicals is eight days.

## Human Exposure

### *Nonoccupational Exposure*

Nonoccupational exposure to 1,3-DCP may be in foods to which acid-HVP has been added. In 1997, the Food Chemicals Codex specified a limit of 50 ppb (0.05 mg 1,3-DCP/kg) calculated on a dry basis in acid-HVP. The highest 1,3-DCP concentration found in a 2000 survey of soy sauces and related products on the U.S. market was 9.8 ppm (9.8 mg/kg). Human per capita intakes of 1,3-DCP from soy sauce and other foods have been estimated at 7 to 27 µg/day and 0.1 µg/day, respectively.

Use of a dimethylamine-epichlorohydrin copolymer in sugar refining and in production of high-fructose corn syrup might lead to a per capita consumption of 210 µg 1,3-DCP/day.

Epichlorohydrin copolymers with polyamines, and polyamides contain low concentrations of 1,3-DCP. Their use as wet-strength resins for paper products subjects them to U.S. Food and Drug Administration (FDA) limits in food-contact applications, and the industry has made strong efforts to reduce concentrations of chloropropanols in the resins.

1,3-DCP has been found in epichlorohydrin polyamine polyelectrolytes used as flocculents and coagulants in drinking water purification. The action level of 9 ppb dichloropropanols in finished drinking water was exceeded nine times in a nine-year survey (1991-1999) of drinking water plants. Limiting the dosing rate of the flocculent to no more than 2.5 mg/L indirectly regulates the concentrations of the chloropropanols 1,3-DCP, 2,3-DCP, and 3-monochloro-1,2-propanediol (3-MCPD).

Thermal degradation, metabolism, or hydrolysis of the flame retardant TDCPP (Fyrol FR-2) might be a source of consumer exposure to 1,3-DCP. TDCPP is used in flexible polyurethane resins (e.g., for upholstery cushions and carpet cushions). 1,3-DCP has been detected in chamber test emissions from carpet cushions, but the probable source was not identified. TDCPP has been found in human adipose tissue sampled from individuals living in the Great Lakes area.

### *Occupational Exposure*

Workers may be exposed to 1,3-DCP during the manufacture and use of epichlorohydrin, 1,3-dichloropropene, and 1,2,3-trichloropropane. Exposure may be due to the presence of 1,3-DCP as an impurity, possibly from the hydrolysis of an epichlorohydrin impurity, or from metabolism of the product. Workers may also be exposed to 1,3-DCP during spray-painting operations that utilize acrylic paints containing glycidyl esters, the use of the quaternary ammonium compound (3-chloro-2-hydroxypropyl) trimethylammonium chloride (CHPTA) to etherify starches used in paper and textile manufacturing, and the use of bis(2-chloro-1-methylethyl) ether in paint and varnish removers. 1,3-DCP is an impurity in these chemicals and may be present in concentrations as high as 1%.

## Regulatory Status

1,3-DCP regulations promulgated in the Code of Federal Regulations include the following:

- 21 CFR 173 Secondary Direct Food Additives Permitted in Food for Human Consumption, Subpart A—Polymeric Substances and Polymer Adjuvants for Food Treatment 173.60 Dimethylamine-epichlorohydrin polymer and 173.357 Materials Used as Fixing Agents in the Immobilization of Enzyme Preparations
- 40 CFR 60 Standards of Performance for New Stationary Sources, Subpart VV Equipment Leaks of VOC in the Synthetic Organic Chemicals Manufacturing Industry

- 40 CFR 261 Identification and Listing of Hazardous Wastes (generally listed as dichloropropanols, not otherwise specified)
- 40 CFR 799 Identification of Specific Chemical Substances and Mixtures Testing Requirements, Subpart D—Multichemical Test Rules (799.5055) Hazardous Waste Constituents Subject to Testing [under the Toxic Substances Control Act].

The Food Chemicals Codex set a limit of 0.050 mg 1,3-DCP/kg (dry basis) in acid-HVP used in foods. The European Commission Regulation EC No. 466/2002 set a legal limit of 0.02 mg 1,3-DCP/kg in acid-HVP and soy sauce. The Australia New Zealand Food Standards Council limits 1,3-DCP in soy and oyster sauces to 0.005 mg/kg calculated on 40% dry weight. Because of its carcinogenicity, the Joint FAO/WHO Expert Committee on Food Additives (JECFA) recommended that no level of 1,3-DCP is safe. A limit of 0.005 mg/kg is close to the analytical detection limit of current methods.

No Occupational Safety and Health Administration (OSHA) permissible exposure limits or American Conference of Governmental Industrial Hygienists (ACGIH)- or National Institute for Occupational Safety and Health (NIOSH)-recommended criteria to limit exposure to 1,3-DCP, dichloropropanols, or dichlorohydrins in workplace air were identified.

### **Toxicological Data**

In 2002, the JECFA published a monograph summarizing the safety data on selected food additives and contaminants including 1,3-DCP (<http://www.inchem.org/documents/jecfa/jecmono/v48je19.htm>; last accessed on May 23, 2003). The data are briefly presented in this report. The United Kingdom Committee on the Carcinogenicity (COC) and the Committee on the Mutagenicity (COM) of Chemicals in Food, Consumer Products and the Environment both published reports in 2001 evaluating studies of the toxicological, carcinogenic, and mutagenic effects of 1,3-DCP. The reports are available in PDF format at <http://www.foodstandards.gov.uk/multimedia/pdfs/COSection.pdf> and <http://www.doh.gov.uk/pdfs/mut016.pdf>, respectively. The JECFA monograph was supplemented with data from these reports.

No data regarding initiation/promotion, anticarcinogenicity, and co- and anti-genotoxicity were available.

### Human Data

In general, 1,3-DCP is "moderately toxic" via inhalation, ingestion, and skin contact.

In five of 12 workers exposed to an unknown concentration of 1,3-DCP (via inhalation) from the cleaning of a saponification tank used in the manufacture of 1,3-DCP, acute hepatitis developed. Two of the five died from hepatic failure 4 and 11 days after the job. Autopsy showed submassive hepatocellular necrosis in one of the individuals.

### Chemical Disposition, Metabolism, and Toxicokinetics

In rats, oral administration of 1,3-DCP (50 mg/kg [0.39 mmol/kg] body weight [bw]) daily for 5 days resulted in the detection of  $\beta$ -chlorolactate (~5% of the dose), *N,N'*-bis(acetyl)-*S,S'*-(1,3-bis(cysteinyl))propan-2-ol (1%), and *N*-acetyl-*S*-(2,3-dihydroxypropyl)cysteine in the urine. The epoxide epichlorohydrin was proposed as an intermediate, which can then conjugate with glutathione (GSH), forming mercapturic acid derivatives. Additionally, epichlorohydrin may hydrolyze to 3-MCPD, which can undergo further metabolism to produce  $\beta$ -chlorolactate.

In another rat study, a single subcutaneous (s.c.) injection of 1,3-DCP (~68 mg/kg [0.53 mmol/kg] bw) resulted in ethyl acetate-extractable metabolites in the 24-hour urine—3-MCPD (0.35% of the dose) and 1,2-propanediol (0.43%).

### Acute Toxicity

Oral acute toxicity values ( $LD_{50}$ ) ranging from 25-125 mg/kg (0.19 mmol/kg-0.969 mmol/kg) were reported for mice and 110-400 mg/kg (0.853-3.10 mmol/kg) for rats. Lethal inhalation concentrations ( $LC_{50}$ ) were 1.7-3.2 mg/L (1700-3200 mg/m<sup>3</sup>; 320-600 ppm) for 1 to 5 days in mice. For 4 hours, the  $LC_{50}$  was 0.66 mg/L (660 mg/m<sup>3</sup>; 125 ppm). In rats, an  $LC_{50}$  of 125 ppm (659 mg/m<sup>3</sup>) was calculated for a 4-hour period. Additionally, intraperitoneal (i.p.)  $LD_{50}$  values of 106 mg/kg (0.822 mmol/kg) and 110 mg/kg (0.853 mmol/kg) have been given for the animals. In rabbits, the dermal  $LD_{50}$  was 800 mg/kg (6.20 mmol/kg).

In rats, i.p. injection of 1,3-DCP (18-290 mg/kg [0.14-2.25 mmol/kg] bw) produced somnolence, liver injury, a significant increase in the activity of serum alanine aminotransferase, erosion of the kidneys and the gastrointestinal tract mucosa, diuresis, precipitation of calcium oxalate in the urine, decreased white blood cell and platelet counts, and increased blood clotting time. Deaths occurred at doses of  $\geq$ 50 mg/kg bw [0.39 mmol/kg bw]. Subcutaneous injection of 1,3-DCP (50 mg/kg [0.39 mmol/kg] bw) decreased platelet counts and at the same time increased the activities of both serum aspartate and serum alanine aminotransferase.

In rabbits, 1,3-DCP (10 mg [0.078 mmol]) on the skin for 24 hours caused mild irritation. The chemical (dose not provided [n.p.]) also produced irritation in the eyes, as well as moderately severe damage.

### Short-term and Subchronic Exposure

In a two-week gavage study, male Sprague-Dawley rats given 1,3-DCP (1, 10, 25, or 75 mg/kg [0.008, 0.078, 0.19, 0.58 mmol/kg] bw) daily had increased liver weights at the 10 and 25 mg/kg doses. In females, this occurred only at the 25 mg/kg dose. At 75 mg/kg, liver weights were increased but body weights were decreased in both sexes. Additionally, kidney weights were increased in males at this dose. In another rat study, 1,3-DCP (10, 20, or 30 mg/kg [0.078, 0.16, or 0.24 mmol/kg] bw) administered *per os* daily for 11 weeks produced no changes in body weight, locomotor activity, or landing foot splay distance.

When male and female Sprague-Dawley rats were administered 1,3-DCP (0.1, 1, 10, or 100 mg/kg [0.8, 8, 78, or 775  $\mu$ mol/kg] bw) daily by gavage in distilled water five days per week for 13 weeks, decreases in body-weight gain and feed consumption, increased liver and kidney weights, alterations in serum chemistry and urinary and hematological parameters, gross pathological changes in the stomach, and histopathological changes in the stomach, kidney, liver, and nasal tissue were observed in both sexes at the highest dose. At 10 and 100 mg/kg bw [78 and 775  $\mu$ mol/kg bw], increased liver weights were found in males and females, whereas histopathological changes in the stomach, kidneys, and liver occurred only in males. The histopathological effects were less frequent and/or less severe at the lower dose. The no-observable adverse effect level (NOAEL) was 1 mg/kg/day.

In a more recent study, Sprague-Dawley rats given 1,3-DCP (15, 30, or 60 mg/kg [0.12, 0.23, or 0.47 mmol/kg] bw) daily via gavage for 13 weeks exhibited dose-dependent increases in liver and kidney weights. An increase in albumin and a dose-dependent decrease in white blood cells, mean corpuscular volume, mean corpuscular hemoglobin (MCH), and basophils were observed in males only. In females, platelets and total cholesterol as well as red blood cell counts, hemoglobin, hematocrit, MCH, and MCH concentration were increased. The number of neutrophils was slightly decreased.

### Chronic Exposure

In male and female Wistar rats administered 1,3-DCP (27, 80, or 240 mg/L [0.21, 0.62, 1.86 mM]) in the drinking water for 104 weeks, no changes in food and water consumption were seen and no treatment-related signs of toxicity were observed. At the high dose, mortality was increased in both males and females compared with controls, and statistically significant decreases in mean body weight gain were

observed for males after 74 weeks and in females after 78 weeks. Dose-related increases in the relative weights of the liver, kidney, and brain were also reported. At the high dose, female rats exhibited hepatotoxicity and nephrotoxicity.

#### Synergistic/Antagonistic Effects

At a low dose (5 mg/kg), diethyldithiocarbamate provided significant protection against 1,3-DCP hepatotoxicity in the rat and inhibited enzyme markers for CYP2E1 activity. At a higher dose (25 mg/kg), complete protection occurred. The hepatotoxicity of 1,3-DCP was therefore concluded to be mediated principally by CYP2E1 (Stott et al., 1997).

#### Cytotoxicity

The cytotoxicity of 1,3-DCP is cytochrome P450- and GSH-dependent. At concentrations between 0.1 and 100 µM (0.01-12.9 µg/mL), 1,3-DCP failed to produce *in vitro* neurotoxic effects in PC12 and N18D3 cells.

#### Reproductive and Teratological Effects

In male albino Wistar rats, 1,3-DCP (5 or 20 mg/kg [0.04-0.16 mmol/kg] bw) given daily via gavage for 14 days produced spermatocoele unilaterally in the ductuli efferentes of one of ten rats at the high dose. A single i.p. injection of the compound (44 mg/kg [0.34 mmol/kg] bw) in the animals resulted in a significant decrease in sperm count in the epididymis.

#### Carcinogenicity

In male and female Wistar rats administered 1,3-DCP (27, 80, or 240 mg/L [0.21, 0.62, 1.86 mM]) in the drinking water for 104 weeks, treatment-related non-neoplastic lesions occurred in the liver, kidney, and thyroid. Neoplastic lesions were also observed. In both males and females, statistically significant dose-related increases in the combined incidences of the following tumors were observed: in the liver, hepatocellular adenoma and carcinoma; in the tongue/oral cavity, squamous cell papilloma and carcinoma; and in the thyroid, follicular cell adenoma and carcinoma. In the kidney, the combined numbers of renal tubular adenoma and carcinoma were markedly and dose-dependently increased in males only.

#### Genotoxicity

Numerous *in vitro* assays report that 1,3-DCP is genotoxic. In *Salmonella typhimurium* strains TA100, TA1535, and TM677, 1,3-DCP (0.1-130 mg/plate [0.8-1000 µmol/plate]) induced reverse mutations in the presence and absence of metabolic activation (S9). Most studies in TA97, TA98, TA1537, and TA1538 found 1,3-DCP (0.1-26 mg/plate [0.8-200 µmol/plate]) to be not mutagenic.

In *Escherichia coli* strain TM930, 1,3-DCP (0.26-26 mg/plate [2.0-200 µmol/plate]) induced reverse mutation, while in strains PM21 and GC4798, it (0.3-3.9 mg/sample [2.3-30 µmol/sample]) produced DNA damage. In mouse lymphoma cells, 1,3-DCP (2-9 mg/mL [15-70 mL]; 0.1-1.9 µL/mL) caused gene mutation. Mutations were also produced in mouse fibroblasts at doses of 0.1-1 mg/mL [0.8-8 mM] and in HeLa cells at a dose of 320 µg/mL [2.48 mM] with S9. In Chinese hamster V79 cells, 1,3-DCP (16-430 µg/mL [0.12-3.33 mM]) induced sister chromatid exchange (SCE). In Chinese hamster ovary cells, SCE and chromosomal aberrations were induced at doses ranging from 0.015-1 µL/mL.

In *Drosophila melanogaster*, 1,3-DCP (0.006-1.3 mg/mL [0.05-10 mM]) was negative for somatic mutations. In rats, 1,3-DCP (25-100 mg/kg [0.19-0.0775 mmol/kg]) failed to increase the frequency of micronucleated polychromatic erythrocytes in bone marrow and levels of unscheduled DNA synthesis (UDS) in the liver.

### Immunotoxicity

In Hartley guinea pigs, 1,3-DCP at 0.75% in distilled water was used in a 24-hour rechallenge application two weeks after initial challenge with hexanedioic acid, polymer with *N*-(2-aminoethyl)-1,2-ethanediamine, *N*-(1-oxohexyl) derivatives, epichlorohydrin-quaternized (CASRN 236400-71-8). Sensitization was elicited in one guinea pig. The same result was observed using 1,3-DCP at 0.75% in corn oil.

### Other Data

The genotoxic and carcinogenic activity of 1,3-DCP have been reported to depend on the formation of the epoxide intermediate during metabolism. *In vitro*, 1,3-DCP has been reported to be mutagenic in most bacterial studies both in the absence and presence of metabolic activation. Additionally, in the SOS chromotest with *E. coli* strain GC4798, chemical conversion of 1,3-DCP to epichlorohydrin in the rat hepatocytes medium was proposed to be the genotoxic mechanism of action. A postulated alternative active metabolite is 1,3-dichloroacetone (1,3-DCA), formed from 1,3-DCP by the action of alcohol dehydrogenase or CYP2E. The proposed detoxication pathway is GSH conjugation, since 1,3-DCP depletes GSH both *in vitro* and *in vivo* and GSH depletion can potentiate the toxicity of 1,3-DCP in rat hepatocytes. 3-MCPD, a known metabolite of 1,3-DCP, has no significant *in vivo* genotoxic potential.

### **Structure-Activity Relationships**

Carcinogenicity, genotoxicity, and toxicity to reproduction and development were compiled for a limited group of C3-compounds and their derivatives related to 1,3-DCP. Oxygen-containing compounds that induced malignancies in rodents included epichlorohydrin, 2,3-DCP, and tris(2,3-dibromopropyl) phosphate (TDPP). Oxygen-containing compounds that induced only benign tumors were 3-MCPD and TDCPP. Two related chlorinated hydrocarbons, 1,3-dichloropropene and 1,2,3-trichloropropane, were also carcinogens. No long-term study was available for 2,3-dichloropropanol. The compounds causing tumors, including 1,3-DCP, were genotoxic in at least some *in vitro* mammalian systems. The metabolic conversions of all of these compounds was not explored, but the ability to be converted to epichlorohydrin or epibromohydrin might be involved in their mode of action for tumor induction.

## Table of Contents

<b>Abstract.....</b>	i
<b>Executive Summary .....</b>	ii
<b>1.0 Basis for Nomination .....</b>	1
<b>2.0 Introduction.....</b>	2
<b>2.1 Chemical Identification and Analysis .....</b>	2
<b>2.2 Physical-Chemical Properties .....</b>	4
<b>2.3 Commercial Availability .....</b>	4
<b>3.0 Production Processes .....</b>	5
<b>4.0 Production and Import Volumes .....</b>	6
<b>5.0 Uses .....</b>	7
<b>6.0 Environmental Occurrence and Persistence .....</b>	7
<b>7.0 Human Exposure .....</b>	9
<b>8.0 Regulatory Status.....</b>	14
<b>9.0 Toxicological Data.....</b>	16
<b>9.1 General Toxicology .....</b>	16
<b>9.1.1 Human Data .....</b>	16
<b>9.1.2 Chemical Disposition, Metabolism, and Toxicokinetics.....</b>	17
<b>9.1.3 Acute Exposure .....</b>	17
<b>9.1.4 Short-term and Subchronic Exposure .....</b>	18
<b>9.1.5 Chronic Exposure .....</b>	21
<b>9.1.6 Synergistic/Antagonistic Effects .....</b>	21
<b>9.1.7 Cytotoxicity.....</b>	22
<b>9.2 Reproductive and Teratological Effects.....</b>	22
<b>9.3 Carcinogenicity .....</b>	22
<b>9.4 Initiation/Promotion Studies.....</b>	22
<b>9.5 Anticarcinogenicity .....</b>	22
<b>9.6 Genotoxicity.....</b>	23
<b>9.7 Cogenotoxicity .....</b>	27
<b>.8 Antigenotoxicity .....</b>	27
<b>9.9 Immunotoxicity .....</b>	27
<b>9.10 Other Data (Mechanisms of Action) .....</b>	27
<b>10.0 Structure-Activity Relationships .....</b>	29
<b>Appendix A. Units and Abbreviations .....</b>	54
<b>Appendix B. Search Strategy Description .....</b>	56

**Tables:**

<b>Table 1. Federal Regulations Relevant to 1,3-DCP, Dichlorohydrins, and Dichloropropanols, n.o.s .....</b>	15
<b>Table 2. Acute Toxicity Values for 1,3-DCP.....</b>	18
<b>Table 3. Acute Exposure to 1,3-DCP.....</b>	19
<b>Table 5. Genotoxicity Studies of 1,3-DCP.....</b>	24
<b>Table 6. Carcinogenicity, Genotoxicity, and Reproductive and Developmental Toxicity of Selected Structural Analogues .....</b>	30

**Figure:**

<b>Figure 1. Microbial Transformation Pathway for 1,3-DCP .....</b>	28
---------------------------------------------------------------------	----

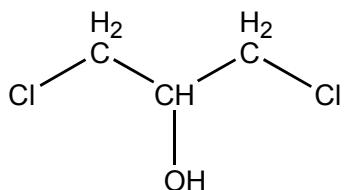
## 1.0 Basis for Nomination

1,3-Dichloro-2-propanol (herein abbreviated as 1,3-DCP) was nominated by the National Institute of Environmental Health Sciences for toxicological characterization, including metabolism and disposition, reproductive toxicity, and carcinogenicity studies. The nomination is based on high volume production and use, potential for human exposure in the workplace and through the diet, and suspicion of toxicity based on existing data as well as structural similarity to known rodent reproductive toxicants and carcinogens. Further studies are necessary to adequately characterize the potential human reproductive and carcinogenic hazard resulting from exposure to this substance. 1,3-Dichloro-2-propanol (1,3-DCP) is a high-production-volume (HPV) chemical that is produced in millions of pounds annually, primarily as an intermediate in the production of epichlorohydrin, the monomer used widely in epoxy resin production. The potential for human exposure and the possible need for further toxicological studies are reflected by the following concerns:

- The National Toxicology Program (NTP) has found several haloalcohols, including 1,3-DCP, genotoxic in *Salmonella* bacteria. 1,3-DCP is genotoxic in *S. typhimurium* tester strains TA100 and TA1535 with and without metabolic activation.
- 1,3-DCP is genotoxic in several *in vitro* mammalian systems.
- 1,3-DCP is structurally analogous to several haloalcohols that have been shown to be carcinogenic and reproductive toxicants in mice and rats in National Cancer Institute (NCI)/NTP bioassays.
- A 1986 study in the non-peer-reviewed literature reported that 1,3-DCP was carcinogenic to rats. The carcinogenesis study has been thoroughly discussed in a recent review by the Joint Committee of the Food and Agriculture Organization of the United Nations and the World Health Organization (Joint FAO/WHO Expert Committee on Food Additives [JECFA], 2002).
- In setting priorities for future evaluations under the IARC Monographs Programme on the Evaluation of Carcinogenic Risks to Humans, an IARC Advisory Group considered the existing data on 1,3-DCP inadequate to support an evaluation of carcinogenicity (IARC, 1998; <http://193.51.164.11/htdocs/internrep/98-004.html>).
- The potential for public exposure to 1,3-DCP and its precursor, 3-monochloro-1,2-propanediol (3-MCPD), in foods such as soy sauce that contain acid-hydrolyzed vegetable proteins (acid-HVP) has instigated market surveys of commercial soy sauces and related products by the U.S. Food and Drug Administration (FDA) and similar government agencies in the United Kingdom and other countries. FDA and other food safety oversight organizations in other countries have set limits for at least 3-MCPD or both 3-MCPD and 1,3-DCP.
- 1,3-DCP is a hydrolysis product and metabolite of the carcinogen epichlorohydrin, and epichlorohydrin may be formed from 1,3-DCP by the action of bacterial enzymes.
- Epoxy resins and other chemicals produced from epichlorohydrin often contain 1,3-DCP as an impurity.

## 2.0 Introduction

1,3-Dichloro-2-propanol  
[96-23-1]



### 2.1 Chemical Identification and Analysis

#### Identification

1,3-Dichloro-2-propanol ( $C_3H_6Cl_2O$ ; mol. wt. = 128.9858) is also called:

- $\alpha,\gamma$ -Dichlorohydrin
- $\alpha$ -Dichlorohydrin
- 1,3-Dichloro-2-hydroxypropane
- 1,3-Dichlorohydrin
- 1,3-Dichloroisopropanol
- 1,3-Dichloroisopropyl alcohol
- 2-Chloro-1-(chloromethyl)ethanol
- Bis(chloromethyl)methanol
- Glycerol  $\alpha,\gamma$ -dichlorohydrin
- Glycerol 1,3-dichlorohydrin
- Propylene dichlorohydrin
- sym*-Dichloroisopropyl alcohol
- sym*-Glycerol dichlorohydrin

1,3-DCP is a member of the broad chemical class halohydrins, which include halogenated alcohols. Specifically, 1,3-DCP (boiling point [b.p.] 174.3 °C) is one of the glycerol (glycerin) chlorohydrins in which one or two of the hydroxyl groups of glycerol (1,2,3-trihydroxypropane) have been replaced by one or two chlorine atoms. Glycerol chlorohydrins also include 3-MCPD (b.p. 213 °C), 2-chloro-1,3-propanediol (b.p. 146 °C), 2,3-dichloro-1-propanol (2,3-DCP) (b.p. 182 °C), and epichlorohydrin (b.p. 30–32 °C). The hydroxy compounds are also called chloropropanols. 1,3-DCP and 2,3-DCP are called dichlorohydrins and dichloropropanols. 1,3-DCP often co-occurs with one or more of the other chlorohydrins.

#### Analysis

Several analytical methods based on gas chromatography (GC) are available for determining 1,3-DCP in water and other environmental media, hazardous wastes, foods, and commercial products. Matthew and Anastasio (2000) developed a method for determining 1,3-DCP and other halohydrins, which included derivatization of the halohydrins in extracts from water samples with heptafluorobutyric acid followed by GC with electron-capture detection (GC/EC). The method detection limit for 1,3-DCP was 1.7 µg/L in a 5-mL sample. Munch and Eichelberger (1992) evaluated the suitability of U.S. Environmental Protection Agency (EPA)

Method 524.2 revision 3.0 (capillary GC/mass spectrometry [MS]) for determining 1,3-DCP and other compounds in contaminated drinking water.

U.S. EPA analytical methods have been validated for determination of 1,3-DCP and selected other volatile organic compounds (VOCs) in hazardous wastes. GC/MS methods include 8240B, which uses a packed column GC, and 8260B, which uses a capillary column GC. Method 8010B is a packed-column GC method for halogenated VOCs in hazardous wastes that uses an electrolytic conductivity detector (ELCD). Most analytes require purge-and-trap concentration before analysis. Packed column methods were generally to be replaced by capillary GC methods in 1997. Method 8260B is to be used instead of 8240B and Method 8021B replaced Method 8010B. Method 8021B uses tandem photoionization/ELCD detection (Restek Corporation, 2003; U.S. EPA, 1997).

Apparatus and methodology for GC determination of 1,3-DCP and other chloropropanols in epichlorohydrin resins were described in paragraphs 0069 and 0072 of the patent by Riehle et al. (2003).

Boden et al. (1997) developed a capillary GC/MS method for determining 1,3-DCP and 3-MCPD in papers treated with polyamidoamine-epichlorohydrin wet-strength resins. The compounds were derivatized and extracted by a solution of *N,O*-bis(trimethylsilyl) trifluoroacetamide in acetonitrile. The mass spectrometer was operated in selective-ion-monitoring (SIM) mode. The limits of detection for both compounds were 0.04 mg/kg.

An analytical method for determining 1,3-DCP in dimethylamine-epichlorohydrin copolymer may be obtained from the U.S. FDA Center for Food Safety and Applied Nutrition (CFSAN) (FDA, 2002 [21 CFR 173.60]). The method was not described in the regulation.

Liu et al. (2002) described a GC method with flame ionization detector (FID) to determine 1,3-DCP and epichlorohydrin in a chloroform extract of the quaternary ammonium compound (3-chloro-2-hydroxypropyl)trimethylammonium chloride (CHPTA). The detection limit for 1,3-DCP was 10 µg/g.

Daniels et al. (1981) described a GC method for determining moderately volatile compounds such as 1,3-DCP and 1-chloro-2-propanol in cornstarch. Samples were prepared by distillation from aqueous or methanolic suspensions at 50 to 60 °C and cryogenic trapping. The method was suitable for 1,3-DCP concentrations in the range 0.5 to 600 ppm.

Velisek et al. (1978) used GC/MS to determine 1,3-DCP, 2,3-DCP, and 3-chloro-1-propanol in protein hydrolyzates. 1,3-DCP was found at concentrations of 0.17 to 0.94 mg/kg. Van Rillaer and Beernaert (1989) developed a GC/EC method for determining 1,3-DCP in protein hydrolyzates and soy sauces in the range 0.1 to 1 mg/kg. The method involved micro-steam distillation solvent extraction. This methods-only paper used spiked samples. The GC/MS (SIM mode) method developed by Wittman (1991) for determining 1,3-DCP and 3-MCPD in seasoned foods had a detection limit of <0.05 mg/kg for 1,3-DCP.

The GC/MS method developed by the United Kingdom (UK) Central Science Laboratory (CSL) for determination of 3-MCPD in soy sauce was validated by international collaborative trial and "is now the official first action method of the Association of Official Analytical Chemists" (AOAC) (CCFAC, March 2003). 1,3-DCP is so much more volatile than 3-MCPD that the AOAC method published in 2000 for 3-MCPD had to be modified to avoid 1,3-DCP loss during concentration steps. In the modification by the FDA, the diethyl ether/hexane extract is partitioned with acetonitrile. The acetonitrile solution can be concentrated without 1,3-DCP loss (ANZFA, 2001). The FDA CFSAN GC/MS method for determining 1,3-DCP in soy and related sauces gave results comparable to the headspace GC/MS method developed by CSL (Nyman et al., 2003a). Crews et al. (2002) of the UK CSL described an automated headspace GC/MS method with cryogenic trapping and a deuterium labeled internal standard for determining 1,3-DCP in soy sauce with a limit of detection of 3 µg/kg. 1,3-DCP was found at concentrations up to about 1 mg/kg in 10 of 40 soy and oyster sauces known to contain 3-MCPD. Chung et al. (2002) developed a capillary GC/MS method for determining 1,3-DCP in soy sauce with simultaneous separation and determination of 3-MCPD. The limit of detection was 5 µg/kg for both compounds. Sample preparation included solid-phase extraction and derivatization with heptafluorobutyric acid anhydride.

Soy sauce and related samples (282 of 2035 samples supplied by Germany, UK, Austria, and Finland) were analyzed for 3-MCPD and 1,3-DCP using automated headspace procedure with GC/MS detection. The maximum concentration of 1,3-DCP found in any of the samples was 1.37 mg/kg. Assuming a chloropropanol level of 0 mg/kg, the overall mean concentration of 1,3-DCP was calculated to be 0.070 mg/kg; assuming a chloropropanol level between 0 mg/kg and the LOQ, the overall mean concentration was 0.092 mg/kg (European Union, 2004).

## 2.2 Physical-Chemical Properties

Property	Information	Reference(s)
Physical State	Liquid	Budavari (1996)
Odor	Ethereal	Budavari (1996)
Boiling Point (°C)	174.3 at 760 Torr; 28-114.8 at 1-100 Torr	Budavari (1996)
Melting Point (°C)	-4	Budavari (1996)
Density (g/cm <sup>3</sup> at 17°C)	1.3506	Budavari (1996)
Water Solubility	1 part per 10 parts water	Budavari (1996)
Solubility in:	Ethanol, diethyl ether, vegetable oils, and most organic solvents	Budavari (1996); HSDB (2002)
Vapor pressure, mm Hg at 0 °C (Torr)	0.75; 0.377425 (calculated)	HSDB (2002); Registry (2003) <sup>a</sup>
pK <sub>a</sub>	12.87±0.20 (calculated)	Registry (2003) <sup>a</sup>
Log K <sub>ow</sub>	0.663±0.5 (calculated)	Registry (2003) <sup>a</sup>
Octanol-water partition coefficient	54.6 at pH 1-10 (calculated)	Registry (2003) <sup>a</sup>

<sup>a</sup>Calculated values appearing in Registry (2003) were derived by use of Advanced Chemical Development (ACD) Software Solari V4.67 (© 1994-2003).

## 2.3 Commercial Availability

Chemcyclopedia 2003 lists one German supplier (Raschig GmbH) and two U.S. suppliers of 1,3-DCP (Contract Chemicals, Inc., in Virginia and Sachem, Inc., in Texas). The current online ChemBuyers Guide (undated) lists 20 U.S. suppliers of 1,3-DCP, including ICC Chemical Corporation, Sachem, Inc., Solvay Interox, Inc., and Spectrum Chemical Manufacturing

Corporation. To judge from statements in the ChemBuyers Guide, Contract Chemicals, Inc., imports 1,3-DCP from a manufacturing site in the United Kingdom.

Small quantities of high purity 1,3-DCP can be purchased from companies such as Aldrich (2003-2004). 1,3-DCP is also available in mixtures of VOCs to be used as analytical standards for hazardous waste analysis by U.S. EPA Methods (e.g., McCampbell Analytical, Inc., 2002).

Most 1,3-DCP in the United States has been produced and used captively by Dow Chemical and Shell Chemicals, primarily in the production of epichlorohydrin. Epichlorohydrin is the only chlorohydrin sold on a large scale (Riesser, 1985). The Shell Chemicals facilities that produced epichlorohydrin, after divestiture of Shell's epoxy resins business, are now operated by Resolution Performance Products (RPP LLC, 2001).

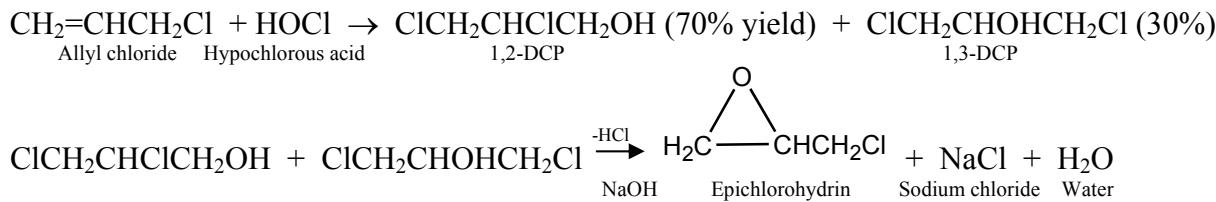
A search of the 1998 Inventory Update Rule (IUR) database for producers of greater than 10,000 lb 1,3-DCP annually retrieved Dow Chemical Company and Inspec Fine Chemicals, Inc. In 2002, only Cincinnati Specialties, LLC was listed (U.S. EPA, 2003b, 2004b). A search for dichloropropanols, n.o.s. (not otherwise specified) using CASRN 26545-73-3 gave no results. However, both Dow Chemicals and Shell were listed as epichlorohydrin producers as well as Aga Chemicals, Inc., ICC Chemical Corporation, Morton International Inc., and Sumitomo Corporation of America. Of the latter four, only Morton International reported releases of epichlorohydrin wastes in the year 2000 Toxic Chemicals Release Inventory (TRI, 2000). Other epichlorohydrin producers would be expected to produce 1,3-DCP as an intermediate.

### 3.0 Production Processes

Glycerol chlorohydrins were originally produced commercially by treating glycerol with hydrochloric acid (Riesser, 1985). In a laboratory-scale process, glycerol was hydrochlorinated by hydrogen chloride gas in acetic acid (Conant and Quayle, 1922; cited by Budavari, 1996 [see also Conant, 1941, from online version of 1941 print edition of J.B. Conant's *Organic Syntheses*]). Less than 1 kg of dichlorohydrin was produced. The product, boiling over a seven-degree range, was primarily 1,3-DCP since oxidation gave 1,3-dichloroacetone.

Base-catalyzed reactions of glycerol dichlorohydrins (1,3-DCP and 2,3-DCP) give epichlorohydrin, which is used to produce synthetic glycerol, epoxy resins, and derivatives of glycerol and glycidol (Riesser, 1985). A comprehensive list of epichlorohydrin uses may be found at the following URL: <http://www.speclab.com/compounds/c106898.htm> (Spectrum Laboratories, undated).

The chemical reactions in which dichlorohydrins are produced in high volume and used as intermediates in epichlorohydrin production are as follows:



Sodium carbonate, calcium hydroxide, or calcium carbonate may also be used as the basic catalyst (U.S. EPA, 1984). The hypochlorous acid is formed from chlorine and water.

In 1984, the dichlorohydrins were produced as epichlorohydrin intermediates by Shell Chemicals in Norco, Louisiana, and the crude epichlorohydrin was shipped to the Deer Park, Texas, facility to be refined. Dow Chemical produced epichlorohydrin from allyl chloride in a continuous process at its Freeport, Texas, facility, where Dow Chemical produced its D.E.R.<sup>®</sup> brand of epoxy resins, synthetic glycerol (sold as glycerine by Dow Chemical [Chemcyclopedia 2003]), and glycerol derivatives. (The chlorohydrin intermediate in glycerol production by epichlorohydrin hydrolysis is 3-MCPD.) Shell-produced refined epichlorohydrin was sold to other epoxy resin producers and used to produce Shell's EPON<sup>®</sup> brand epoxy resins (U.S. EPA, 1984). According to a recent undated Chemical Backgrounder on epichlorohydrin (NSC, 2002), Dow Chemical and Shell Chemicals were the only U.S. epichlorohydrin producers. In November 2000, the epoxy resins and intermediates business was taken over by Resolution Performance Products LLC, formerly operating as a wholly owned Shell Chemicals subsidiary (Shell Resins and Versatics) (Hoover's Online, 2003; RPP LLC, 2003). The RPP intermediates are apparently not sold to outside companies (RPP LLC, 2002).

#### 4.0 Production and Import Volumes

Dow Chemical reported high-volume production of dichloropropanols, n.o.s. (CASRN 26545-73-3) and use on-site at its Freeport, Texas, plant in the initial Toxic Substances Control Act (TSCA) Inventory reporting in 1975-1977. The plant produced dichloropropanols in the range of 100 to 500 million pounds (45.4 to 227 metric tons). In the initial reporting, two companies reported production of 1,3-DCP under the CASRN 96-23-1: Arsynco, Inc., in Carlstadt, New Jersey, produced only 1,000 to 10,000 lb (0.454 to 4.540 metric tons). American Hoechst Corporation imported an unspecified amount to its Bridgewater, NJ, plant (TSCA Plant and Producers [TSCAPP]). No TSCAPP record was found for Shell Chemicals under either CASRN.

Under the 1990 IUR, an aggregate production volume ranging between >50 million lb ( $2.3 \times 10^7$  kg) and 100 million lb ( $4.5 \times 10^7$  kg) was reported for 1,3-DCP. In 1994 and 2002, volumes ranging between 10,000 lb (4535.9 kg) and 500,000 lb (226,800 kg) were submitted by various companies. In 1998, >1 million lb (453,600 kg) to 10 million lb ( $4.5 \times 10^6$  kg) was reported. The production volume given for epichlorohydrin, however, was greater than one billion pounds (U.S. EPA, 2004a).

Companies that produce other chemicals associated with 1,3-DCP and which might be expected to produce 1,3-DCP as a byproduct were considered. Dixie Chemical Company, Hampshire Chemical Corporation, and Lonza Inc. produce 3-MCPD (CASRN 96-24-2). Only Dow Chemical reported production of 2,3-dichloro-1-propanol (CASRN 616-23-9), which is also an intermediate in epichlorohydrin production. Only Dow Chemical and Shell Chemicals produced 1,3-dichloropropene (CASRN 542-75-6) and 1,2,3-trichloropropane (CASRN 96-18-4). Aceto Corporation and BASF Corporation manufactured a quaternary ammonium compound (CHPTA) that may be produced from 1,3-DCP or epichlorohydrin.

## 5.0 Uses

1,3-DCP is used in high volume as an intermediate in epichlorohydrin production (Riesser, 1985). Several publications have reported use of 1,3-DCP for enzymatic conversions to racemic or chiral (optically active) epichlorohydrin. For example, Nakamura et al. (1994) used bacterial halohydrin halide lyases to produce racemic and (*R*)-epichlorohydrin.

1,3-DCP has been used as a solvent for hard resins and nitrocellulose and to manufacture photographic lacquers, Zapon lacquer, cement for celluloid, and a binder for water colors (Budavari, 1996; HSDB, 2002). 1,3-DCP has been used in the analytical determination of vitamin A (ChemFinder, 2003) and is listed in the Industrial Solvents Handbook, 4<sup>th</sup> edition (Flick, 1991).

1,3-DCP has been used in the production of several industrially important organic compounds besides epichlorohydrin. Substitution at the chlorine atom of chlorohydrins may be used to form products such as mono- and diazides (Riesser, 1985). Hydrolysis of dichlorohydrins gives glycerol (Blytas and Deal [Shell Oil], 1979). 1,3-Dichloropropene, sold as the Dow soil fumigant Telone II, may be produced by dehydration of 1,3-DCP with phosphoryl chloride ( $\text{POCl}_3$ ) or with phosphorus pentoxide ( $\text{P}_2\text{O}_5$ ) in benzene (HSDB, 2002; Budavari, 1996). One of the many industrial methods for producing 1,2,3-trichloropropane is the chlorination of 1,3-DCP or 2,3-DCP by phosphorus pentachloride. Dow Chemical USA, Freeport, Texas, and Shell Oil Company, Deer Park, Texas, were listed as the 1,2,3-trichloropropane producers in the early 1990s (ATSDR, 1992).

Several recent U.S. patents and patent applications for fabric care and detergent formulations by Procter and Gamble and by Unilever examined in June 2003 mentioned use of "aminated glycerol dichlorohydrins" in discussions of prior art for dye fixatives/anti-fading agents. They were not claimed as part of the invention. (For example, see paragraph 0198 of the invention description in the patent application by Smerznak and Boreckx, 2002, and paragraph 023 of the invention description in the patent application by Kuzmenka et al., 2002.)

## 6.0 Environmental Occurrence and Persistence

Epichlorohydrin producers generate RCRA-listed hazardous waste designated K017, which is the heavy ends (still bottoms) from the purification column in the production of epichlorohydrin. The dichloropropanols 1,3-DCP and 2,3-DCP are present in the K017 wastes and, presumably, other wastes containing epichlorohydrin.

Releases and management of epichlorohydrin wastes generated by numerous facilities, not just the K017 wastes, may be found in the annual TRI database available on the TOXNET system. A National Safety Council (NSC, undated) Chemical Backgrounder for epichlorohydrin summarized the disposition of epichlorohydrin releases and wastes containing epichlorohydrin for the 1998 reporting period. Although there were only two epichlorohydrin producers, 79 other facilities produced and/or managed epichlorohydrin-containing wastes according to the 1998 TRI. Because epichlorohydrin slowly hydrolyzes in water at neutral and lower pH, epichlorohydrin releases to air and water may be expected to be sources of environmental chloropropanols. Of the 229,451 lb released by the 81 facilities in 1998, 198,189 lb were air emissions and 434 lb were discharges to surface water. The total releases in 1998 were down

considerably from the total 1988 environmental release of 783,605 lb. Nearly 42 million pounds of epichlorohydrin-containing wastes were managed in 1998: About 10.5 million pounds were recycled on-site, about 4.9 million pounds were used for energy recovery on-site, and about 25 million pounds were treated on-site. On-site and off-site releases from these activities totaled 223,317 lb. The remaining wastes were recycled, used for energy recovery, or treated off-site. A brief inspection of the reports of 78 facilities reporting in TRI 2000 indicated that the bulk of Shell Chemicals epichlorohydrin K017 wastes were treated off-site by OxyChem (Occidental Chemical Corp.), Deer Park, Texas (probably mostly by RCRA-permitted incineration) (U.S. EPA, 1999).

Products and wastes containing epichlorohydrin may be hydrolyzed in aqueous media in the presence of chloride ions to 1,3-DCP. Hydrochloric acid hydrolysis at pH 1 is very rapid, faster at pH 1 than hydrolysis at pH 2 (the rate of alkaline hydrolysis at pH 13 is intermediate). Hydrochloric acid or solutions of inorganic bases may be used in decontamination solutions (e.g., to decontaminate tanks and drums). The 1,3-DCP produced by hydrochloric acid treatment requires that the waste be treated (e.g., by controlled incineration) (Solvay Interrox, Inc., 2003).

In a survey of facilities in the Centralized Waste Treatment Industry, 1,3-DCP was never detected as a pollutant in influent wastes from the oils, metals, and organics subcategories (U.S. EPA, undated [<http://www.epa.gov/ostwater/guide/owt/final/develop/oh6.pdf>]). In addition, 1,3-DCP has never been detected in leachates from hazardous and nonhazardous waste landfills (U.S. EPA, 2002b) (Source: Final Effluent Limitations Guidelines and Standards for the Landfills Point Source Category [<http://www.epa.gov/ostwater/guide/landfills/final/>]).

Two studies were identified in which 1,3-DCP was reported in pulp mill effluents (Suntio et al., 1988) and spent kraft paper bleaching liquors (Shimada, 1986).

Schaefer et al. (1996) qualitatively detected 1,3-DCP in VOC emissions from "prime [poly]urethane carpet cushions." The Consumer Product Safety Commission (CPSC, 1996) reported the presence of 1,3-DCP at a concentration of 0.01 to 0.1 mg/m<sup>3</sup> in chamber test emissions from carpet backing. The CPSC document did not identify the source. The flame retardant TDCPP (Fyrol FR-2), which is a 3:1 ester of 1,3-DCP with phosphoric acid (actually produced from epichlorohydrin instead of 1,3-DCP), is used as a flame retardant in polyurethane foam (e.g., in automobile upholstery [Polyurethane Foam Association, 1996]), but it does not hydrolyze readily to give 1,3-DCP (Akzo Nobel, 1998). However, 1,3-DCP is produced as a minor product during thermal degradation of TDCPP (NICNAS, 2001).

Yasuhara et al. (1993; cited by HSDB, 2002) reported determination of 27.9 µg 1,3-DCP/L in a municipal waste landfill leachate in Japan.

Many studies have been published on biodegradation of 1,3-DCP by soil and sewage organisms. 1,3-DCP is more readily biodegraded than 2,3-DCP (Effendi et al., 2000). 1,3-DCP biodegrades slowly with acclimation of the organism(s) (BIOLOG, 2003). For example, Fauzi et al. (1996) reported that non-growing cells of a bacterial strain (probably an *Agrobacterium* species) isolated from soil dehalogenated 1,3-DCP at low concentrations. Bastos et al. (2002) reported that enriched microbial consortia from wastewater (Rhizobiaceae strains) capable of degrading 1,3-

DCP degraded the compound at the rate of 45 mg/L/day compared to a single-species rate of 74 mg/L/day. Pure *Pseudomonas* cultures degraded 1,3-DCP to 1-chloro-2,3-propylene glycol, glycidol, epichlorohydrin, and glycerol (HSDB, 2002). Bridie et al. (1979) reported results of biological oxygen demand and chemical oxygen demand values for 1,3-DCP and numerous other chemicals marketed by Shell.

Dow Chemical Company (1989b; cited by U.S. EPA, 2002a), responding to a TSCA Section 4 request for soil and sediment adsorption data, reported soil sorption of about 90 to 96% for loam soils. Soil extracts showed degradation of about 77 to 95% in the equilibrium pH range 6.90 to 7.15. Correlation coefficients in the Freundlich model for the determined isotherms were 0.8724 to 0.9383.

The Hazardous Substances Data Bank profile (HSDB, 2002) summarized fate and persistence information in environmental media. 1,3-DCP is expected to have very high soil mobility based on an estimated  $K_{oc}$  value of 4. 1,3-DCP is also expected not to be adsorbed to suspended solids or sediments in water bodies. Because of the estimated low Henry's Law Constant ( $6 \times 10^{-7}$  atm-m<sup>3</sup>/mol) and the low experimental vapor pressure (0.75 mm Hg), volatilization from dry soil and water surfaces is not expected.

At neutral pH, the hydrolysis rate (0.0031 L/hr) corresponds to a half-life in water of 1.4 years. At pH 8, the rate of 850 L/mol-hr corresponds to a half-life of 34 days (HSDB, 2002).

In air, vaporous 1,3-DCP reacts with hydroxyl radicals with an estimated rate constant of  $1.84 \times 10^{-12}$  atm-m<sup>3</sup>/mol and an estimated half-life of eight days (HSDB, 2002).

## 7.0 Human Exposure

### Food

If processing conditions are not well controlled, 1,3-DCP and its precursor 3-MCPD may be formed in "high" concentrations during hydrochloric acid-catalyzed hydrolysis of vegetable proteins. Heating with strong hydrochloric acid for several hours causes chlorination of residual lipid in the protein source, which leads to formation of chloropropanols from the glycerol of the triglyceride. Acid-hydrolyzed vegetable proteins (acid-HVP) are ingredients in processed foods such as soups, frozen dinners, "savoury snacks," gravy mixes, and stock (bouillon) cubes (Farrington and Baty, 2002; CCFAC, March 2001). Enzymes may also be used in the production of HVP. The functions of the food additives containing HVP include leavening, stabilizers, thickeners, flavorings, and flavor enhancers. HVPs have been broken down into amino acids and may be used as a nutrient (Segal, undated). Soy sauces may be produced by fermentation, but lower grades may be manufactured by acid treatment. In addition, acid-HVP may be added. Thus, 3-MCPD and 1,3-DCP may be found in these products. Manufacturing controls developed for acid-HVP production were expected in 2001 to control chloropropanol concentrations in soy sauces. In surveys, 1,3-DCP has been found in acid-HVP only when 3-MCPD concentrations were high. The relative values varied, but 3-MCPD concentrations were generally at least 20 times higher than 1,3-DCP concentrations (JECFA, 2001). Other foods in which 3-MCPD has been found include toasted bread, some grilled cheeses, and fried batters prepared by domestic cooking. Lower concentrations were found in samples of gravy, cooked meat, and stock. In addition, low 3-MCPD concentrations have been found in roasted cereals, malt extracts and

foods and drinks flavored with malt extracts, and fermented sausages such as salami. Surveys in the United Kingdom have found 3-MCPD in baked goods, bread, and cooked/cured meat and fish. The presence of 3-MCPD in the cured meats may be due to reaction of sodium chloride with fats or migration from the resins used in sausage casings (CCFAC, March 2001; CCFAC, March 2003). CCFAC (March 2001) recommended further studies of 3-MCPD formation from lipids during baking, roasting, and toasting. [Increasingly better analytical methods might be expected to find 1,3-DCP as well.]

The need to control concentrations of chloropropanols in acid-HVP was recognized in the early 1990s by the International Hydrolyzed Protein Council (IHPC) and the FDA. Both organizations surveyed 3-MCPD concentrations in acid-HVP. In December 1997, the Food Chemicals Codex specified limits of no more than 1 mg 3-MCPD/kg (1 ppm) calculated on a dry basis and no more than 0.05 mg 1,3-DCP/kg (50 ppb) calculated on a dry basis. The limits on a liquid basis are 0.4 mg/kg and 0.02 mg/kg, respectively (CCFAC, March 2003). The U.S. food industry voluntarily complied with these specifications (CCFAC, March 2001).

Beginning in 2000, the FDA surveyed soy sauces and related products on the U.S. market. Thirty-three (60%) of 55 retail samples contained more than 0.025 mg 3-MCPD/kg. 1,3-DCP was found in 14 (36%) of 39 samples. The highest concentrations of 1,3-DCP and 3-MCPD were 9.8 mg/kg and 876 mg/kg, respectively. FDA estimated that soy sauces with more than 10 mg 3-MCPD/kg may be expected to contain 1,3-DCP at concentrations of 0.250 to 10 mg/kg (CCFAC, March 2003; Nyman et al., 2003b). A 2002 FDA survey of chloropropanols in 13 canned tuna samples did not find any 3-MCPD above the lower quantitation limit of 0.014 mg/kg. One sample contained 1,3-DCP at slightly >0.019 mg/kg. FDA monitoring continued in 2003 (CCFAC, March 2003).

CCFAC (March 2003) summarized ongoing survey and monitoring activities in the European communities and the limits set by the United States and other countries for chloropropanols in foods. The UK released results of a survey of 100 soy sauces and related products that had been purchased at retail in February 2001. Concentrations of at least 0.01 to 93.1 mg 3-MCPD/kg were found in 31% of the products. Up to 0.345 mg 1,3-DCP/kg was found in 17 products that had more than 0.02 mg 3-MCPD/kg (see also UK Food Standards Agency [FSA], 2001). A 2002 UK survey of 99 soy sauces and related products from retail sources found 3-MCPD at concentrations >0.01 mg 3-MCPD/kg in only nine samples. The sample with the highest 3-MCPD concentration (35.9 mg/kg) was the only one that contained 1,3-DCP (0.017 mg/kg). A European Community Scientific Co-operation (SCOOP) task to be completed in 2003 collected and collated data on 3-MCPD and related chloropropanols, including 1,3-DCP, in foods. More information on the relative concentrations of 3-MCPD and 1,3-DCP should "inform the discussion on whether or not establishment of limits for 3-MCPD will obviate the need for limits for 1,3-DCP." While the 3-MCPD concentration is always higher than that of 1,3-DCP, no clear relationship has been observed between the relative concentrations (COC, 2001b; cited by UK FSA, 2001).

In the UK, Crews et al. (2000) reported detection of 1,3-DCP and 3-MCPD in five of 14 samples of soy sauces and 3-MCPD alone in six samples. Four of the samples with 1,3-DCP contained high levels of both chloropropanols: 0.6 to 4.3 mg 1,3-DCP/kg and 42 to 101 mg 3-MCPD/kg;

the other had only 0.01 mg 1,3-DCP with 15 mg 3-MCPD/kg. The UK FSA has advised the food industry to reduce 3-MCPD concentrations as low as technologically feasible (CCFAC, March 2001) after UK surveys in 1990 and 1992 found 3-MCPD concentrations commonly up to 100 mg/kg. In the UK survey conducted in August 2000, the 100 samples comprised 67 soy sauces plus mushroom soy, oyster, and teriyaki sauces. The sample descriptions and analytical results for 1,3-DCP in the survey are available in a food survey information sheet published on the Internet by the UK FSA (2001). In another 2000 UK survey of chloropropanols in soy sauces and related products, 3-MCPD concentrations were  $\geq 0.02$  mg/kg in 25 of the 32 samples analyzed (16 were  $> 1$  mg/kg). 1,3-DCP was also detected in 17 of the samples at levels ranging from 0.006 to 0.345 mg/kg. In the 2002 survey, 3,-MCPD concentrations were  $\geq 0.02$  mg/kg in seven of eight samples analyzed. In the sample with the highest 3-MCPD concentration (35.9 mg/kg) 1,3-DCP was detected at 0.017 mg/kg (Crews et al., 2003).

The European Commission Regulation EC No. 466/2002, in force since April 2002, set a legal limit of 0.02 mg/kg for 3-MCPD in acid-HVP and soy sauce based on 40% dry matter content (UK FSA, 2002; IFST, 2003).

JECFA (2001) estimated that human per capita intake of 1,3-DCP from soy sauce may be in the range of 7 to 27  $\mu\text{g}/\text{day}$  and that exposure from other foods gives a per capita intake of approximately 0.1  $\mu\text{g}/\text{day}$ .

1,3-DCP may be present in concentrations up to 1,000 ppm in a dimethylamine-epichlorohydrin copolymer (DEC) used at concentrations of up to 150 ppb by weight of sugar solids in sugar refining. [DEC is used as a flocculent or decolorizing agent for sugar liquors. It is also used to immobilize glucose isomerase enzymes for production of high-fructose corn syrup.] Thus, the maximum concentration of 1,3-DCP would be 0.15 ppm by weight of sugar solids. FDA estimated that human exposure to 1,3-DCP from this source would be 210  $\mu\text{g}/\text{person/day}$ . FDA performed a cancer risk assessment based on the rat carcinogenesis bioassay discussed in subsection 9.3 and found the risk to be negligible [FDA 21 CFR Part 173.60 per 67(122) FR 427114-427117 (June 25, 2002)].

### Paper Products

The epichlorohydrin copolymers with polyamines and/or polyamides are described variously in the following discussion. When both are used in a name, it may be a generalization indicating either a polyamine or a polyamide copolymer.

Papers treated with epichlorohydrin-based wet-strength resins may be used in food contact such as in tea bag paper, coffee filters, absorbents packaged with meats, and cellulose casings [for ground meat products such as sausage]. They may also be used in medical and cosmetic applications. Other consumer paper products are paper tissues and towels. Industry has made strong efforts to reduce concentrations of chloropropanols in these resins (CCFAC, March 2001; Laurent et al., 2002; Hardman et al., 1997). For example, in a U.S. Patent assigned to Atofina, France, carbon adsorption of aminopolyamide-epichlorohydrin copolymer resins useful for paper wet-strength additives reduced the 1,3-DCP concentration to undetectable by ordinary "vapor-phase" chromatography (Laurent et al., 2002). In another example, Yamamoto et al. (2001) in a U.S. patent application described a process for producing water-soluble polyamide polyamine-

epichlorohydrin resins for wet-strength agents in which 1,3-DCP concentrations did not exceed 2.6% of the solid content of the resin in four examples within the application. Solutions were not mutagenic to *Salmonella* tester strain TA1535. Hardman et al. (1997) described a microbiological process to reduce the concentration of 1,3-DCP and 3-MCPD in Kymene (a Hercules brand) neutral-curing poly(aminoamide)-epichlorohydrin wet-strength resins.

The abstract of a publication by scientists of the CSL Food Science Laboratory, Japanese Ministry of Agriculture, Fisheries and Food (MAFF) reported the presence of several organics found by headspace GC/MS in extracts of 32 paper and paperboard materials intended for food contact, but did not mention 1,3-DCP despite its being one of the analytes (Castle et al., 1997).

Polyamine-epichlorohydrin resins accumulate chloropropanediol (CPD)-forming species (presumably 1,3-DCP is included) in storage. Several methods, including acid, base, and enzyme treatments, have been described to reduce CPD levels. Riehle et al. (2003) in a U.S. Patent assigned to Hercules, Inc., USA described processes for reducing CPD-forming species to parts-per-million levels (dry basis) in polyamine polyamide-epichlorohydrin resins even after storage or heating. Such an additive added at 1% would give papers with CPD at parts-per-billion levels.

### Drinking Water

Drinking water treatment chemicals are tested for compliance with ANSI/NSF [American National Standards Institute/NSF International (a nongovernmental organization)] Standard 60. In noncompliance, the product fails to meet the Standard's requirements at concentrations that may be added to drinking water under actual use conditions. In the period 1991-1999, NSF International found noncompliance nine times due to exceedence of the 9-ppb action level for dichloropropanols. 1,3-DCP, 2,3-DCP, and related contaminants are found in epichlorohydrin polyamine polyelectrolytes used in drinking water treatment chemicals (coagulation and flocculation products). Only dimethylamine and a confidential compound exceeded their action levels more often than the dichloropropanols (NSF Int., 2000). Low concentrations of 3-MCPD have been found in finished water from flocculent use in the United Kingdom (CCFAC, March 2001). The UK Drinking Water Inspectorate (2001) concluded that limiting the dosing rate of the flocculent to no more than 2.5 mg/L drinking water would indirectly regulate concentrations of the chloropropanols 1,3-DCP, 2,3-DCP, and 3-MCPD.

### Occupational

Workers using acrylic paints in spray painting operations may be exposed to low concentrations of 1,3-DCP. 1,3-DCP at 0.20%, chloropropanediol (1331-07-3) at 0.01%, glycidyl methacrylate at 0.01%, and 2-ethylhexyl methacrylate at 0.30% were reported as impurities in the acrylic paint Synocure 899.SA (NICNAS, undated). The SIDS document on glycidyl methacrylate reported impurities of 0.3% epichlorohydrin and 0.6% dichlorohydrins (OECD, 2002).

The National Institute of Occupational Safety and Health (NIOSH) National Occupational Exposure Survey (NOES), conducted in 1981-1983, reported that 200 employees, six of whom were females, were potentially exposed to 1,3-DCP at three facilities in one industry (NIOSH, 1990 [<http://www.cdc.gov/noes/noes1/x5378sic.html>]; RTECS, 2000). Chemical technicians (103) and supervisors, production occupations, were the largest occupational groups potentially

exposed. Other occupations included repairers of cameras, watches, and musical instruments (13); chemical engineers (6); electricians (6); electrical and electronic technicians (3), and chemists (3) (<http://www.cdc.gov/noes/noes2/x5390occ.html>). [The NOES estimate for potential occupational exposure to dichloropropanol, n.o.s. (CASRN 26545-73-3) was 206 workers (<http://www.cdc.gov/noes/noes1/x5390sic.html>).]

Pesticide applicators and farm workers might be exposed to 1,3-DCP from use of the soil fumigant Telone II (1,3-dichloropropene), which is produced by Dow Chemical from dichlorohydrins). GC/MS analysis of a complex mixture of mutagenic compounds in 1,3-dichloropropene led Talcott and King (1984) to tentatively identify 1,3-DCP and epichlorohydrin.

Wienecke (1993 letter) proposed that 1,3-DCP, an epichlorohydrin impurity and possible metabolite (Koga et al., 1992; cited by JECFA, 2002), might be used as an indicator of exposure to epichlorohydrin. Numerous facilities use epichlorohydrin to produce epoxy resins and other chemicals. The NOES survey estimated that 80,170 employees, 14,921 of whom were female, were potentially exposed to epichlorohydrin in the early 1980s (NIOSH, 1990 [<http://www.cdc.gov/noes/noes1/29010sic.html>]).

Workers producing or using 1,2,3-trichloropropane might also be exposed to 1,3-DCP. *In vitro* studies of 1,2,3-trichloropropane metabolism found that human hepatic microsomes oxidize 1,2,3-trichloropropane to 1,3-dichloroacetone; in the presence of alcohol dehydrogenase and NADH, 1,3-DCP formed from 1,3-dichloroacetone (Weber and Sipes, 1992).

Workers producing or using the flame retardant Fyrol FR-2, which is tris(1,3-dichloro-2-propyl) phosphate, might be exposed to 1,3-DCP as a metabolite. Nomeir et al. (1981) and Lynn et al. (1981) reported 1,3-DCP as a rat metabolite. The general public may also be exposed to 1,3-DCP in this way since Fyrol FR-2 has been found in human adipose tissue in a study of implications of Great Lakes pollution on human health (LeBel and Williams, 1986).

Workers producing and using other compounds containing 1,3-DCP impurities would include those involved in the manufacture of bis(2-chloro-1-methylethyl) ether (BCMEE) (CASRN 108-60-1) and the quaternary ammonium compound CHPTA (Dextrosil, Dowquat 188) (CASRN 3327-22-8). BCMEE has been used in paint and varnish removers and cleaning solutions. Technical BCMEE comprises about 70% diether of 1-chloro-2-propanol (CASRN 127-00-4) and 30% ether of 1-chloro-2-propanol and 2-chloro-1-propanol. The technical grade product contains about 1% each dichloropropene and 1,3-DCP (Faust, 1999 [<http://www.oehha.ca.gov/prop65/pdf/DBCME.pdf>]). CHPTA is used in the manufacture of cationic starch by etherification; the starch is used in paper and textile manufacturing (ChemicalLand21.com). Xinxiang RuiFeng Chemical Co., Ltd. (2002) offers CHPTA with up to 20 ppm 1,3-DCP and <1 ppm epichlorohydrin. Degussa produces similar quaternary ammonium compounds from epichlorohydrin. The 1,3-DCP concentrations specified are no more than 100 or 1,000 ppm (QUAB Specialties, undated).

Workers may be exposed to 1,3-DCP in manufacturing flexible polyurethane (based on the presence of CASRN 96-23-1 in the CAPLUS abstract indexing). The article by Boeniger (1991)

would need to be retrieved to discover the source, which might be the flame retardant Fyrol FR-2.

Production and use of 3-MCPD, the 1,3-DCP precursor in hydrochlorination, may be another source of potential 1,3-DCP exposure. For example, a Solvay product of minimum 98.5% purity contains up to 1000 mg 1,3-DCP/kg (Solvay, 2002).

## 8.0 Regulatory Status

U.S. government regulations pertaining to 1,3-DCP are summarized in **Table 1**.

1,3-DCP is among the U.S. HPV chemicals for which no sponsor is identified in the HPV Challenge Program (U.S. EPA, 2004 [<http://www.epa.gov/opptintr/chemrtk/opptsrch.htm>]). Testing requirements for 1,3-DCP were not identified.

Under TSCA 8(d) and 8(e), producers and importers of 1,3-DCP and of products containing 1,3-DCP as an impurity submitted five and 14 studies, respectively. One TSCATS Section 2 (FYI) submission has been made. FYI submissions are voluntary; content is similar to TSCA 2.0 8(e) submissions. Submitters may describe known uses, workplace practices, exposure risks, and market information in an FYI submission (U.S. EPA, 2003a [[http://oaspub.epa.gov/srs/srs\\_proc\\_qry.navigate/?P\\_SUB\\_ID=16725](http://oaspub.epa.gov/srs/srs_proc_qry.navigate/?P_SUB_ID=16725)]). 1,3-DCP is a reportable chemical under the TSCA IUR under TSCA rule or order 4 (U.S. EPA, 2002a; [http://www.epa.gov/oppt/iur/urregadvisor/iur-orig-reptchems-pge\\_1.htm](http://www.epa.gov/oppt/iur/urregadvisor/iur-orig-reptchems-pge_1.htm)) and subject to reporting every four years in the TSCA Chemical Update System, which contains non-CBI (confidential business information) production volume aggregates (U.S. EPA, 1990).

In the United Kingdom, 1,3-DCP is on the Schedule 2 list "Substances referred to in regulations 6A, 6B, and 6C" of "The Dangerous Substance and Preparations (Safety) (Consolidation) (Amendment) Regulations 1996" (UK Statutory Instrument, 1996).

The European Commission "Consolidated List of C/M/R [Carcinogenic, Mutagenic or Toxic to Reproduction] Substances" includes 1,3-DCP in the group "Carcinogens, category 2" (EC Number 202-491-9] per point 30 of Annex I of Directive 76/769/EEC [European Economic Community] as amended (European Commission, 2002).

1,3-DCP is included on the "2000 OECD List of High Production Volume Chemicals" for which member countries "shall co-operatively investigate...to identify those which are potentially hazardous to the environment and/or to the health of the general public or workers..." (OECD, 2001).

Fewer limits have been set for 1,3-DCP in acid-HVP, soy sauces, and related products than for 3-MCPD. When both 3-MCPD and 1,3-DCP are present, the 3-MCPD concentration is always higher than that for 1,3-DCP. 3-MCPD is often found in the absence of 1,3-DCP. The Food Chemicals Codex specified limits of no more than 1 mg 3-MCPD/kg (1 ppm) calculated on a dry basis and no more 0.05 mg 1,3-DCP/kg (50 ppb) in acid-HVP calculated on a dry basis in

**Table 1. Federal Regulations Relevant to 1,3-DCP, Dichlorohydrins, and Dichloropropanols, n.o.s.**

Reference		Summary of Regulation
F D A	21 CFR Part 173 Secondary Direct Food Additives Permitted in Food for Human Consumption, Subpart A—Polymeric Substances and Polymer Adjuvants for Food Treatment §173.60 Dimethylamine-epichlorohydrin copolymer [DEC]  21 CFR Part 173 357 Materials Used as Fixing Agents in the Immobilization of Enzyme Preparations [Addition according to the final rule promulgated in 67(122) FR 42714-42717, June 25, 2002.]	Dimethylamine-epichlorohydrin copolymer (DEC) is used as a decolorizing agent or flocculating agent in the clarification of refined sugar liquids and juices. Its concentration is limited to 150 ppm of sugar solids. Concentrations of 1,3-DCP and epichlorohydrin in DEC are required to be less than 1,000 ppm and 10 ppm, respectively.  §173.357 is amended in the table in paragraph (a)(2) by addition of the following information. DEC may be used as a fixing material to immobilize glucose isomerase enzyme preparations. The fixed enzyme preparations are used in production of high-fructose corn syrup in accordance with §184.1372 of this chapter. The mandated residual limit of 1,000 ppm 1,3-DCP in DEC was estimated to pose minimal lifetime cancer risk to humans exposed to the impurity.
E P A	40 CFR 60 ... Subpart NN—Standards of Performance for Volatile Organic Compound (VOC) Emissions from Synthetic Organic Chemicals Manufacturing Industry (SOCMI)  40 CFR Part 60 Standards of Performance for New Stationary Sources, Subpart VV Equipment Leaks of VOC in the Synthetic Organic Chemicals Manufacturing Industry  40 CFR Part 192—Health and Environmental Protection Standards for Uranium and Thorium Mill Tailings, Subpart E—Standards for Management of Thorium By-Product Materials Pursuant to Section 84 of the Atomic Energy Act.  40 CFR Part 261 Identification and Listing of Hazardous Wastes, Subpart D—Lists of Hazardous Wastes §261.32  40 CFR Part 261 Subpart D...§261.38 Comparable/Syngas Fuel Exclusion  40 CFR 261, Appendix VII Basis for Listing  40 CFR 261, Appendix VIII Hazardous Wastes.  40 CFR Part 799—Identification of Specific Chemical Substance and Mixtures Testing Requirements, Subpart D—Multichemical Test Rules §799.5055 Hazardous Waste Constituents Subject to Testing [under the Toxic Substances Control Act (TSCA)]	§60.667 is a list of chemicals affected by Subpart NN. 1,3-DCP is listed as dichlorohydrin (96-23-1).  §60.489 is a list of chemicals produced by affected facilities. 1,3-DCP is listed as dichlorohydrin (96-23-1).  1,3-DCP is listed in Appendix I to Part 192—Listed Constituents  §261.32 includes RCRA hazardous waste K017, the heavy ends (still bottoms) from the purification column in the production of epichlorohydrin. See 40 CFR 261 Appendix VII. Synthetic gaseous fuel generated from incinerators burning hazardous waste must contain less than 1 ppmv (parts per million by volume) of 1,3-DCP. According to 63(118) FR 32781-33829 (June 19, 1998), wastes that meet the comparable/syngas fuel requirements are not solid wastes. 1,3-DCP is in Table 1 for §261.38, Detection and Detection Limit Values for Comparable Fuel Specification. The concentration limit is nondetected with a minimum required detection limit of 30 mg/kg. Appendix VII, Basis for Listing, lists the hazardous constituents for which hazardous waste K017 [see 40 CFR 261.32] was listed: epichlorohydrin, chloroethers [bis(chloromethyl) ether and bis(2-chloroethyl) ether], trichloropropene, and dichloropropanols. Dichloropropanols, n.o.s., CASRN 26545-73-3, are designated as a RCRA hazardous waste. TSCA Section 4 testing requirements included an oral gavage subchronic toxicity test with rats and a soil adsorption isotherm test. Provisions of 796.2750(b)(vii)(A) shall not apply to 1,3-dichloropropanol. Conditional exemptions from the TSCA Section 4 test rule requirements was granted to McDermid Inc., a 1,3-DCP manufacturer, via the <i>Federal Register</i> March 31, 1995.

December 1997. The limits on a liquid basis are 0.4 mg/kg and 0.02 mg/kg, respectively (CCFAC, March 2003). The U.S. food industry voluntarily complied with these specifications (CCFAC, March 2001).

The UK FSA has advised the food industry to reduce 3-MCPD concentrations as low as technologically feasible (CCFAC, March 2001).

In June 2001, JECFA recommended a provisional maximum tolerable daily intake for 3-MCPD of 0.002 mg/kg body weight (bw). Because of its carcinogenicity, JECFA concluded that no level of 1,3-DCP is safe.

The Australia New Zealand Food Standards Council agreed on maximum limits for 3-MCPD and 1,3-DCP to become enforceable in November 2001 in the Food Standards Code for soy and oyster sauces. These limits for the two countries are 0.2 mg 3-MCPD/kg and 0.005 mg 1,3-DCP/kg calculated on 40% dry weight. A limit for 1,3-DCP of 0.005 mg/kg is close to the analytical detection limit of current methods (Bavor, 2002).

The European Commission Regulation EC No. 466/2002, in force since April 2002, set a legal limit of 0.02 mg/kg for 3-MCPD in acid-HVP and soy sauce based on 40% dry matter content (UK FSA, 2002; IFST, 2003).

## **9.0 Toxicological Data**

### **9.1 General Toxicology**

In 2002, JECFA published a monograph summarizing the safety data on selected food additives and contaminants including 1,3-DCP. The following sections briefly present the data. More information is available at <http://www.inchem.org/documents/jecfa/jecmono/v48je19.htm> (last accessed on May 23, 2003). The United Kingdom Committee on the Carcinogenicity (COC) and the Committee on the Mutagenicity (COM) of Chemicals in Food, Consumer Products and the Environment both published reports in 2001 that evaluated the toxicological, carcinogenic, and mutagenic effects of 1,3-DCP. The COC and COM reports are available online in PDF format at <http://www.foodstandards.gov.uk/multimedia/pdfs/COCsection.pdf> and <http://www.doh.gov.uk/pdfs/mut016.pdf>, respectively. Most of the studies cited by JECFA (2002) can be found in these two reports.

#### **9.1.1 Human Data**

In general, 1,3-DCP is "moderately toxic" via inhalation, ingestion, and skin contact. It produces effects similar to carbon tetrachloride but is more irritating to the mucous membranes (Hawley, 1977; Lewis, 1996; both cited by HSDB, 2002). Oral intake results in severe irritation of the throat and stomach (Gosselin, 1976; cited by JECFA, 2002).

In five of 12 workers exposed to an unknown concentration of 1,3-DCP (via inhalation) from the cleaning of a saponification tank used in the manufacture of 1,3-DCP, acute hepatitis developed. Two of the five died from hepatic failure four and 11 days after the job. Autopsy showed submassive hepatocellular necrosis in one of the individuals (e.g., total bilirubin levels were significantly increased). At ~48 hours after exposure, the 1,3-DCP plasma level was 200 ng/mL

(Shiozaki et al., 1994 [cited by JECFA, 2002]; Haratake et al., 1993 [cited by HSDB, 2002]). [It was noted that potential exposure to other chemicals was not reported.]

### 9.1.2 Chemical Disposition, Metabolism, and Toxicokinetics

In rats, oral administration of 1,3-DCP (50 mg/kg [0.39 mmol/kg] bw) daily for 5 days resulted in the detection of  $\beta$ -chlorolactate (~5% of the dose), *N,N'*-bis(acetyl)-*S,S'*-(1,3-bis(cysteinyl))propan-2-ol (1%), and *N*-acetyl-*S*-(2,3-dihydroxypropyl)cysteine in the urine. The epoxide epichlorohydrin was proposed as an intermediate, which can then conjugate with glutathione (GSH), forming mercapturic acid derivatives. (Genotoxic and carcinogenic activity have been reported to depend on the formation of the epoxide intermediate during metabolism [Hahn et al., 1991; cited by COM, 2001]. See Section 9.10.) The metabolic conversion of 2-chloropropane-1,3-diol to *N*-acetyl-*S*-(2,3-dihydroxypropyl)cysteine confirmed that an epoxide intermediate was involved. Additionally, epichlorohydrin may hydrolyze to 3-MCPD, which can undergo further metabolism to produce  $\beta$ -chlorolactate (Jones and Fakhouri, 1979 [cited by COC, 2001a; COM, 2001, and JECFA, 2002]).

In another rat study, a single subcutaneous (s.c.) injection of 1,3-DCP (~68 mg/kg [0.53 mmol/kg] bw) resulted in ethyl acetate-extractable metabolites in the 24-hour urine—1,2-propanediol (0.43% of the dose) and 3-MCPD (0.35%). The parent compound comprised 2.4% (Koga et al., 1992; cited by JECFA, 2002).

#### GSH Depletion

*In vitro* and *in vivo* studies have demonstrated the ability of 1,3-DCP to deplete GSH. Assays using hepatocyte cultures indicate a pathway through CYP2E1 to dichloroacetone prior to the depletion (COC, 2001a; COM, 2001). (See Section 9.10.)

### 9.1.3 Acute Exposure

Acute toxicity values for 1,3-DCP are presented in Table 2. The details of studies discussed in this section, except where noted, are presented in Table 3.

In rats, intraperitoneal (i.p.) injection of 1,3-DCP (18-290 mg/kg [0.14-2.25 mmol/kg] bw) produced somnolence, liver injury (specifically, hepatocellular necrosis), and a significant increase in the activity of serum alanine aminotransferase. In addition, erosion of the kidneys and the gastrointestinal tract mucosa was observed (Katoh et al., 1998 [cited by JECFA, 2002]; Haratake et al., 1994 [cited by HSDB, 2002, and JECFA, 2002]; Stott et al., 1997). (Other studies involving a single i.p. injection in rats [further details not provided] have reported mild liver cell damage, such as congestion, at 25 mg/kg bw [0.19 mmol/kg bw]; diuresis, precipitation of calcium oxalate in the urine, and deaths at doses of  $\geq$ 50 mg/kg bw [0.39 mmol/kg bw]; and decreased white blood cell and platelet counts and increased blood clotting time at 110 mg/kg bw [0.853 mmol/kg bw] (Fry et al., 1999; Haratake et al., 1993; Hodgkinson, 1977; Katoh et al., 1998; all cited by COM, 2001).) Subcutaneous injection of 1,3-DCP (50 mg/kg [0.39 mmol/kg] bw or 100 mg/mL [775 mM]) in rats decreased platelet counts, while increasing the activities of both serum aspartate and serum alanine aminotransferase (Fujishiro et al., 1994; cited by JECFA, 2002; Imazu et al., 1992).

In rabbits, 1,3-DCP (10 mg [0.078 mmol]) on the skin for 24 hours caused mild irritation (RTECS, 2000). The chemical (dose n.p.) also produced irritation in the eyes, as well as moderately severe damage (Smyth et al., 1962 [cited by JECFA, 2002]; Grant, 1974 [cited by HSDB, 2002, and JECFA, 2002]).

**Table 2. Acute Toxicity Values for 1,3-DCP**

Route	Species (sex and strain)	LD <sub>50</sub> /LC <sub>50</sub>	Reference(s)
oral	mouse (sex and strain n.p.)	LD <sub>50</sub> = 25 mg/kg (0.19 mmol/kg) bw	RTECS (2000)
		LD <sub>50</sub> = 93-125 mg/kg (0.72-0.969 mmol/kg) bw	BIBRA (1999; cited by COM, 2001)
		LD <sub>50</sub> = 100 mg/kg (0.775 mmol/kg) bw	HSDB (2002)
	rat (sex and strain n.p.)	LD <sub>50</sub> = 110 mg/kg (0.853 mmol/kg) bw	HSDB (2002); RTECS (2000)
		LD <sub>50</sub> = 120 mg/kg (0.930 mmol/kg) bw	Pallade et al. (1963; cited by JECFA, 2002)
		LD <sub>50</sub> = 140 mg/kg (1.09 mmol/kg) bw	Smyth et al. (1962; cited by JECFA, 2002)
		LD <sub>50</sub> = 110-400 mg/kg (0.853-3.10 mmol/kg) bw	BIBRA (1999; cited by COM, 2001)
inh.	mouse (sex and strain n.p.)	LC <sub>50(1-5 days)</sub> = 1.7-3.2 mg/L (1700-3200 mg/m <sup>3</sup> ; 320-600 ppm)	Pallade et al. (1963; cited by JECFA, 2002)
		LC <sub>50(4 h)</sub> = 0.66 mg/L (660 mg/m <sup>3</sup> ; 125 ppm)	Smyth et al. (1962; cited by JECFA, 2002)
	rat (sex and strain n.p.)	LC <sub>50(4 h)</sub> = 125 ppm (659 mg/m <sup>3</sup> )	RTECS (2000)
		LC <sub>50</sub> = 300-1000 ppm (1580-5276 mg/m <sup>3</sup> )	BIBRA (1999; cited by COM, 2001)
i.p.	rat (sex and strain n.p.)	LD <sub>50</sub> = 106 mg/kg (0.822 mmol/kg) bw	BIBRA (1999; cited by COM, 2001)
		LD <sub>50</sub> = 110 mg/kg (0.853 mmol/kg) bw	Pallade et al. (1963; cited by JECFA, 2002)
dermal	rabbit (sex and strain n.p.)	LD <sub>50</sub> = 800 mg/kg (6.20 mmol/kg) bw	HSDB (2002); Smyth et al. (1962; cited by JECFA, 2002)

Abbreviations: bw = body weight; h = hour(s); inh. = inhalation; i.p. = intraperitoneal(ly); LC<sub>50</sub> = concentration lethal to 50% of test animals; LD<sub>50</sub> = lethal dose for 50% of test animals; n.p. = not provided

#### 9.1.4 Short-term and Subchronic Exposure

In a two-week gavage study, male Sprague-Dawley rats given 1,3-DCP (1, 10, 25, or 75 mg/kg [0.008, 0.078, 0.19, 0.58 mmol/kg] bw) daily had increased liver weights at the 10 and 25 mg/kg doses. In females, this occurred only at the 25 mg/kg dose. At 75 mg/kg, body weights were decreased and liver weights increased in both sexes. Additionally, kidney weights were increased in males (Breslin et al., 1989; cited by Dow Chem. Co., 1989a).

**Table 3. Acute Exposure to 1,3-DCP**

<b>Species, Strain, and Age, Number, and Sex of Animals</b>	<b>Chemical Form and Purity</b>	<b>Route, Dose, Duration, and Observation Period</b>	<b>Results/Comments</b>	<b>Reference(s)</b>
Rats, Wistar, age and number n.p., M	1,3-DCP, purity n.p.	i.p.; 18, 36, 73, 140, or 290 mg/kg bw (0.14, 0.28, 0.57, 1.09, or 2.25 mmol/kg bw) [17-25% LD <sub>50</sub> ]; observation period n.p.	Diffuse massive hepatocellular necrosis was observed. Serum alanine aminotransferase activity was significantly increased. In the kidneys, degeneration of the tubular epithelium and erosion of the entire organs occurred. Erosion was also seen in the gastrointestinal tract mucosa.	Katoh et al. (1998; cited by JECFA, 2002)
Rats, Wistar, age and number n.p., M	1,3-DCP, purity n.p.	i.p.; 50 mg/kg bw (0.39 mmol/kg bw); observed up to 72 h	Zonal necrosis of the centrilobular space, peaking between 24 and 48 h after injection, was observed. At 4 h after dosing, destruction of the sinusoidal lining occurred. At 6 h, monocytic influx into the necrotic areas was seen. At 24 h, serum alanine aminotransferase activity was increased. At 48 h, centrilobular spaces collapsed. Additionally, active phagocytosis of macrophages, proliferation of perisinusoidal cells, and accumulation of collagen fibrils were seen. At 72 h, numerous regenerating sinusoidal structures and hepatocytes were observed. After 1 wk, healing with slight perivascular fibrosis and scattered granulomas was observed, and serum alanine aminotransferase activity returned to baseline values.	Haratake et al. (1994; cited by HSDB, 2002, and JECFA, 2002)
Rats (strain, age, number, and sex n.p.)	1,3-DCP, purity n.p.	i.p.; 70 mg/kg (0.54 mmol/kg [LD <sub>Lo</sub> ]; observation period n.p.	Somnolence and hepatocellular necrosis (56.7%; concentrated around the central veins) were observed. Loss of parenchymal and sinusoidal structure, highly eosinophilic cellular debris, and inflammatory cell infiltration occurred in damaged areas.	Stott et al. (1997)
Rats, Wistar, age and number n.p., M	1,3-DCP, purity n.p.	s.c.; 100 mg/mL (775 mM) dissolved in saline; observed at ≥6 h	At 6 h after injection, the number of white blood cells and platelets were significantly decreased. Transaminases, alkaline phosphatase, lactate dehydrogenase, and blood urea, nitrogen, and creatinine were markedly increased.	Imazu et al. (1992)
Rats, Wistar, age and number n.p., M	1,3-DCP, purity n.p.	s.c.; 50 mg/kg bw (0.39 mmol/kg bw); observed up to 72 h	At 6 and 24 h after injection, platelet counts were decreased, while serum aspartate aminotransferase activity was increased. Serum alanine aminotransferase activity was also elevated but only at 6 h. At 72 h, there were no significant changes in hematological or serum chemical endpoints.	Fujishiro et al. (1994; cited by JECFA, 2002)
Rabbits (strain, age, number, and sex n.p.)	1,3-DCP, purity n.p.	dermal; 10 mg (0.078 mmol) for 24 h to the unoccluded skin; observation period n.p.	Mild irritation was seen.	RTECS (2000)

**Table 3. Acute Exposure to 1,3-DCP (Continued)**

Species, Strain, and Age, Number, and Sex of Animals	Chemical Form and Purity	Route, Dose, Duration, and Observation Period	Results/Comments	Reference(s)
Rabbits (strain, age, number, and sex n.p.)	1,3-DCP, purity n.p.	topical application to the eyes; dose, duration, and observation period n.p.	Irritation and severe damage occurred. A grade of 8 on a scale of 1-10 was reported.	Smyth et al. (1962; cited by JECFA, 2002); Grant (1974; cited by HSDB, 2002, and JECFA, 2002)

Abbreviations: bw = body weight; h = hour(s); LD<sub>50</sub> = lethal dose for 50% of test animals; LD<sub>Lo</sub> = lethal dose, low; M = male(s); n.p. = not provided; s.c. = subcutaneous(ly); wk = week(s)

In another study, 1,3-DCP (10, 20, or 30 mg/kg [0.078, 0.16, or 0.24 mmol/kg] bw) administered daily *per os* for 11 weeks produced no changes in body weight, locomotor activity, or landing foot splay distance in male and female Sprague-Dawley rats (Song et al., 2004).

When male and female Sprague-Dawley rats were administered 1,3-DCP (0.1, 1, 10, or 100 mg/kg [0.8, 8, 78, or 775  $\mu$ mol/kg] bw) daily by gavage in distilled water five days per week for 13 weeks, decreases in body-weight gain and feed consumption, increased liver and kidney weights, alterations in serum chemistry and urinary and hematological parameters, gross pathological changes in the stomach, and histopathological changes in the stomach, kidney, liver, and nasal tissue were observed in both sexes at the highest dose. At 10 mg/kg bw [78  $\mu$ mol/kg bw] per day, increased liver weights were found in males and females, while histopathological changes in the stomach, kidneys, and liver occurred only in males. The effects were less frequent and/or less severe than those reported for the highest dose (Jersey et al., 1991 abstr.; cited by JECFA, 2002). (Note: Specific details can be found in the full report submitted to the U.S. EPA [TSCATS] by Dow Chem. Co. [1989a].) A no-observable adverse effect level (NOAEL) of 1 mg/kg/day was therefore established (COC, 2001a).

In a more recent study, Sprague-Dawley rats given 1,3-DCP (15, 30, or 60 mg/kg [0.12, 0.23, or 0.47 mmol/kg] bw) daily via gavage for 13 weeks exhibited dose-dependent increases in liver and kidney weights. In males only, an increase in albumin and dose-dependent decreases in white blood cells, mean corpuscular volume, mean corpuscular hemoglobin (MCH), and basophils were observed. In females, red blood cells, hemoglobin, hematocrit, MCH, MCH concentration, and neutrophils were slightly decreased and platelets and total cholesterol were increased (Lym et al., 2003).

### 9.1.5 Chronic Exposure

In male and female Wistar rats administered 1,3-DCP (27, 80, or 240 mg/L [0.21, 0.62, 1.86 mM]; equivalent to 2, 6, or 19 mg/kg bw/day [0.02, 0.05, or 0.15 mmol/kg bw/day] for males and 3, 10, or 30 mg/kg bw/day [0.02, 0.078, or 0.23 mmol/kg bw/day] for females) in the drinking water for 104 weeks, no treatment-related signs of toxicity were observed. Furthermore, no changes in food and water consumption were seen. At the high dose, mortality was increased in both males and females compared with controls, and statistically significant decreases in mean body weight gain were observed for males after 74 weeks and in females after 78 weeks. Dose-related increases in the relative weights of the liver, kidney, and brain were also reported. At the high dose, female rats appeared to have hepatotoxicity (increases in cholesterol level, serum aspartate and alanine aminotransferase activities, alkaline phosphatase activity,  $\gamma$ -glutamyl transferase activity, and GSH level, and a decreased cytochrome P450 content), as well as nephrotoxicity (statistically significant increases in urinary levels of amylase and protein) (Hercules Inc., 1986).

### 9.1.6 Synergistic/Antagonistic Effects

At a low dose (5 mg/kg), diethyldithiocarbamate provided significant protection against 1,3-DCP hepatotoxicity in the rat and inhibited enzyme markers for CYP2E1 activity. At a higher dose (25 mg/kg), complete protection occurred. The hepatotoxicity of 1,3-DCP was therefore concluded to be mediated principally by CYP2E1 (Stott et al., 1997).

### 9.1.7 Cytotoxicity

The cytotoxicity of 1,3-DCP is cytochrome P450- and GSH-dependent (Hammond et al., 1999).

Results from *in vitro* neurotoxicity studies with PC12 and N18D3 cell lines, showed that 72 hour treatment with 1,3-DCP (0.1-100 µM [0.01-12.9 µg/mL]) produced no dose-related effects or cell death. The addition of a metabolic activation fraction in PC12 cultures for 24 hours did not cause significant changes in cell viability (Song et al., 2004).

### 9.2 Reproductive and Teratological Effects

In male albino Wistar rats, 1,3-DCP (5 or 20 mg/kg [0.04-0.16 mmol/kg] bw) given daily via gavage for 14 days produced spermatocoele unilaterally in the ductuli efferentes of one of ten rats at the high dose. No other signs of toxicity were observed (Shell Oil Company, 1979). A single i.p. injection of 1,3-DCP (44 mg/kg [0.34 mmol/kg] bw) in male Wistar rats produced a significant decrease in sperm count in the body and tail of the epididymis six weeks post-treatment (Omura et al., 1995; cited by JECFA, 2002).

### 9.3 Carcinogenicity

Treatment-related non-neoplastic lesions were observed in the liver (e.g., increased incidence of slight to moderate fatty change and of hemosiderin-containing Kupffer cells), kidney (increased level of chronic progressive nephrosis), and thyroid (follicular cell hyperplasia) of male and female Wistar rats given 1,3-DCP (27, 80, or 240 mg/L [0.21, 0.62, 1.86 mM] in their drinking water for 104 weeks. This treatment is equivalent to a dose of 3, 10, or 30 mg/kg bw/day [0.02, 0.078, or 0.23 mmol/kg bw/day] in **female** and 2, 6, or 19 mg/kg bw/day [0.02, 0.05, or 0.15 mmol/kg bw/day] in **male rats**. Statistically significant, dose-related increases in the combined incidences of the following tumors were also observed in both males and females (see **Table 4**): in the liver, hepatocellular adenoma and carcinoma; in the tongue/oral cavity, squamous cell papilloma and carcinoma; and in the thyroid, follicular cell adenoma and carcinoma. The combined numbers of renal tubular adenoma and carcinoma were markedly and dose-dependently increased in males only (Hercules Inc., 1986). Additional details (e.g., the time of occurrence and actual frequencies) are provided in the COC and COM reports, which are available in PDF format at <http://www.foodstandards.gov/uk/multimedia/pdfs/COCsection.pdf> and <http://www.doh.gov.uk/pdfs/mut016.pdf>, respectively.

### 9.4 Initiation/Promotion Studies

No data were available.

### 9.5 Anticarcinogenicity

No data were available.

**Table 4. Summary of Incidences of Neoplasms in Rats (n=80, except where noted)**

Organ and Finding	Doses (mg/kg body weight per day)							
	0	2.1	6.3	19	0	3.4	9.6	30
	Males				Females			
<b>Kidneys</b>								
Tubule adenoma	0	0	3	10 <sup>d</sup>	0	0	0	1/79
Tubule carcinoma	0	0	0	1	0	0	0	0/79
<b>Liver</b>								
Hepatocellular adenoma	1	0	1	0	1	1	1	6 <sup>c</sup>
Hepatocellular carcinoma	0	0	2	11 <sup>d</sup>	0	0	1	44 <sup>e</sup>
Hemangiosarcoma	0	0	0	1	0	0	0	1
<b>Thyroid</b>								
Follicular adenoma	0	0	3 <sup>a</sup>	3/78 <sup>a</sup>	1/79	0	3	4/79
Follicular carcinoma	0	0	2	1/78	0/79	0	0	2/79 <sup>a</sup>
<b>Tongue</b>								
Papilloma	0	1	0/79	6 <sup>e</sup>	0	0	0	7/79 <sup>e</sup>
Carcinoma	0	0	1/79	6 <sup>e</sup>	0	1	1	4/79 <sup>b</sup>

<sup>a</sup>statistically significant at p<0.05; <sup>b</sup>statistically significant at p<0.01; <sup>c</sup>statistically significant at p<0.005;<sup>d</sup>statistically significant at p<0.001; <sup>e</sup>statistically significant at p<0.0005

## 9.6 Genotoxicity

The details of the following studies are presented in **Table 5**.

### *In Vitro Assays*

In *Salmonella typhimurium* strains TA100, TA1535, and TM677, 1,3-DCP (0.1-130 mg/plate [0.8-1000 µmol/plate]) induced reverse mutations in the presence and absence of metabolic activation (S9) (Hahn et al., 1991; Majeska and Matheson, 1983 abstr.; Nakamura et al., 1979; Ohkubo et al., 1995; Silhanková et al., 1982; Stolzenberg and Hine, 1980; Zeiger et al., 1988; all cited by JECFA, 2002). In one study, 1,3-DCP (0.26-26 mg/plate [2.0-200 µmol/plate]) was not mutagenic in TA98, TA1537, and TA1538 with or without S9, but two other studies reported negative results in TA97 and TA98 only without S9 (Ohkubo et al., 1995; Silhanková et al., 1982; Zeiger et al., 1988; all cited by JECFA, 2002).

In *Escherichia coli* strain TM930, 1,3-DCP (0.26-26 mg/plate [2.0-200 µmol/plate]) induced reverse mutation, while in strains PM21 and GC4798, it (0.3-3.9 mg/sample [2.3-30 µmol/sample]) produced DNA damage (Hahn et al., 1991; Silhanková et al., 1982; both cited by JECFA, 2002). In mouse lymphoma cells, 1,3-DCP (2-9 mg/mL [15-70 mL]; 0.1-1.9 µL/mL) caused gene mutation (Henderson et al., 1987 [cited by JECFA, 2002]; Hercules Inc., 1990). Mutations were also produced in mouse fibroblasts at doses of 0.1-1 mg/mL [0.8-8 mM] and in HeLa cells at a dose of 320 µg/mL [2.48 mM] with S9 (Painter and Howard, 1982; Piasecki et al., 1990; both cited by JECFA, 2002). In Chinese hamster V79 cells, 1,3-DCP (16-430 µg/mL [0.12-3.33 mM]) induced sister chromatid exchange (SCE) (von der Hude et al., 1987; cited by JECFA, 2002). SCE was also induced in Chinese hamster ovary (CHO) cells at doses of 0.015, 0.05, and 0.15 µL/mL without S9 and at doses of 0.15 and 0.5 µL/mL with S9. In addition, chromosomal aberrations were observed in CHO cells at 0.25 and 0.5 µL/mL without S9 and at 0.5 and 1 µL/mL with S9 (Hercules Inc., 1990).

An unpublished health and safety study submitted to the U.S. EPA [TSCATS] reported that in the hepatocyte primary culture/DNA repair assay, 1,3-DCP (doses n.p.) did not induce DNA damage (Confidential, 1983).

**Table 5. Genotoxicity Studies of 1,3-DCP**

Test System or Species, Strain, and Age, Number, and Sex of Animals	Biological Endpoint	Metabolic Activation (S9)	Chemical Form and Purity	Dose	Results	Reference(s)
<b><i>In Vitro Assays</i></b>						
<i>Salmonella typhimurium</i> strains TA97 and TA98	reverse mutation	+/-	1,3-DCP, purity n.p.	100-6700 µg/plate (0.775-51.94 µmol/plate) <sup>a</sup>	positive (+S9) negative (-S9)	Zeiger et al. (1988; cited by JECFA, 2002)
<i>S. typhimurium</i> strain TA98	reverse mutation	-	1,3-DCP, purity n.p.	≤1.2 mg/plate (9.3 µmol/plate)	negative	Ohkubo et al. (1995; cited by JECFA, 2002)
<i>S. typhimurium</i> strains TA98 <sup>b</sup> , TA1537, and TA1538	reverse mutation	+/-	1,3-DCP, purity n.p.	0.26-26 mg/plate (2.0-200 µmol/plate)	negative	Silhanková et al. (1982; cited by JECFA, 2002)
<i>S. typhimurium</i> strain TA100	reverse mutation	+/-	1,3-DCP, purity n.p.	10-100 µg/plate (0.078-0.775 µmol/plate)	positive (+S9) negative (-S9)	Gold et al. (1978; cited by COM, 2001)
<i>S. typhimurium</i> strain TA100	reverse mutation	-	1,3-DCP, purity n.p.	100-1000 µg/plate (0.775-7.753 µmol/plate)	positive	Lynn et al. (1981; cited by COM, 2001)
<i>S. typhimurium</i> strain TA100	reverse mutation	+	1,3-DCP, purity n.p.	≤500 µg/plate (3.88 µmol/plate)	positive	Majeska and Matheson (1983 abstr.; cited by JECFA, 2002)
<i>S. typhimurium</i> strain TA100	reverse mutation	+/-	1,3-DCP, purity n.p.	0.13-8.1 mg/plate (1.0-62.8 µmol/plate)	positive	Hahn et al. (1991; cited by JECFA, 2002)
<i>S. typhimurium</i> strain TA100	reverse mutation	+/-	1,3-DCP, purity n.p.	1.3-130 mg/plate (10-1000 µmol/plate)	positive	Stolzenberg and Hine (1980; cited by JECFA, 2002)
<i>S. typhimurium</i> strain TA1535	reverse mutation	+/-	1,3-DCP, purity n.p.	0.13-10 mg/plate (1.0-78 µmol/plate)	positive	Hahn et al. (1991; cited by JECFA, 2002)
<i>S. typhimurium</i> strain TA1535	reverse mutation	+/-	1,3-DCP, purity n.p.	0.26-26 mg/plate (2.0-200 µmol/plate)	positive	Silhanková et al. (1982; cited by JECFA, 2002)
<i>S. typhimurium</i> strains TA100 and TA1535	reverse mutation	+/-	1,3-DCP, purity n.p.	100-6700 µg/plate (0.775-51.94 µmol/plate) <sup>a</sup>	positive	Zeiger et al. (1988; cited by JECFA, 2002)
<i>S. typhimurium</i> strains TA100 and TA1535	reverse mutation	+/-	1,3-DCP, purity n.p.	0.39-39 mg/plate (3.0-300 µmol/plate)	positive	Nakamura et al. (1979; cited by JECFA, 2002)
<i>S. typhimurium</i> strains TA100 and TA1535	reverse mutation	+/-	1,3-DCP, purity n.p.	≤1.2 mg/plate (9.3 µmol/plate)	positive	Ohkubo et al. (1995; cited by JECFA, 2002)

**Table 5. Genotoxicity Studies of 1,3-DCP (Continued)**

Test System or Species, Strain, and Age, Number, and Sex of Animals	Biological Endpoint	Metabolic Activation (S9)	Chemical Form and Purity	Dose	Results	Reference(s)
<i>S. typhimurium</i> strain TM677	reverse mutation	+/-	1,3-DCP, purity n.p.	≤0.1 mg/plate (0.8 µmol/plate)	positive	Ohkubo et al. (1995; cited by JECFA, 2002)
<i>Escherichia coli</i> strain TM930	reverse mutation	+/-	1,3-DCP, purity n.p.	0.26-26 mg/plate (2.0-200 µmol/plate)	positive (+S9) negative (-S9)	Silhanková et al. (1982; cited by JECFA, 2002)
<i>E. coli</i> strains PM21 and GC4798	DNA repair	+/-	1,3-DCP, purity n.p.	0.3-3.9 mg/sample (2.3-30 µmol/sample)	positive (+S9) negative (-S9)	Hahn et al. (1991; cited by JECFA, 2002)
Mouse lymphoma cells, <i>Tk</i> locus	gene mutation	+/-	1,3-DCP, purity n.p.	2-9 mg/mL (15-70 mM)	positive	Henderson et al. (1987; cited by JECFA, 2002)
Mouse lymphoma cells, L5178Y <i>Tk</i> +/- locus	gene mutation	+/-	1,3-DCP, purity n.p.	0.4-1.9 µL/mL (-S9) 0.1-0.6 µL/mL (+S9)	positive	Hercules Inc. (1990)
Mouse fibroblasts, M2 clone	mutation (malignant transformation)	+	1,3-DCP, purity n.p.	0.1-1 mg/mL (0.8-8 mM)	positive	Piasecki et al. (1990; cited by JECFA, 2002)
HeLa cells	mutation	+	1,3-DCP, purity n.p.	320 µg/mL (2.48 mM)	positive	Painter and Howard (1982; cited by JECFA, 2002)
Chinese hamster V79 cells	SCE	+/-	1,3-DCP, purity n.p.	16-430 µg/mL (0.12-3.33 mM)	positive <sup>c</sup>	von der Hude et al. (1987; cited by JECFA, 2002)
CHO cells	SCE	+/-	1,3-DPC, purity n.p.	0.005, 0.015, 0.05, 0.15, 0.5, 1, and 5 µL/mL	positive	Hercules Inc. (1990)
CHO cells	CA	+/-	1,3-DPC, purity n.p.	0.063, 0.125, 0.25, 0.5, and 1 µL/mL	positive	Hercules Inc. (1990)
<b>In Vivo Assays</b>						
<i>Drosophila melanogaster</i>	somatic mutation (wing spot test)	N/A	1,3-DCP, purity n.p.	0.006-1.3 mg/mL (0.05-10 mM)	negative	Frei and Würgler (1997; cited by JECFA, 2002)

**Table 5. Genotoxicity Studies of 1,3-DCP (Continued)**

Test System or Species, Strain, and Age, Number, and Sex of Animals	Biological Endpoint	Metabolic Activation (S9)	Chemical Form and Purity	Dose	Results	Reference(s)
Rat, Han Wistar, age n.p., 6M/group	frequency of micronucleated polychromatic erythrocytes (in bone marrow)	N/A	1,3-DCP, purity n.p.	25, 50, or 100 mg/kg (0.19, 0.39, or 0.775 mmol/kg) once daily for 2 consecutive days	negative	Howe (2002; cited by COM, 2003)
Rat, Han Wistar, age n.p., 4M/group	UDS	N/A	1,3-DCP, purity n.p.	40 or 100 mg/kg (0.31 or 0.775 mmol/kg)	negative	Beevers (2003; cited by COM, 2003)

<sup>a</sup>COM (2001) reports this as 100-6666 µmol/plate.

<sup>b</sup>JECFA (2002) reports this as TA100. In agreement with all other data, it is inferred to be TA98, as reported by COM (2001).

<sup>c</sup>Almost inactivated by S9.

Abbreviations or Symbols: +/- = presence/absence; CA = chromosomal aberrations; CHO = Chinese hamster ovary; M = male(s); MN = micronucleus; N/A = not applicable; n.p. = not provided; SCE = sister chromatid exchange; UDS = unscheduled DNA synthesis

### In Vivo Assays

In *Drosophila melanogaster*, 1,3-DCP (0.006-1.3 mg/mL [5-10 mM]) was negative for somatic mutations (Frei and Würgler, 1997; cited by JECFA, 2002). In rats, 1,3-DCP (25-100 mg/kg [0.19-0.0775 mmol/kg]) failed to increase the frequency of micronucleated polychromatic erythrocytes in bone marrow and levels of unscheduled DNA synthesis (UDS) in the liver (Howe, 2002; Beevers, 2003; both cited by COM, 2003).

### **9.7 Cogenotoxicity**

No data were available.

### **.8 Antigenotoxicity**

No data were available.

### **9.9 Immunotoxicity**

In Hartley guinea pigs (5 males, 5 females), 1,3-DCP at 0.75% in distilled water was used in a 24-hour rechallenge application two weeks after initial challenge with hexanedioic acid, polymer with *N*-(2-aminoethyl)-1,2-ethanediamine, *N*-(1-oxohexyl) derivatives, epichlorohydrin-quaternized (CASRN 236400-71-8). Sensitization was elicited in one guinea pig. In another experiment, 1,3-DCP at 0.75% in corn oil was used, and the same result was obtained (Confidential, 2000).

1,3-DCP was one of 255 chemicals evaluated for its growth inhibitory effects on mouse splenic lymphocyte mitogenesis using lipopolysaccharide and Con A as the specific mitogen for B and T cells (Sakazaki et al., 2001). Results of this test were not provided in the search abstract.

### **9.10 Other Data (Mechanisms of Action)**

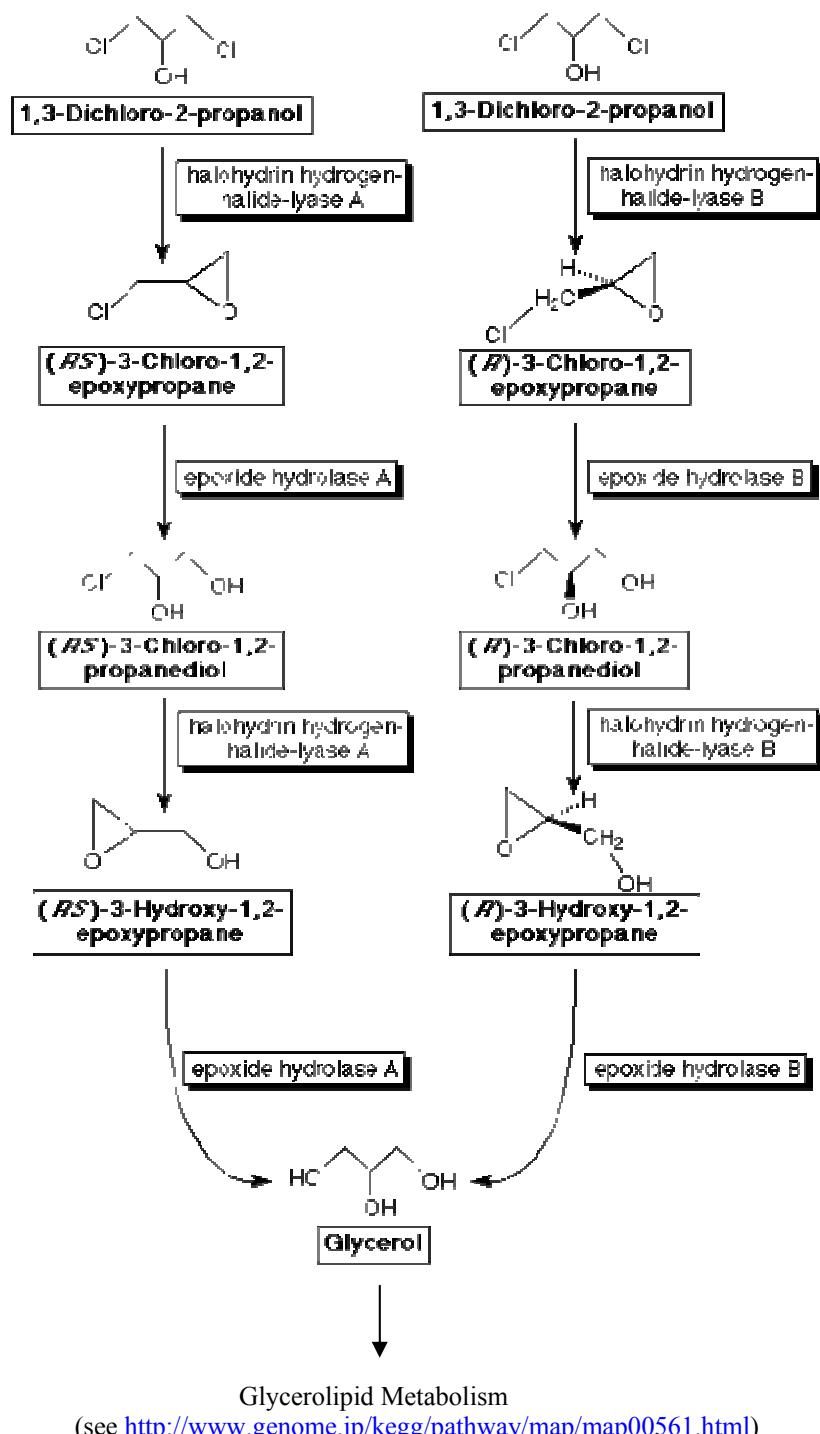
COM concluded that the role of 1,3-DCP metabolism in *in vitro* mutagenicity remains unclear and considers it to be of no significant genotoxic potential *in vivo* (COM, 2003).

#### 1,3-DCP Metabolism *in vitro*

The genotoxic and carcinogenic activity of 1,3-DCP have been reported to depend on the formation of the epoxide intermediate during metabolism (COM, 2001). *In vitro*, 1,3-DCP has been reported to be mutagenic in most bacterial studies both in the absence and presence of metabolic activation. (See **Section 9.6**.) Bacteria such as *Corynebacterium* sp. strain N-1074 have been found capable of converting 1,3-DCP to epichlorohydrin (see **Figure 1**), which would explain the mutagenicity of 1,3-DCP in the absence of S9 (COM, 2003; Nakamura et al., 1992). Additionally, in the SOS chromotest with *E. coli* strain GC4798, chemical conversion of 1,3-DCP to epichlorohydrin in the rat hepatocytes medium was proposed to be the genotoxic mechanism of action (Zeiger et al., 1988; cited by COM, 2003). In a separate study, chemically formed epichlorohydrin was found in the media for Ames and SOS chromotest assays with 1,3-DCP (Hahn et al., 1991).

A postulated alternative active metabolite is 1,3-dichloroacetone (1,3-DCA), formed from 1,3-DCP by the action of alcohol dehydrogenase or CYP2E (Hammond and Fry, 1997; Hammond et al., 1996 [cited by COM, 2003]). The proposed detoxication pathway is GSH conjugation, since 1,3-DCP depletes GSH both *in vitro* and *in vivo* and GSH depletion can potentiate the toxicity of

*Arthrobacter* sp. strain AD2      *Corynebacterium* sp. strain N-1074  
*Corynebacterium* sp. strain N-1074



**Figure 1. Proposed Microbial Transformation Pathway for 1,3-DCP**

Sources: Ellis et al. (2003) [[http://umbbd.ahc.umn.edu/dcp/dcp\\_image\\_map.html](http://umbbd.ahc.umn.edu/dcp/dcp_image_map.html)] and Natarajan et al. (2002) [[http://umbbd.ahc.umn.edu/dcp/dcp\\_map.html](http://umbbd.ahc.umn.edu/dcp/dcp_map.html)]

1,3-DCP in rat hepatocytes [see subsection below] (COM, 2003). 3-MCPD, the known metabolite of 1,3-DCP, has no significant *in vivo* genotoxic potential (Koga et al., 1992; cited by COM, 2003).

### 1,3-DCP Metabolism *in vivo*

The negative findings in genotoxicity assays *in vivo* (see **Section 9.6**) indicate that reactive genotoxic metabolites, if formed, must be too transient for 1,3-DCP to be genotoxic *in vivo* or that the target tissues and/or endpoints evaluated are not relevant to 1,3-DCP-induced genotoxicity. In rats treated with 1,3-DCP, the significantly increased hepatic malondialdehyde level was associated with decreases of liver GSH *S*-transferase activity and GSH content. Lipid peroxidation was suggested as a causative mechanism of the hepatotoxicity [diffuse massive necrosis] (Katoh et al., 1998; Kuroda et al., 2002). Inhibition of CYP2E1 lowered the hepatotoxicity in the animals (Stott et al., 1997).

### GSH Depletion

Several *in vitro* and *in vivo* studies reported the ability of 1,3-DCP to deplete GSH and to induce and/or be metabolized by P450 CYP2E1 (e.g., Fry et al., 1999; Garle et al., 1997 abstr., 1999; Hammond et al., 1996 [all cited by JECFA, 2002]; Hammond et al., 2002). 1,3-DCP (up to 1000 µM [129 µg/mL]) dose-dependently depleted GSH when incubated with cofactors (i.e., an NADPH-generating system) and liver microsomes from untreated rats. Inclusion of pyridine or omission of the cofactor, however, inhibited the depletion (Garle et al., 1999). In rat hepatocyte cultures, isoniazid was found to increase the rate and extent of GSH depletion by 1,3-DCP, as well as its toxicity, whereas cyanamide did neither. Pretreatment of cultures with 1-aminobenzotriazole (a cytochrome P450 inhibitor) prevented the toxicity of 1,3-DCP, while pretreatment with diethyl maleate or buthionine sulfoximine (GSH inhibitors) increased its toxicity (Hammond and Fry, 1996, 1997, 1999). In an *in vitro* model using monolayer cultures of genetically engineered NIH-3T3 or V79 cells expressing individual human or rat CYP450 isoforms, respectively, cell lines expressing cytochrome P450 enzymes metabolized 1,3-DCP. Compared to controls, increased toxicity was observed (Bull et al., 2001).

## **10.0 Structure-Activity Relationships**

Several structural analogs, including precursors and derivatives, were considered for inclusion in this discussion. Readily available summaries of studies on carcinogenesis, genotoxicity, and toxicity to reproduction for these compounds were sought from authoritative sources such as the NTP descriptions of long-term and short-term studies, the NTP *Report on Carcinogens* (RoC), the International Agency for Research on Cancer (IARC) (especially the IARC Monographs), the U.S. EPA, the International Programme for Chemical Safety/World Health Organization (IPCS/WHO) (especially the Environmental Health Criteria series), and other government agencies and international organizations. Brief descriptions of available information including selected studies from the primary literature have been compiled in **Table 6**. To augment the information, URLs for many of the documents available on the Internet are included in the table.

**Table 6. Carcinogenicity, Genotoxicity, and Reproductive and Developmental Toxicity of Selected Structural Analogues**

Name [Comment]	CASRN	Structure	Carcinogenicity	Genotoxicity	Reproductive and Developmental Toxicity
Bis(2-chloro-1-methylethyl) ether [Diether of 1-chloro-2-propanol]	108-60-1		<p>Faust (OEHHA) (1999) reviewed evidence.</p> <p>IARC Group 3  <a href="http://193.51.164.11/htdocs/monographs/vol41/bcmee.html">http://193.51.164.11/htdocs/monographs/vol41/bcmee.html</a>  <a href="http://193.51.164.11/htdocs/monographs/vol71/063-bis2ch1meteth.html">http://193.51.164.11/htdocs/monographs/vol71/063-bis2ch1meteth.html</a></p> <p>NTP TR-191 rats tested by gavage at up to 200 mg/kg/bw: negative (neg.)  <a href="http://ntp-server.niehs.nih.gov/htdocs/LTstudies/TR191.html">http://ntp-server.niehs.nih.gov/htdocs/LTstudies/TR191.html</a></p> <p>NTP TR-239 mice tested by gavage at up to 200 mg/kg/bw: positive (pos.) (hepatocellular tumors in males, etc.) Tested technical product with 30% 2-chloro-1-methylethyl 2-chloropropyl ether (CASRN 83270-31-9)  <a href="http://ntp-server.niehs.nih.gov/htdocs/LTstudies/TR239.html">http://ntp-server.niehs.nih.gov/htdocs/LTstudies/TR239.html</a></p> <p>IRIS (No. 0407) cited a 104-wk assay with 98.5% pure BCME in SPF-ICR mice (diet up to 10,000 ppm). No elevated tumor incidence  <a href="http://www.epa.gov/iris/subst/0407.htm">http://www.epa.gov/iris/subst/0407.htm</a></p>	<p>NTP Testing Status: Usually Salmonella positive (pos.). CA &amp; SCE pos. <i>in vitro</i>, neg. <i>in vivo</i>. Mouse lymphoma assay pos. Drosophila inconclusive, SLRL/reciprocal translocation assay [<a href="http://ntp-server.niehs.nih.gov/htdocs/Results_Status/ResstatB/10523-N.html">http://ntp-server.niehs.nih.gov/htdocs/Results_Status/ResstatB/10523-N.html</a>]</p>	No data were available for the 1986 IARC review (vol. 41). No publications found in DART/ETIC database in June 2003.
3-Bromo-1-propanol	627-18-9			NTP Salmonella pos. [ <a href="http://ntp-server.niehs.nih.gov/htdocs/Results_Status/Resstatb/11541-G.html">http://ntp-server.niehs.nih.gov/htdocs/Results_Status/Resstatb/11541-G.html</a> ]	
1-Bromo-2-propanol	19686-73-8			NTP Salmonella pos. [ <a href="http://ntp-server.niehs.nih.gov/htdocs/Results_Status/Resstatb/11542-K.html">http://ntp-server.niehs.nih.gov/htdocs/Results_Status/Resstatb/11542-K.html</a> ]	

**Table 6. Carcinogenicity, Genotoxicity, and Reproductive and Developmental Toxicity of Selected Structural Analogues (Continued)**

Name [Comment]	CASRN	Structure	Carcinogenicity	Genotoxicity	Reproductive and Developmental Toxicity
3-Chloro-1,2-propanediol; $\alpha$ -Chlorohydrin; 3-MCPD  [Precursor of 1,3-DCP in acid-HVP, soy sauces, etc.]	96-24-2		Benign tumors in rats See COC (2000) <a href="http://www.doh.gov.uk/mcpd1.htm">http://www.doh.gov.uk/mcpd1.htm</a> or JECFA (2001) <a href="http://www.who.int/pcs/jecfa/trs909.pdf">http://www.who.int/pcs/jecfa/trs909.pdf</a>	Not genotoxic <i>in vivo</i> . Pos. <i>in vitro</i> .  See SCF HCPD EC (2001) <a href="http://europa.eu/comm/food/fs/sc/scf/out9_1_en.pdf">http://europa.eu/comm/food/fs/sc/scf/out9_1_en.pdf</a>  COM (2000) <a href="http://www.doh.gov.uk/mcpd2.htm">http://www.doh.gov.uk/mcpd2.htm</a>  UK Food Advisory Committee (2000) <a href="http://archive.food.gov.uk/pdf_files/papers/fac_48.pdf">http://archive.food.gov.uk/pdf_files/papers/fac_48.pdf</a>	Anti-fertility effects reported in DART/ETIC records for several primary publications.  Omura et al. (1995) reported testicular toxicity.
1-Chloro-2-propanol	127-00-4		No evidence in NTP TR-477 (mice and rats exposed to technical product via drinking water at concentrations up to 1,000 ppm) <a href="http://ntp-server.niehs.nih.gov/htdocs/Levels/TR477.html">http://ntp-server.niehs.nih.gov/htdocs/Levels/TR477.html</a> <a href="http://ntp-server.niehs.nih.gov/htdocs/LT-studies/tr477.html">http://ntp-server.niehs.nih.gov/htdocs/LT-studies/tr477.html</a>	Weakly pos. in Salmonella strains TA100 + S9, TA1535 + and - S9. Pos. SCE and CA in CHO cells. Neg. micronucleus test in mice (peripheral blood). [ <a href="http://ntp-server.niehs.nih.gov/htdocs/LT-studies/tr477.html">http://ntp-server.niehs.nih.gov/htdocs/LT-studies/tr477.html</a> ]	NTP neg. for fertility effects in rats exposed in drinking water at concentrations up to 1,300 ppm. (NTP Report #RACB88075, 1990) [ <a href="http://ntp-server.niehs.nih.gov/htdocs/RT-studies/RACB88075.html">http://ntp-server.niehs.nih.gov/htdocs/RT-studies/RACB88075.html</a> ]
3-Chloro-1-propanol	627-30-5			NTP Salmonella pos. [ <a href="http://ntp-server.niehs.nih.gov/htdocs/Results_Status/Resstab/11539-F.html">http://ntp-server.niehs.nih.gov/htdocs/Results_Status/Resstab/11539-F.html</a> ]	
2,3-Dibromo-1-propanol  [Metabolite of TDPP]	96-13-9		In 10 <sup>th</sup> RoC.  IARC 77:439-454 (2000): Group 2B <a href="http://www.inchem.org/documents/iarcl/vol77/77-12.html">http://www.inchem.org/documents/iarcl/vol77/77-12.html</a>  NTP TR-400: Clear evidence in mice and rats given topical applications of up to 177 mg/kg/day 5 days/week for 56 weeks. Multiple tumor sites, including gastrointestinal tract, skin, liver, kidney, and nasal cavity. <a href="http://ntp-server.niehs.nih.gov/htdocs/LT-studies/tr400.html">http://ntp-server.niehs.nih.gov/htdocs/LT-studies/tr400.html</a>	NTP TR-400: Pos. Salmonella TA98, TA100, TA1535 without S9. Pos. in mouse lymphoma assay and in SCE and CA assays in CHO cells. Neg. micronucleus assay in male mice (bone marrow). <a href="http://ntp-server.niehs.nih.gov/htdocs/LT-studies/tr400.html">http://ntp-server.niehs.nih.gov/htdocs/LT-studies/tr400.html</a>	NMRI mice were treated on day 11 of gestation with 2,3-dibromo-1-propanol at doses of 56 or 100 mg/kg bw (route not given in the DART record). Observations included fetal weight reduction and increased incidence of fetal cleft palates and resorptions (Platzek and Pauli, 1998 abstr.).

**Table 6. Carcinogenicity, Genotoxicity, and Reproductive and Developmental Toxicity of Selected Structural Analogues (Continued)**

Name [Comment]	CASRN	Structure	Carcinogenicity	Genotoxicity	Reproductive and Developmental Toxicity
2,3-Dichloro-1-propanol; 1,2-Dichloro-3-propanol  [2,3-DCP is other dichlorohydrin produced as an intermediate in epichlorohydrin production.]	616-23-9		IRIS (No. 0465) not completely evaluated. No long-term toxicity study available <a href="http://www.epa.gov/iris/subst/0465.htm">http://www.epa.gov/iris/subst/0465.htm</a>	NTP Salmonella positive [ <a href="http://ntp-server.niehs.nih.gov/htdocs/Results_Status/Resstab/11539-F.html">http://ntp-server.niehs.nih.gov/htdocs/Results_Status/Resstab/11539-F.html</a> ]  COM (2001): genotoxic <i>in vitro</i> +/-S9 in bacteria and mammalian cells (limited number of studies); no <i>in vivo</i> studies [ <a href="http://www.doh.gov.uk/pdfs/mut017.pdf">http://www.doh.gov.uk/pdfs/mut017.pdf</a> ]	Omura et al. (1995) studied testicular toxicity.
1,3-Dichloro-2-propanone; 1,3-Dichloroacetone  [Oxidation product of 1,3-DCP]	534-07-6			SOS, Ames, newt micronucleus tests (Le Curieux et al., 1994).  Salmonella pos. (Merrick et al., 1987)	
1,3-Dichloropropene  [May be produced by dehydration of 1,3-DCP]	542-75-6		In 5 <sup>th</sup> -10 <sup>th</sup> RoC.  NTP TR-269: Rats and mice exposed to technical product with 1% epichlorohydrin by gavage at doses up to 50 (rats) or 100 mg/kg bw (mice) induced forestomach (CE MR, FM), urinary bladder (CE FM), lung (CE FM), and liver (CE MR) neoplasms [where CE = clear evidence, FM = female mice, MR = male rats]. <a href="http://ntp-server.niehs.nih.gov/htdocs/Levels/TR269levels.Html">http://ntp-server.niehs.nih.gov/htdocs/Levels/TR269levels.Html</a> <a href="http://ntp-server.niehs.nih.gov/htdocs/LT-studies/tr269.html">http://ntp-server.niehs.nih.gov/htdocs/LT-studies/tr269.html</a>  EHC 146: Inhalation of pure 1,3-dichloropropene induced benign tumors in the bladder and neoplasms in the forestomach and nasal mucosa of mice. Rats were not affected. <a href="http://www.inchem.org/documents/ehc/ehc146.htm">http://www.inchem.org/documents/ehc/ehc146.htm</a>	Neg. mammalian <i>in vivo</i> ; pos. some <i>in vitro</i> mammalian tests. Neg. in a mouse bone marrow micronucleus assay and Drosophila SLRL assay (Section 8.6 IPCS/WHO EHC 146, 1993) <a href="http://www.inchem.org/documents/ehc/ehc146.htm">http://www.inchem.org/documents/ehc/ehc146.htm</a>	Embryotoxic in rats and rabbits. Maternal toxicity observed. Not teratogenic at concentrations up to 1,362 mg/m <sup>3</sup> .  See section 8.5 IPCS/WHO EHC 146 (1993) and U.S. EPA (2000). <a href="http://www.epa.gov/iris/toxrevws/0224-tr.pdf">http://www.epa.gov/iris/toxrevws/0224-tr.pdf</a>

**Table 6. Carcinogenicity, Genotoxicity, and Reproductive and Developmental Toxicity of Selected Structural Analogues (Continued)**

Name [Comment]	CASRN	Structure	Carcinogenicity	Genotoxicity	Reproductive and Developmental Toxicity
Epichlorohydrin; 3-Chloro-1,2-propane oxide; 1-Chloro-2,3-epoxypropane  [Product produced from 1,3-DCP. A 1,3-DCP metabolite and biodegradation product.]	106-89-8		In 4 <sup>th</sup> -10 <sup>th</sup> RoC  IARC 71:603- (1999): Group 2A. Carcinogenic in rats and mice dosed orally and by s.c. and i.p. injection. Oral dosing induced increased tumor incidences of neoplasms in lung, forestomach, and nasal cavity and at s.c. injection site. <a href="http://www.inchem.org/documents/iarcl/vol71/020-epichlorohydrin.html">http://www.inchem.org/documents/iarcl/vol71/020-epichlorohydrin.html</a>	IARC 71:603- (1999): Epichlorohydrin induces genotoxicity in most <i>in vivo</i> and <i>in vitro</i> assays without metabolic activation.  NTP Status: Pos. CA and SCE <i>in vitro</i> . Salmonella pos. [ <a href="http://ntp-server.niehs.nih.gov/htdocs/Results_Status/Resstate/10512-C.Html">http://ntp-server.niehs.nih.gov/htdocs/Results_Status/Resstate/10512-C.Html</a> ]	30 relevant records in DART/ETIC and 15 in MEDLINE in June 2003.
3-Iodo-1,2-propanediol	554-10-9			NTP Testing Status: <i>In vitro</i> : Chromosome aberrations neg.; SCE neg. Drosophila: SLRL pos.; reciprocal translocation neg. Micronucleus neg. Salmonella pos. [ <a href="http://ntp-server.niehs.nih.gov/htdocs/Results_Status/Resstate/554109.html">http://ntp-server.niehs.nih.gov/htdocs/Results_Status/Resstate/554109.html</a> ]	
1,2,3-Trichloropropane  [May be produced from 1,3-DCP. 1,3-DCP may be a metabolite.]	96-18-4		In 8 <sup>th</sup> -10 <sup>th</sup> RoC.  NTP TR-384: Clear evidence in mice and rats dosed orally. Tumors in multiple organs, including oral cavity (MR, FR, FM), mammary gland (FR), and zymbal gland (MR, FR). <a href="http://ntp-server.niehs.nih.gov/htdocs/Levels/TR384levels.html">http://ntp-server.niehs.nih.gov/htdocs/Levels/TR384levels.html</a> <a href="http://ntp-server.niehs.nih.gov/htdocs/LT-studies/tr384.html">http://ntp-server.niehs.nih.gov/htdocs/LT-studies/tr384.html</a>  IARC 63:223- (1995): Group 2A. <a href="http://www.inchem.org/documents/iarcl/vol63/1,2,3-trichloropropane.html">http://www.inchem.org/documents/iarcl/vol63/1,2,3-trichloropropane.html</a>	IARC 63:223- (1995): Rodents treated <i>in vivo</i> showed DNA binding and DNA breaks but not dominant lethal mutations. In <i>in vitro</i> systems pos. for gene mutation, SCE, and CA, and neg. for DNA damage. Metabolic activation was required for <i>in vitro</i> studies. Mutagenic in bacteria. Specific systems tested are in TR-384.	IARC 63:223- (1995): No data on human reproduction. No evidence of fertility effects or embrotoxicity in rats. Female mice in a two-generation study showed impaired reproductive systems.
Tris(1-chloro-2-propyl) phosphate; TCPP	13674-84-5		IPCS/WHO EHC 209 (1998): No data identified regarding carcinogenic potential. <a href="http://www.inchem.org/documents/ehc/ehc209.htm">http://www.inchem.org/documents/ehc/ehc209.htm</a>	NTP Salmonella neg. [ <a href="http://ntp-server.niehs.nih.gov/htdocs/Results_Status/Resstatt/M20263.Html">http://ntp-server.niehs.nih.gov/htdocs/Results_Status/Resstatt/M20263.Html</a> ]  EHC 209: No clear evidence from a battery of genotoxicity tests.	EHC 209: No studies on reproductive toxicity, embryotoxicity, or teratogenicity were identified.

**Table 6. Carcinogenicity, Genotoxicity, and Reproductive and Developmental Toxicity of Selected Structural Analogues (Continued)**

Name [Comment]	CASRN	Structure	Carcinogenicity	Genotoxicity	Reproductive and Developmental Toxicity
Tris(2,3-dibromopropyl) phosphate; TDPP; Tris-BP; TRIS [Phosphate triester of 2,3-dibromo-1-propanol]	126-72-7		In 2 <sup>nd</sup> -10 <sup>th</sup> RoC  NCI TR-76 (1978): Pos. in mice and rats fed a diet with up to 1,000 ppm TDPP. Tumors in kidney tubular cells (MR, FR, MM), forestomach (MM, FM), lung (MM, FM), and liver (FM) [ <a href="http://ntp-server.niehs.nih.gov/htdocs/Levels/TR076levels.html">http://ntp-server.niehs.nih.gov/htdocs/Levels/TR076levels.html</a> <a href="http://ntp-server.niehs.nih.gov/htdocs/LT-studies/TR076.html">http://ntp-server.niehs.nih.gov/htdocs/LT-studies/TR076.html</a> ]  IARC 71:905- (1999): Group 2A. <a href="http://www.inchem.org/documents/irc/vol71/033-tris23dibrpr.html">http://www.inchem.org/documents/irc/vol71/033-tris23dibrpr.html</a>  See also IPCS/WHO reviews: EHC 173 (1995) Bis- and Tris(2,3-dibromopropyl) phosphate <a href="http://www.inchem.org/documents/ehc/ehc/ehc173.htm">http://www.inchem.org/documents/ehc/ehc/ehc173.htm</a> EHC 192 (1997) Flame retardants <a href="http://www.inchem.org/documents/ehc/ehc/ehc192.htm">http://www.inchem.org/documents/ehc/ehc/ehc192.htm</a>	NTP Salmonella pos. [ <a href="http://ntp-server.niehs.nih.gov/htdocs/Results_Status/Resstatt/10571-V.Html">http://ntp-server.niehs.nih.gov/htdocs/Results_Status/Resstatt/10571-V.Html</a> ]  IARC 71:905- (1999): “[C]onsistently active in a wide range of mammalian <i>in vivo</i> and <i>in vitro</i> test systems.”	Several database records are in DART/ETIC and MEDLINE for publications reporting studies on pre- and post-natal development and male infertility.
Tris(1,3-dichloro-2-propyl) phosphate; 1,3-Dichloro-2-propanol phosphate (3:1); Fyrol FR-2; TDCPP [1,3-DCP is a minor metabolite and minor thermal degradation product.]	13674-87-8		IPCS/WHO EHC 209 (1998): Section 7.7.2 Benign neoplasms in rats given TDCPP in the diet at doses up to 80 mg/kg bw/day <a href="http://www.inchem.org/documents/ehc/ehc209.htm">http://www.inchem.org/documents/ehc/ehc209.htm</a>  NAP (2000) identified the study as a Stauffer TSCA test submission on Fyrol FR-2, Microfiche No. OTS0204911 [See page 384.] <a href="http://www.nap.edu/books/0309070473/html/358.html">http://www.nap.edu/books/0309070473/html/358.html</a>	IPCS/WHO (1998): Section 7.6.2 Table 5. Neg. <i>in vivo</i> ; neg. mouse lymphoma assay; pos. +S9 some Salmonella strains.  NTP Salmonella pos. [ <a href="http://ntp-server.niehs.nih.gov/htdocs/Results_Status/Resstatt/10923-J.Html">http://ntp-server.niehs.nih.gov/htdocs/Results_Status/Resstatt/10923-J.Html</a> ]	See IPCS/WHO (1998): Dose-response in rats given TDCPP orally (maternal toxicity, malformations not specified; neg. fertility effects in rabbits).  See also NAP (2000) and NICNAS (2001).

Abbreviations or Symbols: +/- = absence/presence; CA = chromosomal aberrations; CHO = Chinese hamster ovary; N/A = not applicable; n.p. = not provided; neg. = negative; pos. = positive; SCE = sister chromatid exchange; SLRL = sex-linked recessive lethal.

The closest structural analogues of 1,3-DCP in **Table 6** are the halogenated secondary alcohols (2-propanol derivatives)—1-bromo-2-propanol, 3-MCPD, 1-chloro-2-propanol, and 3-iodo-1,2-propanediol. 3-MCPD induced benign tumors in rats, was positive in several *in vitro* genotoxicity assays, and has anti-fertility effects. 1-Chloro-2-propanol was negative in an NTP carcinogenesis bioassay in rats and mice, positive in some *in vitro* genotoxicity assays, and negative in an NTP reproductive toxicity assay in rats. 3-Iodo-1,2-propanediol was negative in genotoxicity assays with mammalian systems.

Among the primary halogenated primary alcohols (1-propanol derivatives other than the diols in the preceding paragraph)—3-bromo-1-propanol, 3-chloro-1-propanol, 2,3-dichloro-1-propanol, and 2,3-dibromo-1-propanol—only the latter has much relevant information. 2,3-Dibromo-1-propanol was positive in the NTP dermal bioassays in rats and mice, positive in some *in vitro* genotoxicity assays in mammalian systems, and positive in a teratogenicity assay in mice.

Four analogues in **Table 6** are derivatives in which the 2-propanol hydroxy group is oxidized [1,3-dichloro-2-propanone], esterified [tris(1-chloro-2-propyl) phosphate (TCPP) and tris(1,3-dichloro-2-propyl) phosphate (TDCPP)], or etherified [epichlorohydrin]. Epichlorohydrin was carcinogenic in oral testing with rats and mice and induced genotoxicity in most *in vivo* and *in vitro* assays without metabolic activation. No attempt was made here to summarize the numerous reproductive/developmental toxicity studies available for epichlorohydrin. The 1,3-DCP phosphate triester TDCPP induced benign tumors in rats (TSCA test submission). TDCPP was negative in genotoxicity studies with mammalian systems but was positive in *Salmonella* with metabolic activation. Oral dosing of rats gave a dose-response in a reproductive toxicity assay.

The phosphate ester derivative of primary alcohol 2,3-dibromo-1-propanol, tris(2,3-dibromopropyl) phosphate (TDPP), was positive in dietary carcinogenesis bioassays in rats and mice and positive in *in vivo* and *in vitro* genotoxicity assays.

The chlorinated hydrocarbon analogues in **Table 6** have both been tested for carcinogenicity. 1,2,3-Trichloropropane was carcinogenic in NTP bioassays in mice and rats, which developed tumors in numerous organs. It is genotoxic in *in vivo* and *in vitro* systems and has shown some reproductive toxicity in female mice. 1,3-Dichloropropene induced benign and malignant tumors in mice exposed to the pure compound by inhalation (no effect on rats) and was positive in some *in vitro* mammalian genotoxicity tests.

In summary, only limited testing results were found for each of the groups. Oxygen-containing compounds that induced malignancies in rodents included epichlorohydrin, 2,3-dibromo-1-propanol (2,3-DCP), and tris(2,3-dibromopropyl) phosphate (TDPP). Oxygen-containing compounds that induced only benign tumors were 3-MCPD and tris(1,3-dichloro-2-propyl) phosphate (TDCPP). Two related chlorinated hydrocarbons, 1,3-dichloropropene and 1,2,3-trichloropropane, were also carcinogens. No long-term study was available for 2,3-dichloropropanol. The compounds causing tumors, including 1,3-DCP, were genotoxic in at least some *in vitro* mammalian systems.

## 11.0 Online Databases and Secondary References

### 11.1 Online Databases

#### Chemical Information System Files

BIOLOG (Biodegradation, bibliographic)

DATALOG (Biodegradation, data)

EMIC and EMICBACK (Environmental Mutagen Information Center)

ENVIROFATE (Environmental Fate, bibliographic)

HSDB (Hazardous Substances Data Bank)

ISHOW (Information System for Hazardous Organics in Water, physical-chemical properties)

SANSS (Structure and Nomenclature Search System)

TSCAPP (TSCA Plant and Producers)

TSCATS (Toxic Substances Control Act Test Submissions)

#### National Library of Medicine Databases

ChemIDplus

DART/ETIC

PubMed (preliminary searches to develop vocabulary for keywords)

TRI (Toxic Release Inventory) 2000

#### STN International Files

AGRICOLA	ESBIOBASE
BIOSIS	MEDLINE
BIOTECHNO	NIOSHTIC
CABA	NTIS
CANCERLIT	Registry
CAPLUS	RTECS
EMBASE	TOXCENTER

TOXLINE includes the following subfiles:

Toxicity Bibliography	TOXBIB
International Labor Office	CIS
Hazardous Materials Technical Center	HMTTC
Environmental Mutagen Information Center File	EMIC
Environmental Teratology Information Center File (continued after 1989 by DART)	ETIC
Toxicology Document and Data Depository	NTIS
Toxicological Research Projects	CRISP
NIOSHTIC®	NIOSH
Pesticides Abstracts	PESTAB
Poisonous Plants Bibliography	PPBIB
Aneuploidy	ANEUPL
Epidemiology Information System	EPIDEM
Toxic Substances Control Act Test Submissions	TSCATS
Toxicological Aspects of Environmental Health	BIOSIS
International Pharmaceutical Abstracts	IPA

Federal Research in Progress	FEDRIP
Developmental and Reproductive Toxicology	DART

Other Internet Databases

Code of Federal Regulations (CFR), National Archives and Records Administration  
 National Occupational Exposure Survey (1981-1983)  
 Chemcyclopedia 2003  
 Environmental Health Information Service  
 EPA's Integrated Risk Information System (IRIS)  
 EPA Inventory Update Rule  
 EPA-OPPT High Production Volume (HPV) Challenge Program—HPV Challenge Summary  
 Report January 31, 2003  
 International Agency for Research on Cancer  
 IPCS Inchem  
 NTP Home Page  
 OECD Screening Information Data Set (SIDS) (vol. 8)  
 OEHHA Toxicity Criteria Database  
 [Plus numerous other databases and web sites via searches by the Google search engine]

In-House Databases

Current Contents on Diskette®  
 The Merck Index, 1996 and 2001, on CD-ROM

**11.2 Secondary References**

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**Appendix A. Units and Abbreviations**

°C = degrees Celsius

µg/L = microgram(s) per liter

µg/m<sup>3</sup> = microgram(s) per cubic meter

µg/mL = microgram(s) per milliliter

µM = micromolar

ACGIH = American Conference of Governmental Industrial Hygienists

bw = body weight

CASRN = Chemical Abstracts Service Registry Numbers

CHPTA = (3-chloro-2-hydroxypropyl)trimethylammonium chloride

COC = Committee on the Carcinogenicity of Chemicals in Food, Consumer Products and the Environment

COM = Committee on the Mutagenicity of Chemicals in Food, Consumer Products and the Environment

FDA = Food and Drug Administration

g = gram(s)

GC = gas chromatography

g/mL = gram(s) per milliliter

GSH = glutathione

h = hour(s)

HD = high dose

HPV = high production volume

HSDB = Hazardous Substances Data Bank

i.p. = intraperitoneal(ly)

JECFA = Joint FAO/WHO Expert Committee on Food Additives

kg = kilogram(s)

L = liter(s)

lb = pound(s)

LC = liquid chromatography

LC<sub>50</sub> = lethal concentration for 50% of test animals

LD<sub>50</sub> = lethal dose for 50% of test animals

LD = low dose

LOD = limit of detection

M = male(s)

MD = mid dose

mg/kg = milligram(s) per kilogram

mg/m<sup>3</sup> = milligram(s) per cubic meter

mg/mL = milligram(s) per milliliter

min = minute(s)

mL/kg = milliliter(s) per kilogram

mm = millimeter(s)

mM = millimolar

mmol = millimole(s)

mmol/kg = millimoles per kilogram

mo = month(s)

mol = mole(s)

mol. wt. = molecular weight

NCI = National Cancer Institute

NIEHS = National Institute of Environmental Health Sciences

NIOSH = National Institute for Occupational Safety and Health

NOEL = no observable effect level

NTP = National Toxicology Program

nm = nanometer(s)

n.p. = not provided

OSHA = Occupational Safety and Health Administration

PEL = permissible exposure limit

pH = measurement of acidity or alkalinity

ppb = parts per billion

ppm = parts per million

p.o. = peroral(ly), *per os*

REL = relative exposure limit

s.c. = subcutaneous(ly)

SCE = sister chromatid exchange

STEL = short-term exposure limit

TSCA = Toxic Substances Control Act

TWA = time-weighted average

U.S. EPA = U.S. Environmental Protection Agency

U.S. FDA = U.S. Food and Drug Administration

wk = week(s)

yr = year(s)

## Appendix B. Search Strategy Description

When one or more recent authoritative reviews are available, ILS generally restricts the search to a year or so before the publication date of the most comprehensive review. Because the review by the Joint FAO/WHO Expert Committee on Food Additives (JECFA, 2002) did not address many of the usual nontoxicological topics that are included in the Reviews of Toxicological Literature for NIEHS, the searches were not restricted by date.

### Databases and Dates Searched

Searches were primarily done between May 20 and June 11, 2003, on the following systems:

- Chemical Information System (CIS), May 20. Retrieved 153 records for CASRN 96-23-1 from multiple databases (no automated count by database) [9 records at a later date for CASRN 26545-73-3 (dichloropropanols, n.o.s.)]. Databases included BIOLOG, DATALOG, ENVIROFATE, ISHOW, SANSS, TSCATS, and TSCAPP. CASRNs are sufficient for a complete search on the CIS system.
- STN International, June 9. Search strategies and record tallies for databases searched are described below.
- PubMed, May 21 and May 27. Retrieved 47 records by use of the CASRN and a limited number of synonyms. About 20 of the 47 were for publications cited by JECFA (2002).
- TOXLINE, June 16. Retrieved 126 records, most of which were cited by JECFA (2002) or had been retrieved in other searches.
- Internet, specific web sites
  - Inchem web site was searched at various times, primarily to find authoritative reviews on the structural analogues. Retrieved documents from IARC (monograph summaries, OPCS/WHO (Environmental Health Criteria series), JECFA (food additive reviews on 1,3-DCP and 3-MCPD in soy sauces and acid-HVP), and OECD (Screening Information Data Set [SIDS] for High Production Volume Chemicals).
  - NTP web site for testing status and abstracts of long-term studies, late June. Sought testing information for structural analogues using their CASRNs. Identified other structural analogues by use of the keyword propanol.
  - U.S. EPA web sites were searched at various times. For example, retrieved 73 records on May 22 using the CASRN and 12 records on June 20 using the word dichloropropanols. Search results included information about regulations from 40 CFR and the *Federal Register*; emissions from epichlorohydrin manufacture; the absence of 1,3-DCP in effluents, landfill leachates, and emissions from hazardous waste incinerators; companies participating in the HPV Challenge program; and companies producing or importing more than 10,000 lb annually of 1,3-DCP in the Inventory Update Rule database (non-CBI [confidential business information]).
  - Code of Federal Regulations Titles 16 (CPSC), 21 (FDA), 29 (OSHA), and 40 (U.S. EPA) via <http://www.access.gpo.gov> on June 11. No records were retrieved for 29 CFR.

- U.S. Patents and Patent Applications via <http://www.uspto.gov>, mid-June. Sought to confirm or explain process and use information that was ambiguous from other sources.
- Several other web sites searched are listed in Section 11 of the report.
- Google Internet searches, May 22-June 30. Various strategies are described below.

### STN International Search Strategy and Results

The STN International files MEDLINE, CANCERLIT, NIOSHTIC, AGRICOLA, CABA, BIOTECHNO, EMBASE, ESBIOBASE, BIOSIS, TOXCENTER, and NTIS were searched simultaneously on June 9. Synonyms used in the search were from the Registry record, which was retrieved earlier along with the 10 most recent publications in the CA file (Chemical Abstracts). Use of the CASRN 96-23-1 and the name "1 3 dichloro 2 propanol" retrieved 374 and 399 records, respectively. Combining these answer sets gave an answer set containing 511 records. Use of the statement "1 3 dichloropropanol" OR "1 3 dichloropropan 2 ol" retrieved 111 records. Use of six additional synonyms retrieved 7 records. When all the answer sets were combined by "OR", the total in the resulting answer set before automated duplicate removal was 577 records. A separate search for chemical classes—glycerol chlorohydrins (23 records), dichlorohydrins (13), and dichloropropanols (64)—retrieved 29 additional records (16 after duplicate removal). The reviews (8 after duplicate removal) were segregated from the set of 577. Duplicate removal reduced the remainder to 299 records. The distribution of records by database was as follows:

Database	No. of Records for Synonyms & CASRN Excluding Reviews	No. of Reviews	No. of Records with Chem. Class Names But Not Synonyms or CASRN	Total
MEDLINE	46	1	2	49
CANCERLIT	1		1	2
NIOSHTIC	5	1		6
CABA	5	1		6
BIOTECHNO	8		1	9
EMBASE	13		5	18
ESBIOBASE	1			1
BIOSIS	14		5	19
TOXCENTER	205	3	2	210
NTIS	1	2		3
Totals	299	8	16	323

Printed the titles with database identifiers (a free format in most files), scanned the titles and selected those of interest, and compared them with the bibliography in JECFA (2002). Grouped the answer numbers of the remaining titles by report topic and made a final selection for downloading and printing results as full records. Because of a limited budget for this fee-based search, of the approximately 60 titles that were not cited by JECFA (2002), only those records (26) on toxicity, structure-activity relationships, and potential exposure were selected for downloading. (More typically, the grouping for downloading would be by database to facilitate use of separate database filters by the reference management software.) Most of the downloaded

records (21) were from TOXCENTER, a database of databases, including many of those in TOXLINE, which is no longer being updated.

### **Google Search Engine: General Internet Search Strategies and Results**

An initial search for "1 3 dichloro 2 propanol" retrieved 724 hits on 1,3-DCP as well as on the phosphate ester TDCPP, a flame retardant. Many of the hits were on the food contamination issue (formation during production of acid-hydrolyzed vegetable proteins). Others were regulations from the *Federal Register* and the *Code of Federal Regulations*. Specifying only files in pdf format reduced the number of hits to 318. This group included numerous government and international reports and descriptions of analytical methods. Use of the string "2 propanol 1 3 dichloro," which is the inverted systematic name often used in regulations, retrieved 65 hits. Not surprisingly, many of the hits were from the *Federal Register* and regulatory lists. The early search for dichlorohydrin AND (toxicity OR toxicology) retrieved 54 hits with unexpected retrievals, which sparked more avenues for searches. Among the retrievals were the trichloropropane manufacturing information from the 10<sup>th</sup> *Report on Carcinogens* and the U.S. EPA Locating and Estimating Document for epichlorohydrin emissions with extensive production process information. It was clear from the latter document that most 1,3-DCP production was captive in 1984 (and further searches showed that this continues to be the case).

Google also proved useful for locating documents referenced in the JECFA (2002) review and other reviews. Exact phrases from titles plus a few keywords were more often successful than not. Once documents in a useful series were identified (e.g., reports from annual meetings), more recent reports were anticipated and retrieved (e.g., CCFAC [Codex Committee on Food Additives and Contaminants], 2003). Google searches for suppliers by use of the keyword MSDS found material safety data sheets from suppliers offering several compounds and compositions that have low concentrations of 1,3-DCP and epichlorohydrin. These unanticipated findings helped shape the discussion of exposure potential in the report. One delightful find via Google was the National Occupational Exposure Survey online at the NIOSH web site (<http://www.cdc.gov/noes/>). In the past, ILS contacted R.A. Young at OSHA to request searches of this database.

### **Special Focus Search on the Metabolic Pathways and Mechanisms of Action**

(November 2003, with Update of May-June 2003 Searches)

#### **I. Search Strategy**

ILS had already identified most of the relevant publications from the original searches conducted for the sample report. All TOXLINE records on 1,3-dichloro-2-propanol (1,3-DCP) and all titles on 1,3-DCP in several STN International biomedical databases were retrieved in May and June of 2003 (see Attachment A [previous strategy in sample report]). The goal of the current search, besides the identification of any new relevant publications, was to determine which references provided information on metabolic pathways in mammalian species, which gave evidence for proposed mechanisms of action, and which gave evidence for the production of carcinogenic metabolites epichlorohydrin and 1,3-dichloro-2-propane (1,3-dichloroacetone; 1,3-DCA). Examination of the clusters of publications retrieved on PubMed by searching combinations of the CASRN and 1,3-DCP synonyms with relevant keywords indicated that the topics of metabolic pathways and mechanisms of action were intertwined.

Examination of the recently available (October 2003) authoritative review by the U.K. Committee on Mutagenicity of Chemicals in Food, Consumer Products and the Environment (COM) (COM, 2003) indicated that epigenetic mechanisms of carcinogenicity are likely involved, including glutathione (GSH) depletion and liver necrosis. Searches for general information on mechanisms of carcinogenesis and of hepatotoxicity were conducted as well as general searches on consequences of glutathione depletion. Readily available toxicity information on the genotoxicity and carcinogenicity of 1,3-DCA, a possible reactive metabolite, was gathered to compare its physiological actions with those of 1,3-DCP. GSH depletion as a mechanism of toxic action of other halogenated compounds was also researched.

The databases MEDLINE, CANCERLIT, NIOSHTIC, AGRICOLA, CABA, BIOTECHNO, EMBASE, ESBIOSBASE, IPA, TOXCENTER, and NTIS were searched simultaneously on November 13, 2003, on STN International. BIOSIS was searched separately on November 14 by the search statement "S L48," after the saved answer set was "activated" in the above databases, and results were compared with the saved results from the November 13 search during automated duplicate removal. (None of the additional nine records was useful.) The keywords and strategy used in the November 13 online session are reproduced below:

```
L1      348 S 96-23-1
L2      361 S 1(W)3(W)DICHLORO(W)2(W)(PROPANOL OR HYDROXYPROPANE)
L3      98 S 1(W)3(W)(DICHLOROPROPANOL OR (DICHLOROPROPAN(W)2(W)OL))
L4      2 S ALPHA(W)GAMMA(W)DICHLOROHYDRIN
L5      3 S (PROPYLENE OR 1(W)3 OR ALPHA(W)DICHLOROHYDRIN
L6      1 S (SYM OR S)(W)GLYCEROL(W)DICHLOROHYDRIN
L7      1 S (SYM OR 1(W)3)(W)(DICHLOROISOPROPANOL OR DICHLOROISOPROPYL(W)ALCOHOL)
L8      0 S 2(W)CHLORO(W)1(W)CHLOROMETHYL(W)ETHANOL
L9      0 S BIS(W)CHLOROMETHYL(W)METHANOL
L10     105 S L3 OR L4 OR L5 OR L6 OR L7
L11     472 S L1 OR L2
L12     528 S L10 OR L11
        SAVE L12 DICLHYDRIN/Q
L13     16 S L12 AND (REVIEW? OR REVIEW/DT OR MEETING/DT)
L14     17 S GLYCEROL(W)CHLOROHYDRINS
L15     10 S DICHLOROHYDRINS
L16     53 S DICHLOROPROPANOLS
L17     80 S L14 OR L15 OR L16
L18     22 S L17 NOT L12
        SET DUPORDER FILE
L19     12 DUP REM L18 (10 DUPLICATES REMOVED)
        ANSWERS '1-2' FROM FILE MEDLINE
        ANSWER '3' FROM FILE CANCERLIT
        ANSWER '4' FROM FILE BIOTECHNO
        ANSWERS '5-9' FROM FILE EMBASE
        ANSWER '10' FROM FILE ESBIOSBASE
        ANSWERS '11-12' FROM FILE TOXCENTER
L20     16 SORT L13 1-16 TI
L21     512 S L12 NOT L13
...
L33     163 S L21 AND (METAB? OR PHARMACOKINETIC? OR TOXICOKINETIC? OR BIOTRANSFORM?
          OR MICHAELIS OR KINETIC?)
L34     79 S L21 AND (MECHANIS? OR MODE?)
L35     60 S L21 AND (GLUTATHIONE OR GSH OR GLUCURON? OR PHASE(W)2)
L36     181 S L21 AND (LYASE? OR PROLIFER? OR CYTOTOXIC? OR SIGNAL? OR DNA OR RNA OR ENZYM?
          OR GENE OR GENES OR PUTATIVE OR PATHWAY? OR PROPOSED)
L37     43 S L21 AND DEHYDROGENASE?
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L38 24 S L21 AND (CYP2E1 OR CYPIIE1 OR P4502E1 OR P450IIIE1)
L39 285 S L33 OR L34 OR L35 OR L36 OR L37 OR L38
L40 69 S L39 AND BACTERIA?
L41 285 S L39 OR L40
...
L44 9 S L39 AND 2003/PY
L45 5 DUP REM L44 (4 DUPLICATES REMOVED)
ANSWER '1' FROM FILE MEDLINE
ANSWERS '2-5' FROM FILE TOXCENTER
L46 5 SORT L45 1-5 TI
L47 276 S L41 NOT L44
L48 120 DUP REM L47 (156 DUPLICATES REMOVED)
ANSWERS '1-32' FROM FILE MEDLINE
ANSWER '33' FROM FILE CANCERLIT
ANSWERS '34-35' FROM FILE NIOSHTIC
ANSWERS '36-38' FROM FILE CABA
ANSWERS '39-44' FROM FILE BIOTECHNO
ANSWERS '45-54' FROM FILE EMBASE
ANSWERS '55-119' FROM FILE TOXCENTER
ANSWER '120' FROM FILE NTIS
L49 120 SORT L48 1-120 TI
SAVE L49 X30MECHMETAB/A

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New *in vivo* mammalian genotoxicity assays in rats (bone marrow micronuclei and unscheduled DNA synthesis [UDS]) described in COM (2003) as available from the U.K. Food Standards Agency (FSA) were not located by searches of the Internet, PubMed, or TSCATS on November 17, 2003. Four new journal publications published in October 2003 were considered for the package.

## II. Search Results

### II.A. Authoritative Reviews

Members of the U.K. COM in its 2001 evaluation of 1,3-DCP (COM, 2001) had agreed that 1,3-DCP metabolism "was likely to produce a reactive epoxide intermediate that could damage DNA" based on positive activity in *Salmonella* strains TA1535 and TA100 and in *in vitro* mammalian genotoxicity (sister chromatid exchange, chromosome aberration, and mouse lymphoma mutation) assays. COM (2003) reviewed results of new *in vivo* genotoxicity assays conducted under COM and OECD (Organisation for Economic Cooperation and Development) guidelines. As mentioned above, ILS has not located the studies designated as Howe (2002) and Beavers (2003) that were said to be available from the U.K. FSA. 1,3-DCP did not induce statistically significant increases in UDS or bone marrow micronuclei in these new *in vivo* rat studies.

COM (2003) discussed the role of metabolism in the toxicity of 1,3-DCP.

- In bacterial assays, bacteria may convert 1,3-DCP to epichlorohydrin, which would explain its mutagenicity in the absence of S9.
- In the SOS chromotest with *Escherichia coli*, chemical conversion to epichlorohydrin in the rat hepatocytes medium was postulated.
- Conjugation with glutathione (GSH) and GSH depletion due to postulated metabolic formation of 1,3-DCA from 1,3-DCP may account for the potentiation of rat hepatotoxicity. The conversion to 1,3-DCA may be mediated by alcohol dehydrogenase (ADH) or cytochrome P4502E1.

- The metabolite 3-MCPD ( $\alpha$ -chlorohydrin; 3-chloro-1,3-propanediol) was considered to have no potential for *in vivo* genotoxicity (negative results in rat UDS and micronucleus assays).

COM (2003) concluded that 1,3-DCP metabolism “has not been fully elucidated.” Epichlorohydrin is “expected to be rapidly deactivated” *in vivo* by GSH and epoxide hydrolase and 1,3-DCA would also be rapidly deactivated by GSH. This would explain the lack of genotoxicity *in vivo* [and the GSH depletion?]. Formation of these or any other reactive metabolite is unlikely to induce genotoxicity *in vivo*.

An authoritative review of the probable modes of action of 1,3-DCP in its induction of carcinogenesis may be available within a few months. After the publication of COM (October 2003), the U.K. Committee on Carcinogenicity of Chemicals in Food, Consumer Products and the Environment (COC, October 2003 [draft only for discussion by members (available on the Internet)] began to consider whether any revision of the previous COC statement is warranted. Could 1,3-DCP be considered a nongenotoxic carcinogen so that a threshold-based risk assessment might be appropriate? Previously, COC had concluded that a high rate of chronic progressive nephropathy might be associated with male rat kidney tumors. Thyroid tumors could be associated with hyperplasia. These tumors were likely secondary to the sustained cell proliferation in these organs. The COC was asked to consider possible modes of action for carcinogenesis in the tongue and liver.

## **II.B. Background Information on Mechanisms of Hepatotoxicity**

- Caro et al. (2003) reviewed the toxicological properties of CYP2E1. They “believe that the linkage between CYP2E1-dependent oxidative stress, mitochondrial injury, and GSH homeostasis contribute to the toxic actions of ethanol on the liver.”
- Comporti et al. (1991) discussed the liver damage produced by three GSH-depleting agents.
- GSH depletion in hepatocyte mitochondria is an important mechanism in alcohol-induced liver damage. Fernandez-Checa et al. (2002) reported that S-adenosyl-L-methionine (SAMe) mitigates the GSH depletion in rats chronically fed alcohol. The role of SAMe in DNA methylation and prevention of hepatocarcinogenesis were discussed by Pascale et al. (2002).
- Kedderis (1996) reviewed the biochemical basis of liver necrosis. Hepatotoxic agents and their reactive metabolites may induce GSH depletion and CYP450 activity, alkylate cellular macromolecules, or induce oxidative stress. These interactions may be followed by decreasing hepatocellular adenosine triphosphate (ATP) concentrations, which comprises the plasma membrane calcium pump and leads to increased cellular calcium concentrations.
- Kitamura et al. (1998) reviewed persistent liver regeneration and liver cancers in chronic liver disease.
- Macaluso et al. (2000) reviewed general genetic and epigenetic mechanisms of carcinogenesis. Williams and Whysner (1996) reviewed epigenetic mechanisms.
- Melnick (2002) reviewed mechanisms of carcinogenesis of epoxides and epoxy-forming chemicals. Solomon (1999) summarized mechanisms of carcinogenesis induced by epoxy compounds and the DNA adducts formed by hydroxyalkylation.

- Nakae (1999) reviewed endogenous liver cancer in rats. Deficiency in methylating amino acids (choline and methionine) leads to liver damage and ultimately to cancer.
- Tirmenstein et al. (2000) reviewed GSH depletion and the production of reactive oxygen species (ROS) in isolated rat hepatocytes. In studies with diethyl maleate and ethyl methanesulfonate (EMS), the GSH depletion was apparently not responsible for the increases in ROS production and the lipid peroxidation that may lead to necrotic cell death.
- Torres et al. (1989) studied GSH depletion and damage in the kidney.
- Xu et al. (1998) reported that GSH modulates rat and mouse hepatocyte sensitivity to tumor necrosis factor  $\alpha$ , which "causes much of the hepatocellular injury and cell death that follows toxin-induced liver damage."

### **II.C. Microbial Metabolism of 1,3-DCP**

Thirteen papers in this group include studies on 1,3-DCP metabolism during bacterial degradation. Most were mentioned in the July draft. A schematic for the metabolic pathway of 1,3-DCP in *Corynebacterium* and other microbial species may be found in Natarajan et al. (2002) and in Stephens (2002) (linked web sites).

Studies that were not discussed in the July draft include the following:

- Assis et al. (1998) (1,3-DCP and 3-MCPD dehalogenation kinetics by two haloalcohol [halohydrin] dehalogenases from an *Arthrobacter* species; one of the enzymes catalyzed the conversion of vicinal halohydrins to epoxides)
- Nakamura et al. (1992) (transient ECH formation in a *Corynebacterium* strain)
- van Hylckama et al. (2001) (kinetics of 1,3-DCP degradation by *Agrobacterium radiobacter* strain AD1)

### **II.D. 1,3-DCP Metabolism *in vitro***

Almost all of the 12 papers in this group of *in vitro* studies were discussed in the July draft.

- 1,3-DCP was more toxic in NIH-3T3 and V79 mammalian cell lines when metabolized by CYP450 isoforms (Bull et al., 2001).
- Garle et al. (1997 abstr.) considered the role of rat P450 in GSH depletion mediated by metabolism of 1,3-DCP and structural analogues.
- Garle et al. (1999) identified 1,3-DCA as a 1,3-DCP metabolite in rat hepatocytes. 1,3-DCP was a more potent depleter of GSH than epichlorohydrin.
- Hahn et al. (1991) found chemically formed epichlorohydrin but no 1,3-DCA in the media for Ames and SOS chromotest assays with 1,3-DCP.
- Hammond and Fry (1996, 1997, 1999) and Hammond et al. (including Fry and Garle) (1996, 1999, 2002) studied effects of CYP4502E1 and of GSH depletion on 1,3-DCP toxicity in rat hepatocytes. Hammond et al. (1996) concluded that 1,3-DCP toxicity is "mediated by cytochrome P450 and involves depletion of glutathione and loss of mitochondrial function."
- Piasecki et al. (1990) reported that 1,3-DCP induced malignant transformation in mouse fibroblasts (endpoint reported in the July draft as mutation).
- Addition of S9 mix to 1,3-DCA and to 1,3-DCP significantly reduced their ability to induce SCE in V79 cells. Apparently, less active metabolites were formed (von den Hude et al., 1987).

### **II.E. 1,3-DCP Metabolism *in vivo***

The *in vivo* studies in this group were cited or considered but not cited in the July draft. Some considered mechanisms of toxicity. See also the discussion above of the two new *in vivo* genotoxicity assays in rats. The negative findings indicate that reactive genotoxic metabolites, if formed, must be too transient for 1,3-DCP to be genotoxic *in vivo*.

- 1,3-DCP was negative in the wing spot genotoxicity assay in *Drosophila melanogaster*. The chemical formation of genotoxic agents in *in vitro* studies was mentioned in the abstract (Frei and Würgler, 1993).
- Jones and Fakhouri (1979) reported that rats excreted mercapturic acid (N-acetylcysteine) derivatives of 1,3-DCP and  $\beta$ -chlorolactate in the urine after dosing with 1,3-DCP. [Mercapturic acids are formed from GSH S-conjugates (De Rooij et al., 1998).] The metabolic conversion of 2-chloropropane-1,3-diol to N-acetyl-S-(2,3-dihydroxypropyl)cysteine confirmed that an epoxide intermediate was involved.
- Katoh et al. (1998) studied GSH depletion and lipid peroxidation in rats treated with 1,3-DCP and concluded that “one of the causative mechanisms of this hepatotoxicity [diffuse massive necrosis] might be the lipid peroxidation.”
- Koga et al. (1992) identified urinary metabolites in rats given dichloropropanols and proposed the metabolic pathway.
- Kuroda et al. (2002) (same research group as Katoh) (Japanese review considered but not cited in the July draft) reported that massive necrosis of the liver induced by 1,3-DCP was accompanied by significant increase in the liver concentration of malondialdehyde and significant reductions in liver glutathione-S-transferase and GSH.
- Smith and Williams (1954) (considered but not cited in the July draft) reported on metabolic glucuronidation of chlorinated alcohols, including 1,3-DCP, in rabbits.
- Inhibition of CYP2E1 lowered 1,3-DCP hepatotoxicity in rats (Stott et al., 1997).

### **II.F. Histopathology of Target Organ Damage and Regeneration**

Studies of liver histopathology of 1,3-DCP-treated rats include Haratake et al. (1993, 1994) and Katoh et al. (1999) (Japanese). Mechanistic information is not included in the abstracts. The 1994 paper followed the development of hepatic necrosis and regeneration.

### **II.G. Mechanisms of Toxicity of Some Related Halogenated Compounds**

Studies on metabolism-mediated toxicity of related compounds are included in this group (sorted in the package alphabetically by boldfaced compound name and then by first author surname).

- Holme et al. (1989) reported that GSH depletion in suspensions of rat liver parenchymal cells reduced the mutagenicity and cytotoxicity of the halogenated alkane 1,2-dibromo-3-chloropropane or its P450-oxidized mutagenic metabolite toward *Salmonella*. Oxidative damage followed GSH depletion.
- The 1,3-DCP metabolite 1,3-dichloroacetone (1,3-dichloro-2-propanone; 1,3-DCA) is mutagenic in microorganisms and in the *in vitro* SCE test with hamster cells. It caused sex chromosome loss and nondisjunction in *D. melanogaster*, was positive in and was a carcinogen in mice (RTECS, 2003). Some studies that may be relevant to mechanisms of toxicity were collected:

- Robinson et al. (1989) induced tumors in an initiation-promotion skin-painting assay (1,3-DCA for 2 wk, TPA for 20 wk).
- Daniel et al. (1993) reported no significant organ toxicity in rats that had been exposed to 5 to 125 ppm 1,3-DCA in their drinking water for 90 days. At 125 ppm, both sexes showed a decrease in BUN. The NOAEL was 5 ppm (0.5 mg/kg/day).
- 1,3-DCA tested in *Salmonella* TA1535 that expressed GSTTI-1, the human theta ortholog of rat theta class glutathione-S-transferase (GST) 5-5, induced higher mutagenicity than when tested in the control strain (Thier et al., 1996).
- 1,3-DCA induced *umu* gene expression and cytotoxic responses in *Salmonella* strain NM5004, which contained both rat GST 5-5 cDNA and *umu* C''lacZ operon, as compared with the original tester strain, TA1535/pSK1002 (Shimada et al., 1996).
- 1,3-DCA was directly mutagenic to *Salmonella* in the nanomolar range (Merrick et al., 1987).
- LeCurieux et al. (1994) reported that 1,3-DCA was clastogenic in the newt micronucleus test (a positive *in vivo* genotoxicity test in a vertebrate).
- 1,3-DCA reacted directly with GSH in rat hepatocytes suspended in a sodium phosphate buffer at pH 7.4. Cellular GSH concentrations declined rapidly prior to the cytotoxic response (Merrick et al., 1987).
- In an *in vitro* liver cytotoxicity assay, 1,3-DCA was the most potent hepatotoxicant among the chlorinated phenols and hydrocarbons tested (Murayama et al., 1990).
- In a study of the metabolism of 2,3-dichloro-1-propene in rats, Eder and Dornbusch (1988) reported that P450-induced epoxidation was followed by rearrangement to 1,3-DCA. 1,3-DCA was metabolized to the dimercapturic acid—1,3-(2-propanone)bis-S-(*N*-acetylcysteine).
- The putative 1,3-DNA metabolite epichlorohydrin is a well known genotoxic carcinogen (RTECS, 2003) that alkylates DNA. In a comprehensive study of the disposition and metabolism of epichlorohydrin (labeled at position 2 with  $^{14}\text{C}$ ) in rats after oral dosing, 50% had been excreted in urine after 3 days. The major urinary metabolites were *N*-acetyl-S-(3-chloro-2-hydroxypropyl)-*L*-cysteine (36% of the administered dose) and 3-MPCD (4%). These metabolites are consistent with epoxide conjugation by GSH and epoxide hydration (Gingell et al., 1985).
- Jones (1988) reported that a metabolite of  $\alpha$ -chlorohydrin (3-monochloro-1,2-propanediol; 3-MCPD) affected the glycolytic pathway within mature spermatozoa. 3-MCPD is a 1,3-DCP metabolite.
- COM (October 2000 [available at <http://www.doh.gov.uk/mcpd2.htm>]) concluded that 3-MCPD has no genotoxic potential *in vivo*.
- Forkert et al. (2002) studied the differential toxicity of trichloroethylene (TCE) ( $\text{Cl}_2\text{C}=\text{CHCl}$ ) in rat epididymis and testis *in vivo*. Chloral (trichloroacetaldehyde) ( $\text{Cl}_3\text{CCHO}$ ) formation, mediated by CYP2E1, was higher in epididymis, where effects were more severe, than in testis.
- Kaneko et al. (1997) proposed an epigenetic mechanism for liver carcinogenesis and kidney disorders in rats. TCE conjugation with GSH generates mutagenic metabolites in the rat kidney.