Screening Assessment for the Challenge

Oxirane, (chloromethyl)-
(epichlorohydrin)

Chemical Abstracts Service Registry Number
106-89-8

Environment Canada
Health Canada

November 2008

Synopsis

The Ministers of the Environment and of Health have conducted a screening assessment of oxirane, (chloromethyl)-, Chemical Abstracts Service Registry Number (CAS RN) 106-89-8 (epichlorohydrin), a substance identified in the categorization of the Domestic Substances List as a high priority for action under the Ministerial Challenge. Epichlorohydrin was identified as a high priority as it was considered to pose greatest potential for exposure to individuals in Canada (GPE) and had been classified by other agencies on the basis of carcinogenicity. The substance did not meet the ecological categorization criteria for persistence, bioaccumulation or inherent toxicity to aquatic organisms. Therefore, the focus of this assessment on epichlorohydrin relates to human health aspects.

Under information reported pursuant to section 71 of CEPA 1999, in 2006 epichlorohydrin was not manufactured in or imported into Canada by any company above the 100 kg threshold. It is likely that epichlorohydrin is being imported in very small amounts as residual monomer in products containing epoxy resin or other resins made using epichlorohydrin. Direct use of epichlorohydrin by consumers is not expected. The principal use of epichlorohydrin is in the production of epoxy and phenoxy resins, which are primarily used in protective coatings and thermoplastic polymers. It may also be used for the production of synthetic glycerol, and in the chemical synthesis of pharmaceutical products, polyols, and surface active agents for washing products and toiletries. Polymers made with epichlorohydrin are used as additives in papermaking, as cross-linking agents for starches, and as anion-exchange resins and flocculants used in treating drinking and wastewater.

In Canada, since epichlorohydrin is present only as a residual, environmental and consumer product exposures are expected to be low to negligible. No empirical data were identified regarding measured concentrations of epichlorohydrin in environmental media (i.e., air, water, soil and food) in Canada. Based on its possible uses, oral exposure to epichlorohydrin via food and/or drinking water may occur at low levels for the general population of Canada. Contributions from ambient air and soil are expected to be negligible due to the lack of manufacture in and/or import of this substance into Canada. There is also the possibility of low level exposure to epichlorohydrin via inhalation during the use of consumer products that contain residual amounts of epichlorohydrin monomer.

Based principally on the weight of evidence based assessments of several international and national agencies, a critical effect for the characterization of risk to human health is carcinogenicity, based on observation of tumours in rats and tumour initiation in mice. Epichlorohydrin was genotoxic in a wide range of *in vitro* and *in vivo* experimental systems, as well as in investigations of occupationally exposed humans. Therefore, although the mode of action has not been fully elucidated, it cannot be precluded that tumours observed in experimental animals resulted from direct interaction with genetic material.

On the basis of carcinogenicity, for which there may be a probability of harm at any level of exposure, it is concluded that epichlorohydrin is a substance which may be entering the environment in a quantity or concentration or under conditions that constitute or may constitute a danger in Canada to human life or health.

On the basis of moderate ecological hazard and low reported releases of epichlorohydrin, it is concluded that this substance is not entering the environment in a quantity or concentration or under conditions that have or may have an immediate or long-term harmful effect on the environment or its biological diversity, or that constitute or may constitute a danger to the environment on which life depends. Although epichlorohydrin does meet the criterion for persistence, it does not meet the criterion for bioaccumulation potential as set out in the *Persistence and Bioaccumulation Regulations.*

In addition and where relevant, research and monitoring will support verification of assumptions used during the screening assessment and, where appropriate, the performance of potential control measures identified during the risk management phase.

Based on the information available, epichlorohydrin meets one or more of the criteria set out in Section 64 of the Canadian Environmental Protection Act, 1999.

Introduction

The *Canadian Environmental Protection Act, 1999* (CEPA 1999) (Canada 1999) requires the Minister of the Environment and the Minister of Health to conduct screening assessments of substances that have met the categorization criteria set out in the Act to determine whether these substances present or may present a risk to the environment or human health. Based on the results of a screening assessment, the Ministers can propose to take no further action with respect to the substance, to add the substance to the Priority Substances List (PSL) for further assessment, or to recommend that the substance be added to the List of Toxic Substances in Schedule 1 of the Act and, where applicable, the implementation of virtual elimination.

Based on the information obtained through the categorization process, the Ministers identified a number of substances as high priorities for action. These include substances that

- met all of the ecological categorization criteria, including persistence (P), bioaccumulation potential (B) and inherent toxicity to aquatic organisms (iT), and were believed to be in commerce; and/or
- met the categorization criteria for greatest potential for exposure (GPE) or presented an intermediate potential for exposure (IPE), and had been identified as posing a high hazard to human health based on classifications by other national or international agencies for carcinogenicity, genotoxicity, developmental toxicity or reproductive toxicity.

The Ministers therefore published a notice of intent in the *Canada Gazette*, Part I, on December 9, 2006 (Canada 2006), that challenged industry and other interested stakeholders to submit, within specified timelines, specific information that may be used to inform risk assessment, and to develop and benchmark best practices for the risk management and product stewardship of those substances identified as high priorities.

The substance oxirane, (chloromethyl)- (epichlorohydrin) was identified as a high priority for assessment of human health risk because it was considered to present GPE and had been classified by other agencies on the basis of carcinogenicity. The Challenge for epichlorohydrin was published in the *Canada Gazette* on May 12, 2007 (Canada 2007b). A substance profile was released at the same time (Canada 2007a). The substance profile presented the technical information available prior to December 2005 that formed the basis for categorization of this substance. As a result of Challenge, submissions of information were received.

Although epichlorohydrin was determined to be a high priority for assessment with respect to risks to human health, it also meets the ecological categorization criteria for persistence, it did not meet the criteria for bioaccumulation or inherent toxicity for aquatic organisms. Therefore, this assessment focuses principally on information relevant to the evaluation of risks to human health.

Under CEPA 1999, screening assessments focus on information critical to determining whether a substance meets the criteria for defining a chemical as toxic as set out in section 64 of the Act, where

> "64. […] a substance is toxic if it is entering or may enter the environment in a quantity or concentration or under conditions that
>
> (*a*) have or may have an immediate or long-term harmful effect on the environment or its biological diversity;
>
> (*b*) constitute or may constitute a danger to the environment on which life depends; or
>
> (*c*) constitute or may constitute a danger in Canada to human life or health."

Screening assessments examine scientific information and develop conclusions by incorporating a weight of evidence approach and precaution.

This screening assessment includes consideration of information on chemical properties, hazards, uses and exposure, including the additional information submitted under the Challenge. Data relevant to the screening assessment of this substance were identified in original literature, review and assessment documents, stakeholder research reports and from recent literature searches, up to April 2008. Key studies were critically evaluated; modelling results may have been used to reach conclusions.

Evaluation of risk to human health involves consideration of data relevant to estimation of exposure (non-occupational) of the general population, as well as information on health hazards (based principally on the weight of evidence assessments of other agencies that were used for prioritization the substance). Decisions for human health are based on the nature of the critical effect and/or margins between conservative effect levels and estimates of exposure, taking into account confidence in the completeness of the identified databases on both exposure and effects, within a screening context. The screening assessment does not represent an exhaustive or critical review of all available data. Rather, it presents a summary of the critical information upon which the conclusion is based.

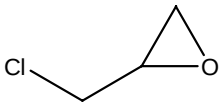
This screening assessment was prepared by staff in the Existing Substances Programs at Health Canada and Environment Canada and incorporates input from other programs within these departments.

This assessment has undergone external written peer review/consultation. Comments on the technical portions relevant to human health were received from scientific experts selected and directed by Toxicology Excellence for Risk Assessment (TERA), including Michael Jayjock (The Life Group), Katherine Walker (Independent Consultant) and Susan Griffin (U.S. Environmental Protection Agency). While external comments were taken into consideration, the final content and outcome of the screening risk assessment remain the responsibility of Health Canada and Environment Canada.
Additionally, the draft of this screening assessment was subject to a 60-day public comment period. The critical information and considerations upon which the assessment is based are summarized below.

Substance Identity

For the purposes of this document, this substance will be referred to as epichlorohydrin, derived from the Japanese Existing and New Chemical Substances (ENCS) and the Korean Existing Chemicals List (ECL) inventories.

Table 1. Substance Identity

Chemical Abstracts Service Registry Number (CAS RN)	106-89-8
Name on Domestic Substances List (DSL)	Oxirane, (chloromethyl)-
Inventory names[a]	Oxirane, (chloromethyl)- (TSCA, AICS, SWISS, PICCS, ASIA-PAC, NZIoC); 1-chloro-2,3-epoxypropane (EINECS, ECL); epichlorohydrin (ENCS, ECL); copolymer of oxirane, (chloromethyl)-(PICCS); propane, 1-chloro-2,3-epoxy (PICCS)
Other names	(±)-Epichlorohydrin; (chloromethyl)ethylene oxide; (chloromethyl)oxirane; (*RS*)-epichlorhydrin; α-epichlorohydrin; γ-chloropropylene oxide; 1,2-epoxy-3-chloropropane; 2,3-epoxypropyl chloride; 2-(chloromethyl)oxirane; 2-chloropropylene oxide; 3-chloro-1,2-epoxypropane; 3-chloro-1,2-propylene oxide; 3-chloropropene-1,2-oxide; 3-chloropropylene oxide; chloropropylene oxide; glycerol epichlorohydrin; glycidyl chloride; J 006; NSC 6747; oxirane, 2-(chloromethyl)-; UN 2023; UN 2023 (DOT)
Chemical group (DSL stream)	Discrete organics
Major chemical class or use	Epoxides
Major chemical sub-class	Halogenated alkyl epoxides
Chemical formula	C_3H_5ClO
Chemical structure	
Simplified Molecular Input Line Entry System (SMILES)	O(C1CCl)C1
Molecular mass	92.52 g/mol

[a] Sources: NCI (National Chemical Inventories) 2007; AICS (Australian Inventory of Chemical Substances); ECL (Korean Existing Chemicals List); EINECS (European Inventory of Existing Chemical Substances); ENCS (Japanese Existing and New Chemical Substances); PICCS (Philippine Inventory of Chemicals and Chemical Substances); ASIA-PAC (Combined Inventories from the Asia-Pacific Region); NZIoC (New Zealand Inventory of Chemicals); TSCA (Toxic Substances Control Act Inventory), and SWISS (SWISS Giftliste 1 and Inventory of Notified New Substances)

Physical and Chemical Properties

A summary of key physical and chemical properties of epichlorohydrin is presented in Table 2.

Table 2. Physical and chemical properties for epichlorohydrin

Property	Type	Value[a]	Temperature (ºC)	Reference
Physical state (normal temperature and pressure)	Experimental	Colourless liquid with irritating, chloroform-like odour	20-25	MP Biomedicals 2006
Density (kg/m^3)	Experimental	1181 (1181 g/cm^3); 1170 (1170 g/cm^3)	20-25	MP Biomedicals 2006; Society of the Plastics Industry 1994; Ullmann's Encyclopedia of Industrial Chemistry 1986
Boiling point (ºC)	Experimental	115.2 to 117		Plunkett 1987; Renfro 1967; Society of the Plastics Industry 1994; Solvay Interox 2000; Physprop 2006; Tamplin et al. 1966; Verschueren 1983
Melting point (ºC)	Experimental	-57.2 to -57 -26		Howard 1989; McDonald 1966; Riddick and Bunger 1970; Riesser 1979; Rowley et al. 2004; Solvay Interox 2000; Physprop 2006
log K_{ow} (octanol-water partition coefficient) (dimensionless)	Experimental	0.3 to 0.45		Howard 1989; Deneer et al. 1988
log K_{oc} (organic carbon-water partition coefficient) (dimensionless)	Modelled	0.652		PCKOCWIN 2000
Henry's Law constant ($Pa \cdot m^3/mol$))	Modelled	0.27 (group method) (2.621×10^{-6} $atm \cdot m^3/mol$); 5.7 (bond method) ($5.621 \times 10^{-5} atm \cdot m^3/mol$)		HENRYWIN 2000
Vapour pressure (Pa)	Experimental	1600 (12 mm Hg); 1700 (17 mbars); 2192 (16.4 mm Hg); 2270 (17 torr); 2280 (17.1 mm Hg)	20-25	Daubert and Danner 1985; Riddick and Bunger 1970; Solvay Interox 2000; Verschueren 1983;WHO 1987
Water solubility (g/L)	Experimental	60 to 65.9	20-25	Solvay 1993; Yalkowsky and Dannenfelser 1992; Verschueren 1983

[a] Originally reported values and units are presented in brackets

Sources

Epichlorohydrin does not occur naturally in the environment. It is manufactured commercially from chlorine and propylene, or from hydrochloric acid and natural glycerine derived from biodiesel (Solvay 2007b).

Annually, global production quantities of epichlorohydrin are around 903 000 tonnes/year (Dow c1995–2008). In 1986, more than 2200 tonnes of epichlorohydrin were reported to the Domestic Substances List as being in commerce in Canada (Environment Canada 1988). However, based on a survey conducted under Section 71 of CEPA 1999, in 2006 epichlorohydrin was not manufactured in or imported into Canada by any company above the 100 kg threshold (Environment Canada 2007). It is likely that epichlorohydrin is being imported as residual monomer in products containing epoxy resin or other resins made using epichlorohydrin, however these residuals would not meet the survey reporting criteria.

Uses

Direct use of epichlorohydrin by consumers is not expected. Epichlorohydrin is a versatile chemical intermediate used to make a wide variety of chemical products. The principal use of epichlorohydrin is in the production of epoxy resins which are primarily used in protective coatings, including those used for lining food and beverage cans (Solvay 2007a). Epoxy resins are also used in structural applications such as printed circuit board laminates, semiconductor encapsulants, and structural composites; tooling, molding, and casting; flooring; and adhesives, paints and other coatings (Pham and Marks 2004). Phenoxy resins, used to make thermoplastic polymers, are also commonly manufactured from epichlorohydrin (Pham and Marks 2004). Other resins or polymers made with epichlorohydrin are used in the textile industry, and for the production of elastomers and phosphorous fireproofing materials (Solvay 2002; Dow c1995–2008).

Epichlorohydrin is also used to make synthetic glycerol, which is used in the manufacture of personal care products, drugs, food and beverages (Solvay 2007a). Residual levels of epichlorohydrin in glycerol are expected to be minimal (e.g., it was not detected at 1.5 ppm) because it is hydrolyzed during the high-temperature production process, thus the potential for exposure from this source is expected to be negligible (US EPA 1985).

Additionally, epichlorohydrin is used in the chemical synthesis of pharmaceutical products, polyols (reactants used for the manufacture of rigid polyurethane foams), and surface active agents for washing products and toiletries (Solvay 2002). Information submitted to Health Canada indicates that polymers manufactured with epichlorohydrin may be used in the production of some cosmetic products, including hair dyes, lipsticks, eye and face makeup, and nail lacquers (Health Canada, Cosmetics Division, Healthy Environments and Consumer Safety Branch, pers. comm., 2008 March 27 and 2008 April 11, unreferenced).

Polymers made with epichlorohydrin are used as additives in papermaking to preserve the strength of the paper in the presence of water (Dulany et al. 2000). This includes paper products such as tissues, toweling, beverage filters and other cellulose products (Dulany et al. 2000). Information submitted to Health Canada indicates that epichlorohydrin is used in the manufacture of various synthetic materials, including polyamide-epichlorohydrin resins. These resins are used in the manufacture of retention aids and wet-strength resins, which are used in Canada in the production of papers used in food contact applications (Health Canada, Food Packaging and Incidental Additives Sections, Health Products and Food Branch, pers. comm., 2008 Feb 27, unreferenced).

Epichlorohydrin is used as a cross-linking agent for starches to form intermolecular bridges between starch molecules to change the gelatinization and swelling properties of the starches (Dumitriu 2005). Cross-linked starch hydrogels may be used as a food additive and in the manufacture of various consumer products such as powder coating inside surgical gloves (Dumitriu 2005).

Epichlorohydrin is listed as a food additive under Division 16 of Canada's *Food and Drug Regulations*, and as such is allowed for use as a starch modifying agent according to good manufacturing practices (Health Canada 2005). However, based on industrial data provided to Health Canada by industry in the late 1970s, it is unlikely that epichlorohydrin is used today by North American starch manufacturers, and if it were used the residual levels of epichlorohydrin in the modified starch would be negligible (Health Canada, Chemical Health Hazards Assessment Division, Health Products and Food Branch, pers. comm., 2007 Nov 01,). Recent editions of the Food Chemicals Codex (Institute of Medicine 1996, 2000) no longer list epichlorohydrin for use as a starch modifying agent, and the internationally recognized Joint WHO/FAO Expert Committee on Food Additives does not include epichlorohydrin in its most recent food-grade specification for modified starches (JECFA 2001).

As a reactive ingredient, epichlorohydrin is used for manufacturing anion-exchange resins and flocculants, used in treating drinking water and wastewater (Solvay 2002). Canada currently has voluntary health-based standards for additives which limit the amount of epichlorohydrin that can be added to drinking water. It may be added indirectly from the epoxy coatings used to coat pipes and pipe-related components used for drinking water. The limit for leaching of epichlorohydrin from these coatings is 0.004 mg/L for National Sanitation Foundation (NSF) certification under the current standards (NSF International 2005a). It may also be added directly as a copolymer for coagulation. Epichlorohydrin/dimethylamine polymers have historically been used for this purpose in Canada and elsewhere at a use level based on a polymer application of 20 mg/L, and a residual epichlorohydrin monomer level of 0.01% in the polymer, for a carryover of not more than 2 ppb of epichlorohydrin in the treated drinking water (as per current NSF International [2005b] standards).

Although epichlorohydrin may possibly be used as a precursor in the manufacture of medical devices, Health Canada cannot currently identify a specified licensed medical

device manufactured using epichlorohydrin in Canada (Health Canada, Medical Devices Bureau, Health Products and Food Branch, pers. comm., 2007 Nov 02).

In Canada, there are no registered pesticides that contain epichlorohydrin as an active ingredient or formulant (PMRA 2007).

Releases to the Environment

Information reported under section 71 of CEPA 1999 indicated that there was no manufacture or import of epichlorohydrin in Canada in 2006 above the reporting threshold of 100 kg, therefore industrial releases are not expected to be significant (Environment Canada 2007). Given the possible uses of this substance in Canada, dispersive releases may occur from consumer or commercial use of products containing residual epichlorohydrin monomer.

Epichlorohydrin is reportable under the National Pollutant Release Inventory (NPRI) but has not been reported since 2003, when a total of 2 kg were released on-site by one company (NPRI 2007).

Environmental Fate

Epichlorohydrin has experimental vapour pressure values of 1600–2200 Pa (Table 2) and is expected to exist solely as a vapour in the ambient atmosphere. Because of its very high water solubility (Table 2), this chemical may also be removed from the atmosphere by wet deposition processes. In water, based on the estimated log K_{oc} value of 0.65 (Table 2), epichlorohydrin is not expected to adsorb to suspended solids and sediments. Volatilization from water surfaces, based upon the estimated Henry's Law constants of 0.3–5.7 Pa m^3/mol, is expected to be moderate. The low log K_{oc} suggests that epichlorohydrin will not adsorb to soil and, therefore, will likely have very high mobility in this environmental compartment. Volatilization of epichlorohydrin from moist soil surfaces may be an important fate process, given estimated Henry's Law constants of 0.3–5.7 Pa m^3/mol (Table 2). Based upon experimental vapour pressure values of 1600–2200 Pa (Table 2), it is thought that volatilization of epichlorohydrin from dry soil surfaces may exist.

A Level III multi-media fate simulation was performed on epichlorohydrin using the Equilibrium Criterion (EQC) model (EQC 2003); a simulation for a type I chemical was run. Results of the Level III modelling suggest that when released into air, the major part of epichlorohydrin (91.6%) will stay in this environmental compartment. The remaining small mass fraction (> 7%) of the substance emitted to air is expected to reach water, while only 1.5% of the substance will partition to soil (Table 3).

When released into the water compartment, almost all of the chemical (98%) will remain in this environmental compartment (Table 3). Due to “water-air” inter-media exchange, a small amount of the chemical (2.3%) will partition to air.

When released into soil, the major part of epichlorohydrin (85%) is expected to remain in this environmental compartment (Table 3). Approximately one tenth part of the chemical will partition to water (due to direct soil–water advection or inter-media exchange via air), while a small portion (4%) of epichlorohydrin is expected to partition to air (due to direct soil–water advection or inter-media exchange via water).

Importantly, in water, soil and sediment, very significant losses of the chemical are expected as a result of abiotic (hydrolysis) and biotic degradation, while no significant degradation of the substance in air will likely occur (see the "Environmental Persistence" section of this report).

Table 3. Results of the Level III fugacity modelling (EQC 2003) for epichlorohydrin[a]

Substance released to	Percentage of substance partitioning into each compartment (%)			
	Air	Water	Soil	Sediment
Air (100%)	91.6	7.0	1.5	0.00
Water (100%)	2.3	97.6	0.04	0.07
Soil (100%)	4.2	11.2	84.6	0.01

[a] As inputs, the following experimental physico-chemical properties were used (see Table 2): water solubility = 60 g/L; vapour pressure = 2008 Pa (average of all vapour pressure values); log K_{ow} = 0.3; melting point = -57 ºC. Half-lives: air – 24.3 days; soil, water, and sediment – 6 days (average hydrolysis half-life) (see Table 4).

Persistence and Bioaccumulation Potential

Environmental Persistence

The half-life of the substance resulting from the reaction of epichlorohydrin with photochemically produced hydroxyl radicals in air can be as high as ~24 days (Table 4), based upon the experimental rate constant of 4.4×10^{-13} cm^3/molecule sec (Atkinson 1989). Therefore, this chemical meets the persistence criterion in air (half-life of ≥ 2 days) set out in the *Persistence and Bioaccumulation Regulations* (Canada 2000).

Epichlorohydrin is a readily hydrolysable chemical (half-life of 4–8 days; see Table 4), resulting in the formation of 3-chloro-1,2-propanediol, which is much less toxic (IPCS INCHEM 1984). Furthermore, the weight of evidence indicates that epichlorohydrin also biodegrades in water (up to 91–97% biodegradation) and soil (half-life of 7–28 days; see Table 4); that is, it is not expected to persist in these two environmental compartments. Epichlorohydrin is also not expected to be persistent in sediment: it has an extrapolated half-life value of 60 days in this medium (Table 4). Therefore, it can be concluded that epichlorohydrin does not meet the persistence criteria in water and soil (half-lives ≥ 182 days), and in sediments (half-life ≥ 365 days), as set out in the *Persistence and Bioaccumulation Regulations* (Canada 2000).

Table 4. Empirical and modeled persistence data for epichlorohydrin

Fate process	Data type	Degradation value	Degradation endpoint (unit)	Reference
OH-radical reaction in air	Experimental	4.4×10^{-13}	Rate constant (cm^3/molecule·sec)	Atkinson 1989
	Experimental	24.3	Half-life (days)	Atkinson 1989
	Modelled	18.95		AOPWIN 2000
Hydrolysis (at 20–25°C)	Experimental	3.9 – 8.2	Half-life (days)	Boelhouwers and deGroot 2001; Kayen and von Hebel 1977; Mabey and Mill 1978; Piringer 1980; Santodonato et al. 1980
Biodegradation in water	Experimental	18 (after 2 weeks); > 40; 67.9[a] (after 2 weeks); 75[a] (after 2 days); 91[a] (after 4 days); 97[a] (after 30 days)	Biodegradation (%)	CITI 1992; Dow Chemical Company 2001; NITE 2002; Popp 1985
	Modelled	15	Half-life (days)	BIOWIN 2000 (Ultimate Survey)
Biodegradation in soil	Experimental	7–28	Half-life (days)	IUCLID Data Set 2002
	Extrapolated	15[b]	Half-life (days)	Boethling et al. 1995
Biodegradation in sediment	Extrapolated	60[b]	Half-life (days)	Boethling et al. 1995

[a] Corresponds to half-life of less than 182 days.
[b] Values were derived from the modeled BIOWIN Ultimate Survey result ($t_{1/2\ water}$ = 15 days), using Boethling's extrapolation factors ($t_{1/2\ water}$: $t_{1/2\ soil}$: $t_{1/2\ sediment}$ = 1:1:4).

With respect to the long-range transport potential (LRTP) of epichlorohydrin from its point of release to air, the TaPL3 model predicted a characteristic travel distance (CTD) value of 4126 km (TaPL3 2000). According to Beyer et al. (2000), CTDs of greater than 2000 km represent high LRTP; therefore, epichlorohydrin has high LRTP, and is judged to be subject to atmospheric transport to remote regions such as the Arctic.

Potential for Bioaccumulation

Experimental log K_{ow} values of 0.3–0.45 (Table 2) suggest that the potential for bioaccumulation of epichlorohydrin in aquatic organisms is low. Modelled bioaccumulation factors (BAF) and bioconcentration factors (BCF) of 1 to 15 L/kg (Table 5) indicate that epichlorohydrin does not meet the bioaccumulation criteria (BCF or BAF ≥ 5000 L/kg) set out in the *Persistence and Bioaccumulation Regulations* (Canada 2000).

Table 5. Predicted bioaccumulation values for epichlorohydrin[a]

Test organism	Endpoint/Units	Value	Reference
Fish	BAF[b] (L/kg, wet weight)	1	Arnot and Gobas 2003
Fish	BCF (L/kg, wet weight)	1–15	Arnot and Gobas 2003; BCFWIN 2000; OASIS Forecast 2005

[a] Metabolism information for this substance was not available, nor was it considered in these models.

Potential to Cause Ecological Harm

As indicated earlier, epichlorohydrin meets the persistence criterion for air but does not meet the persistence criteria for water, soil or sediment, and it does not meet the bioaccumulation criteria as set out in the *Persistence and Bioaccumulation Regulations* (Canada 2000).

Experimental ecological data indicate that epichlorohydrin does not cause acute harm to aquatic organisms at low concentrations. For example, for different aquatic fish species and *Daphnia magna*, acute LC_{50} and EC_{50} values vary within a range of 10.6–72 mg/L (Alabaster 1969; Cowgill 1987; Bridie et al. 1979; Bringmann and Kuhn 1977, 1978, 1982; Dawson et al. 1977; Gersich et al. 1986; Juhnke and Luedemann 1978; Mayes et al. 1983; Wellens 1982). Therefore, based on the weight of experimental ecotoxicological evidence available, epichlorohydrin poses a moderate (acute or immediate) hazard to aquatic organisms.

Epichlorohydrin is reportable under the National Pollutant Release Inventory (NPRI) but has not been reported since 2003, when a total of only 2 kg were released on-site by one company (NPRI 2007). Additionally, there is no indication that this substance is imported or manufactured in Canada in 2006 by any company above the reporting threshold of 100 kg, based on the results of a survey conducted under Section 71 of CEPA (Environment Canada 2007). Given the low quantity of reported releases, there is unlikely to be significant exposure of organisms in the environment.

Based on the available information, it is concluded that epichlorohydrin is unlikely to be causing ecological harm in Canada.

Potential to Cause Harm to Human Health

Exposure Assessment

There were no empirical data identified regarding measured concentrations of epichlorohydrin in environmental media in Canada.

The 1999 national-scale air toxics assessment modelled concentrations of epichlorohydrin in the United States using air dispersion models. The 95th percentile ambient air concentration of epichlorohydrin nationwide was calculated to be

0.001 μg/m^3 (US EPA 1999). Additionally, in sampling of ambient air in a residential area surrounding an industrial zone in New York State conducted between 1997 and 2003, epichlorohydrin was only detected once out of 145 one-hour samples (1.15 μg/m^3) and once out of 233 24-hour samples (0.15 μg/m^3) (NY State Dept. of Health 2005). As there was no manufacture or importation of epichlorohydrin into Canada reported for 2006 (Environment Canada 2007), it is expected that industrial releases are negligible, and so concentrations of epichlorohydrin in ambient air in the United States are not considered relevant to the Canadian population.

Although it is likely that polymers manufactured using epichlorohydrin are used for drinking water treatment in Canada, there were no measured values of residual levels of epichlorohydrin identified in water therefore intake estimates from this source could not be quantified. Currently Canada has voluntary standards of 2 μg/L for use of this substance in drinking water treatment (NSF International 2005b). This value directly corresponds to the drinking water guideline published by the US EPA (2007) but is higher than the guideline value of 0.4 μg/L set by the WHO (2004).

Exposure to epichlorohydrin in food is possible given the use of this substance in a variety of food contact applications, including papers treated with polyamide-epichlorohydrin resins and cans lined with epoxy resin coatings. Based on data submitted to Health Canada, the residual levels of epichlorohydrin in wet-strength resins are up to 0.0775 ppm, which results in an estimated daily intake ranging from 2 to 7.4 ng/kg-bw per day for the general population of Canada (see Appendix 1). Reported residual levels of epichlorohydrin in retention aids are predicted to result in significantly lower exposures. With respect to exposure from residual concentrations of epichlorohydrin in foods from epoxy can linings, information provided to Health Canada indicates that the levels of epichlorohydrin typically found in the epoxy resins supplied to the can coatings manufacturers range from 0 to 1.2 ppm with an average of 0.2 ppm. These epichlorohydrin levels are further reduced in the production of the "wet" can coating. The epichlorohydrin levels are reduced again when that coating is applied and cured in the can manufacturing process (Health Canada, Food Packaging and Incidental Additives Sections, Health Products and Food Branch, pers. comm., 2008 Sep 2, unreferenced). As well, potential migration of epichlorohydrin from food packaging was examined in a study conducted in the United Kingdom, in which epichlorohydrin was not detected in any of 47 samples of canned dry goods and powdered beverages at detection limit of 0.02 mg/kg (MAFF UK 1999). However, it is believed that actual concentrations in food are likely to be much lower than this detection limit; therefore it was not used to quantify estimates of exposure from can linings. Based on the available information, exposure to epichlorohydrin from can linings is expected to be very low.

Concentrations in soil were not available, and modelling for this medium is not considered relevant for this substance, as industrial releases in Canada are unlikely.

Epichlorohydrin is expected to be present in various consumer products. The Household Products Database (HPD 2007) indicates that epichlorohydrin may be found in a variety of epoxy adhesives, coatings and putties as a residual monomer in epoxy resins. The

resins may be present in these products at concentrations ranging from 0.1–100%. However, only trace quantities of epichlorohydrin monomer are likely to be present in the resins (a Material Safety Data Sheet for epoxy resins indicates that residual epichlorohydrin concentrations are less than 0.1% [Evercoat 2005]). Therefore, in spite of its high vapour pressure, emissions of epichlorohydrin to either indoor or ambient air are expected to be negligible. An estimate of exposure to epichlorohydrin from epoxy adhesives predicts air concentrations during use to range from 0.000945 mg/m^3 to 0.0372 mg/m^3 (see Appendix 2). These scenarios correspond to gluing a handle on a coffee mug or gluing a large vase; however, it is expected that the majority of exposures will occur below the lower end of this range. Dermal exposure may also result from the use of this product, but estimated concentrations are lower than those resulting from inhalation (see Appendix 2). The use of two-component epoxy coatings may result in much higher exposures to epichlorohydrin due to a significant increase in the amount of product used and the surface area covered (i.e., coating a basement floor). However, it is believed that the general Canadian population uses these coatings very rarely and that they are used primarily in occupational settings. Residual epichlorohydrin in polymers used to manufacture various types of cosmetics may also lead to exposure via the inhalation and dermal routes. The residual concentrations in these products are unknown and therefore exposure from this source cannot be quantified, however, it is expected to be low. Confidence in these estimates is low as they are based on a number of assumptions; nevertheless, it is likely that they are an overestimate of actual exposures from the use of these products.

Health Effects Assessment

An overview of the toxicological database for epichlorohydrin is presented in Appendix 3.

On the basis of investigations in experimental animals, epichlorohydrin has been classified by the European Commission as a Category 2 carcinogen – "regarded as if carcinogenic to humans" (EC 1993, 2002; ESIS 2007); by the United States National Toxicology Program (NTP) as "reasonably anticipated to be a human carcinogen" (NTP 2005); by the International Agency for Research on Cancer (IARC) as a Group 2A carcinogen – "probably carcinogenic to humans" (IARC 1976, 1999); and by the United States Environmental Protection Agency (US EPA) as a Group B2 carcinogen – "probable human carcinogen" (US EPA 1994). These classifications were based primarily upon rodent studies, in which exposure to epichlorohydrin was by oral, inhalation or intraperitonial administration as described below.

When male rats were exposed to 0, 375, 750 or 1500 mg/L epichlorohydrin in drinking water for 81 weeks, a dose-dependent increase in forestomach hyperplasia was observed in all the exposed groups, while forestomach carcinomas were observed at the highest exposure level (Konishi et al. 1980). Similarly, when male and female rats were exposed to 0, 2 or 10 mg epichlorohydrin/kg-bw/day by gavage for two years, an increased incidence of forestomach hyperplasia, papiloma and carcinoma were observed (Wester et al. 1985).

When male rats were exposed via inhalation to 0, 10 or 30 ppm (0, 38 or 113 mg/m^3) epichlorohydrin for the duration of their lifetime, no neoplastic effects were observed at 10 ppm. In contrast, one rat developed nasal papilloma and another rat developed squamous cell carcinoma of the nasal cavity at 30 ppm. In the same study, when male rats were exposed to 100 ppm epichlorohydrin for six hours a day for 30 days and observed for a lifetime, 17/140 rats developed nasal cavity tumors, including squamous cell carcinomas (15/140) and papillomas (2/140) compared to none in control rats (Laskin et al. 1980).

Intraperitonial exposure of 20, 50 or 100 mg epichlorohydrin/kg-bw/day to mice, three times a week for eight weeks, resulted in a significantly increased incidence of lung papillomas and local sarcomas in the highest exposure group (Stoner et al. 1986).

Dermal administration to mice did not result in an increased incidence of skin tumours, but epichlorohydrin was a skin tumour initiator (Weil et al. 1963; Van Duuren et al. 1974). Subcutaneous administration to mice resulted in local sarcomas (Van Duuren et al. 1974).

A number of cohort studies on workers occupationally exposed to epichlorohydrin have been conducted to examine the carcinogenicity of the substance (Bond et al. 1986; Delzell et al. 1989; Barbone et al. 1992; 1994; Tsai et al. 1996; Olsen et al. 1994). However, these studies were limited by small sample size or confounding factors and therefore, IARC (1999) concluded that there is insufficient evidence in human studies to evaluate carcinogenicity of epichlorohydrin.

Epichlorohydrin is a direct-acting alkylating agent. IARC (1999) has reviewed approximately 114 in vitro and in vivo genotoxicity assays for epichlorohydrin and 98 of those were positive without metabolic activation. Based on those results, IARC (1999) concluded that "Epichlorohydrin induces genetic damage in most bacterial and mammalian tests in vitro or in vivo, not requiring the presence of a metabolic activation system." Positive genotoxicity results were also reported in human case studies, in which cohorts were occupationally exposed to epichlorohydrin (Kučerová et al. 1977; Picciano 1979; Ŝrám et al. 1980; Cheng et al. 1999).

Critical studies of non-cancer effects are summarized below. Please see Appendix 3 for a further overview of the toxicological database.

The critical non-cancer effect induced by epichlorohydrin via inhalation exposure is respiratory damage observed in 167 male workers occupationally exposed to epichlorohydrin in a resin manufacturing factory in Taiwan (Luo et al. 2003). The average exposure in the low exposure group was 0.064 ± 0.05 ppm (0.24 ± 0.02 mg/m^3 or intake of 0.08 ± 0.07 mg/kg-bw/day). The average exposure time (duration of employment) was estimated as 7.9 ± 3.8 years. A significant increase (p = 0.005) in small airway abnormalities (as assessed by significantly lower values for mean mid-expiratory flow) were observed among the workers in the low exposure group. Based on this

observation, the lowest-observed-(adverse)-effect concentration (LO(A)EC) for this study is 0.064 ± 0.05 ppm (0.24 ± 0.02 mg/m^3), which is the lowest chronic LO(A)EC available for this substance. The effects observed in humans are consistent with effects observed in rats and mice at higher inhalation exposure levels (94.4 mg/m^3) (Quast et al. 1979). Short-term inhalation studies were not available, but the lowest acute and subchronic effect levels were 1361 mg/m^3 and 2 mg/m^3, respectively.

Further studies on another cohort from the same resin manufacturing facility indicate that there may be sensitive human subpopulations for pulmonary function abnormality based on examination of human polymorphisms for glutathione S-transferase gene (Luo et al. 2004).

Via oral exposure, the critical non-cancer effect induced by epichlorohydrin is forestomach hyperplasia observed at 2 mg/kg-bw per day when Wistar rats were administered 0, 2, or 10 mg/kg-bw epichlorohydrin daily by gavage for two years (Wester et al. 1985). This is the lowest-observed-(adverse)-effect level (LO(A)EL) available for chronic oral exposure. Similar effects were observed at higher exposure levels in chronic drinking water studies as well as other short-term and subchronic studies.

Additionally, epichlorohydrin has been classified as a dermal sensitizer by the European Union (EC 2002).

The confidence in the toxicity database is moderate to high as data are available for carcinogenicity, genotoxicity, reproductive, developmental, chronic, short-term and acute toxicity. Epichlorohydin was also studied following administration by all relevant routes of exposure. However, no data are available on female reproductive toxicity or two-generation reproductive toxicity, and short-term repeated exposure studies are not available for the inhalation route. As well, the available epidemiology data are insufficient to evaluate carcinogenicity in humans.

Characterization of Risk to Human Health

Based principally on the weight of evidence based assessments or classifications of several national and international agencies (US EPA 1994; IARC 1999; NTP 2005; ESIS 2007), the critical effect for human health risk characterization is carcinogenicity. Epichlorohydrin was genotoxic in a wide range of in vitro and in vivo experimental systems, as well as in investigations of occupationally exposed humans. Therefore, a mode of action for carcinogenicity involving direct interaction with genetic material cannot be precluded.

Based on its possible uses, oral exposure to epichlorohydrin via food/drinking water may occur at low levels for the general population of Canada. Contributions from ambient air and soil are expected to be negligible due to the lack of manufacture in and/or import of this substance into Canada. As exposure from environmental media was not quantified, margins of exposure for chronic non-cancer effects could not be calculated. Margins

between any exposures from environmental media and the chronic oral critical effect level of 2 mg/kg-bw per day, however, are expected to be large.

With respect to consumer product exposure, comparison of the critical non-cancer inhalation effect level in sub-chronically exposed experimental animals (i.e., 2 mg/m^3) with the conservative range of upper-bounding estimates of airborne concentration during use of consumer products containing epichlorohydrin (i.e., 0.000945 mg/m^3 to 0.0372 mg/m^3) results in margins of exposure of 54 to 2116. Given the infrequent use patterns for these consumer products, comparison to short-term inhalation studies would be the most appropriate; however, these studies are not available. As well, since it is likely that the majority of uses will result in exposures below the lower end of the range presented (i.e., 0.000945 mg/m^3), the margin of exposure would likely be closer to the high end of the range (i.e., 2116). The margins of exposure for non-cancer effects are likely sufficiently large to adequately account for uncertainties in the database.

Uncertainties in Evaluation of Risk to Human Health

The scope of this screening assessment of epichlorohydrin does not take into account possible differences between humans and experimental species in sensitivity to effects induced by this substance. However, similar non-cancer effects were observed in mice, rats and humans after inhalation exposure to epichlorohydrin. In addition, the mode of tumour induction has not been fully elucidated. With respect to species differences, carcinogenicity is observed mainly in rats; the same routes of exposure were not examined in mice. Dermal carcinogenicity studies suggest that epichlorohydrin is a tumour initiator in mice. In human studies, there is an indication of carcinogenicity of epichlorohydrin, but IARC 1999 has concluded that "there is inadequate evidence in humans for carcinogenicity of epichlorohydrin." Furthermore, positive genotoxicity results have been observed in human case studies as well as in vivo rodent assays. In the critical non-cancer studies, effects were observed at the lowest exposure levels tested, increasing the uncertainty as to level at which these effects occur. As well, information from short-term inhalation studies would reduce uncertainty in comparison of observed effects with exposure scenarios based on infrequent use patterns.

There are significant uncertainties with respect to the extent of the exposure of the general population to epichlorohydrin. There are no measured concentrations of epichlorohydrin available for any media in Canada, and these measurements are infrequent elsewhere. There is little known about the actual use of epichlorohydrin for water treatment in Canada, and as the standards in place are voluntary, it is possible that these levels may be exceeded, depending upon the treatment technique in place. There has not been any testing for migration of epichlorohydrin from can linings in Canada. Also, there is little known about the actual residual levels of epichlorohydrin in consumer products, as levels are not commonly reported on Material Safety Data Sheets. However, it is believed that the estimates of exposure to consumer products presented here are conservative, and so there is confidence that actual exposure levels do not exceed these estimates.

Conclusion

Based on the available information, it is concluded that epichlorohydrin is not entering the environment in a quantity or concentration or under conditions that have or may have an immediate or long-term harmful effect on the environment or its biological diversity, or that constitute or may constitute a danger to the environment on which life depends.

On the basis of the carcinogenicity of epichlorohydrin, for which there may be a probability of harm at any level of exposure, it is concluded that epichlorohydrin is a substance that may be entering the environment in a quantity or concentration or under conditions that constitute or may constitute a danger in Canada to human life or health.

It is therefore concluded that epichlorohydrin does not meet the criteria in paragraph 64(*a)* and 64(*b)* of CEPA 1999, but it does meet the criteria in paragraph 64*(c)* of CEPA 1999. Additionally, epichlorohydrin meets the criterion for persistence in air, but does not meet the persistence criteria for water, soil or sediment, nor does it meet the criteria for bioaccumulation potential as set out in the *Persistence and Bioaccumulation Regulations.*

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Appendices

Appendix 1

Upper-bounding estimates of exposure to epichlorohydrin from food contact applications (as per email from the Food Packaging and Incidental Additives Section, Health Products and Food Branch, Health Canada, dated Feb. 27, 2008, unreferenced)

Based on data submitted to Health Canada, residual concentrations of epichlorohydrin in paper products treated with wet-strength resins range from 0.0342 to 0.0775 ppm.

Assuming the paper has a density of 150 g/m^2, the concentration of epichlorohydrin is equal to 11.625 µg/m^2 (0.0775 ppm x 150 g/m^2) or 0.00726 µg/in^2. This value was normalized using the packaging ratio of 5 g of food in contact with 1 in^2 (5 g/in^2), resulting in a final value of 0.001 45 µg epichlorohydrin per gram of paper.

It was also assumed that there is 100% migration of epichlorohydrin from the paper product into food, that 30% of all foods eaten are packaged in paper, and that 20% of paper packaging will contain residual epichlorohydrin.

Based on the data received from the Health Products and Food Branch, above, and body weight and food intake assumptions from the Existing Substances Assessment Program (Health Canada 1998), estimated intake was calculated as follows:

Estimated intake = [total intake of food (g) x percent of food packaged in paper x percent of paper containing epichlorohydrin x epichlorohydrin residual level (µg/g)] / body weight

As infants (0-6 months of age) do not typically consume food packaged in paper products, they are not included in the estimates of exposure calculated below.

Table 1. Estimated intake of epicholorohydrin from food

Age group	Total food intake (g)[a]	Body weight (kg)[a]	Estimated intake (ng/kg-bw per day)
0.5–4 yrs	1312.5	15.5	7.4
5–11 yrs	1607.3	31	4.5
12–19 yrs	1752.7	59.4	2.6
20–59 yrs	2005.2	70.9	2.5
60+ yrs	1647.6	72	2

[a] **Health Canada 1998**

Appendix 2

Upper-bounding estimates of exposure to epichlorohydrin from consumer products

Consumer product scenarios	Assumptions	Estimated exposure
Two-component epoxy adhesive – gluing the handle of a coffee mug[1]	**Inhalation** - Used ConsExpo model version 4.1, exposure to vapour: evaporation from an increasing area as mode of release (RIVM 2006) - Assume saturation conditions (i.e., select "limit air concentration to vapour pressure of pure substance" check box) - Based on a reported weight fraction of 0.1 for epoxy resins in epoxy adhesives (Emerson and Cuming 2004) and assuming 0.1% residual epichlorohydrin monomer in epoxy resins (Evercoat 2005) - Assume amount of product used is 0.5 g/event to cover a surface area of 2 cm^2, and an application duration of 5 minutes - Assume a room volume of 20 m^3, exposure duration of 240 minutes, a ventilation rate of 0.6 times/hr, a mass transfer rate based on Langmuir's method and a molecular weight matrix of 3000 g/mol (RIVM 2007)	Mean event concentration = 0.000 945 mg/m^3
Two-component epoxy adhesive – gluing a large vase[1]	**Inhalation** - Used ConsExpo model version 4.1, exposure to vapour: evaporation from an increasing area as mode of release (RIVM 2006) - Assume saturation conditions (i.e., select "limit air concentration to vapour pressure of pure substance" check box) - Based on a reported weight fraction of 0.1 for epoxy resins in epoxy adhesives (Emerson and Cuming 2004) and assuming 0.1% residual epichlorohydrin monomer in epoxy resins (Evercoat 2005) - Assume amount of product used is 20 g/event to cover a surface area of 500 cm^2, an application duration of 30 minutes - Assume a room volume of 20 m^3, exposure duration of 240 minutes, a ventilation rate of 0.6 times/hr, a mass transfer rate based on Langmuir's method and a molecular weight matrix of 3000 g/mol (RIVM 2007)	Mean event concentration = 0.0372 mg/m^3
	Dermal - Used ConsExpo model version 4.1, direct dermal contact with product: instant application as mode of release (RIVM 2006) - Based on a reported weight fraction of 0.1 for epoxy resins in epoxy adhesives (Emerson and Cuming 2004) and assuming 0.1% residual epichlorohydrin monomer in epoxy resins (Evercoat 2005) - Assume the exposed area of skin is 43 cm^2, and an applied amount of 0.1 grams of product (RIVM 2007) - Assume exposed adult weighs 70.9 kg (Health Canada 1998) - Assume 100% uptake	Acute dose per event = 0.000 141 mg/kg

[1] Possible exposure to teenagers (12–19 years old), adults (20–59 years old) and seniors (60+). Scenario was completed using adults.

Appendix 3:

Summary of health effects information for epichlorohydrin

Endpoint	Lowest effect levels/Results
Acute toxicity	Lowest oral LD_{50} (mouse) = 240 mg/kg-bw/day (Lawrence et al. 1972) (Additional studies: Freuder and Leake 1941; Weil et al. 1963; Henck et al. 1980) Lowest inhalation LC_{50} (rat) = 360 ppm (1361 mg/m^3) for 6-hr exposure) (Laskin et al. 1980) (Additional studies: Freuder and Leake 1941; Dietz et al. 1985) Lowest dermal LD_{50} (rabbit) = 515 mg/kg-bw (Keeler 1976) (Additional studies: Freuder and Leake 1941; Smyth and Carpenter 1948; Weil et al. 1963; Lawrence et al. 1972)
Short-term repeated dose toxicity	Lowest oral LO(A)EL (rat) = 3 mg/kg-bw/day for 10 days, based on significant increase in forestomach lesions ($0.01 \geq p \geq 0.001$) (Daniel et al. 1996)
Subchronic toxicity	Lowest oral (gavage) LO(A)EL (m/f rats) = 5 mg/kg-bw/day for 90 days, based on forestomach lesions ($0.01 \geq p \geq 0.001$) (Daniel et al. 1996) (Additional studies: Oser et al. 1975) Lowest inhalation LO(A)EC (male rats) = 2 mg/m^3 (Intake = 0.63 mg/kg-bw/day) for 24 hrs/day for 98 days, based on significantly increased leukocyte count (Fomin 1966) (Additional studies: Quast et al. 1979) Lowest intraperitoneal LO(A)EL (rats)= 22 mg/kg-bw for 12 weeks, based on a significant reduction in the proportion of lymphocytes ($p \leq 0.05$) (Lawrence et al. 1972)
Chronic toxicity/ carcinogenicity	**Neoplastic effects** Oral (drinking water) bioassay in rats: Male rats were exposed by drinking water to 0, 375, 750 and 1500 mg/L (ppm) (54, 107 or 214 mg/kg-bw/day) for 81 weeks. Forestomach hyperplasia (0%, 78%, 90%, 100%), papilloma (0%, 0%, 10%, 58%) and carcinomas (0%, 0%, 10%, 17%) were observed. Data were not statistically analyzed (Konishi et al. 1980; Kawabata 1981). Oral (gavage) bioassay in rats: Male/female rats were exposed by oral gavage.to 0, 2 and 10 mg/kg-bw/day for 5 times/week, 104 weeks. Dose-dependent increase in the incidence of forestomach hyperplasia, papilloma and carcinoma were observed in both sexes. Carcinoma in male rats: 0/50, 6/49, 35/49 and in female rats: 0/50, 2/44 and 24/39 (Wester et al. 1985). Inhalation carcinogenicity bioassay in rats: Male rats were exposed by whole-body inhalation to 0, 10, 30 ppm (0, 38 or 113 mg/m^3) for 6 hrs/day, 5 days/week, for lifetime, and another group to 0 or 100 ppm (0 or 385 mg/m^3) for 6 hrs/day for 30 days followed by lifetime

	observation. No neoplastic changes were observed for 10 ppm, while one nasal papilloma and one squamous-cell carcinoma of the nasal cavity were observed for 30 ppm after 402 and 752 days, respectively. In the 100-ppm group, 15 squamous cell carcinomas and 2 papillomas were observed after 330 and 933 days following exposure. One bronchial papilloma was observed at 583 days after exposure. Four pituitary adenomas and one squamous-cell carcinoma of the forestomach were also reported. Data were not statistically analyzed (Laskin et al. 1980). Dermal carcinogenicity bioassay in mice: No tumors found when female mice were exposed by skin application, 2 mg for 3 times/week for 580 days (Van Duuren et al. 1974) Epichlorohydrin was found to be an active initiator of skin tumours in 30 female mice exposed by single dermal application of 2 mg of epichlorohydrin in 0.1 mL acetone and, 2 weeks later, by dermal applications of phorbol myristate acetate 3 times/week for 385 days. Skin papillomas and carcinomas were seen in 9 and 1 of the treated mice respectively, compared with 3 papillomas in 30 control animals treated with phorbol myristate acetate alone (Van Duuren et al. 1974). Other exposure routes: Female mice exposed by subcutaneous injections of 0 or 1 mg epichlorohydrin once a week for 580 days. Malignant tumors, local sarcomas: 1/50, 6/50. Adenocarcinomas: 0/50, 1/50 (Van Duuren et al. 1974) Female mice exposed by intraperitoneal injections of 0 or 1 mg once a week for 580 days. Lung papillomas: 10/50, 11/30. Local carcinomas: 1/50, 0/30 (Van Duuren et al. 1974) Non-cancer effects: The LO(A)EL for non-cancer effects in rats by oral (drinking water) exposure = 375 mg/L (ppm) (54 mg/kg-bw/day) when male rats were exposed to 0, 375, 750 and 1500 mg/L (ppm) (0, 54, 107 or 214 mg/kg-bw/day) for 81 weeks, based on forestomach hyperplasia (Konishi et al. 1980). The LO(A)EL for non-cancer effects in rats by oral (gavage) exposure = 2 mg/kg-bw/day when male/female rats were exposed to 0, 2 and 10 mg/kg-bw/day for 5 times/week, 104 weeks, based on forestomach hyperplasia (Wester et al. 1985).
Reproductive toxicity	Lowest oral LO(A)EL (rat, male) = 15 mg/kg-bw/day for 7 days based on impaired fertility. Fertility restored after about 7 days without treatment (Hahn 1970) (Additional studies: Cooper et al. 1974; Šrám et al. 1976; Cassidy et al. 1983; Toth et al. 1989) Lowest inhalation (whole-body) LO(A)EC (rat, male) = 25 ppm (94.5 mg/m^3 or intake of 29.7 mg/kg-bw/day) for 6 hrs/day for 10 weeks based on reduced number of implantation sites observed in females bred to exposed males (John et al. 1983a)
Developmental toxicity	Lowest oral (gavage) LO(A)EL(mice) = 120 mg/kg-bw/day, exposure during days 6–15 of gestation based on a significant reduction of fetal weight (Marks et al. 1982)

	No developmental toxicity or teratogenicity was observed in rats or rabbits in inhalation exposure to 0, 2.5 or 25 ppm (0, 9.4 or 94.5 mg/m^3) for 7 hours/day, on gestation days 6–15 for rats and 6–18 for rabbits (John et al. 1983b)			
Genotoxicity and related endpoints-*in vitro*				
Endpoint	**Results and references**			
Genetic mutation	Species, strain	Result	Metabolic activation	Reference
	Escherichia coli polA	Positive	+/-	Tweats 1981
			-	Rosenkranz and Leifer 1980
	Bacillus subtilis rec strains	Negative	-	Elmore et al. 1976
			+	Laumbach et al. 1977; Kada et al. 1980
	Salmonella typhimurium Forward mutation	Positive	+	Skopek et al. 1981
	Salmonella typhimurium TA 100, reverse mutation	Positive	-	Elmore et al. 1976; Šrám et al. 1976; Laumbach et al. 1977; Anderson et al. 1978; Bridges 1978; Simmon 1978; Wade et al. 1978; Bartsch et al. 1979, 1983; Hemminki and Falck 1979; Connor et al. 1980
			+	Imamura et al. 1983
			+/-	Stolzenberg and Hine 1979; Eder et al. 1980; Martire et al. 1981; Nagao and Takahashi 1981; Richold and Jones 1981; Hughes at al. 1987
	Salmonella typhimurium TA 102, reverse mutation	Positive	+/-	Hughes et al. 1987
	Salmonella typhimurium TA 1535, reverse mutation	Positive	+/-	Anderson et al. 1978; Stolzenberg and Hine 1979; Rowland and Severn 1981; Simmon and Shephard 1981; De Flora et al. 1984
			-	Biles et al. 1978; Bridges 1978; Wade et al. 1978; Richard and Jones 1981; Bartsch et al. 1983
		Negative	+	Richard and Jones 1981

	Salmonella typhimurium TA 1537, reverse mutation	Positive	-	Richard and Jones 1981
		Negative	+	
	Salmonella typhimurium TA 1538, reverse mutation	Positive	-	Richard and Jones 1981
		Negative	+	Stolzenberg and Hine 1979
	Salmonella typhimurium TA 98, reverse mutation	Positive	+/-	Stolzenberg and Hine 1979
	Salmonella typhimurium G46, reverse mutation	Positive	-	Šrám et al. 1976
	Escherichia coli WP2 uvrA, reverse mutation	Positive	-	Hemminki and Falck 1979; Hemminki et al. 1980
		Positive	+/-	Gatehouse 1981; Matsushima et al. 1981
	Escherichia coli WP2, reverse mutation	Positive	+/-	Matsushima et al. 1981
	Escherichia coli WP2, uvrA/pkM101, reverse mutation	Positive	+/-	Matsushima et al. 1981
	Escherichia coli 3431M31, uvrB, reverse mutation	Positive	+/-	Mohn et al. 1981
	Klebsiella pneumoniae, forward mutation	Positive	-	Voogd et al. 1981; Knaap et al. 1982
		Negative	+	Voogd et al. 1981
	Neurospora crassa, reverse mutation	Positive	+	Kolmark and Giles 1955
	Saccharamyces cerevisiae rad strains, differential toxicity	Positive	+/-	Sharp and Parry 1981a
	Saccharamyces cerevisiae D7, gene conversion	Positive	-	Zimmermann and Scheel 1981; Vashishat et al. 1980
	Saccharamyces cerevisiae D7, homozygosis	Positive	-	Vashishat et al. 1980
	Saccharamyces cerevisiae 'race XII,' homozygosis	Negative	-	Kassinova et al. 1981
		Positive	+	
	Saccharamyces cerevisiae XV 185-14C, reverse mutation	Positive	-	Mehta and von Borstel 1981
	Schizosaccharomyces pombe, forward mutation	Positive	+/-	Migliore et al. 1982
	Schizosaccharomyces pombe, forward mutation	Positive	+/-	Rossi et al. 1983b
			-	
			+	Loprieno 1981
		Negative	-	Loprieno 1981
	Schizosaccharomyces pombe, reverse mutation	Positive	-	Heslot 1962
	Arabidopsis species, mutation	Positive	-	Acedo and Rédei 1982
		Negative	-	Wurgler and Graf 1981

	Unscheduled DNA synthesis, rat primary hepatocytes	Negative	-	Probst et al. 1981
	Gene mutation, Chinese hamster ovary cells	Positive	-	Amacher and Zelljadt 1984
	Gene mutation, Chinese hamster lung V79 cells, hprt locus	Negative	-	Nishi et al. 1984
	Gene mutation, mouse lymphoma L5178Y cells, tk locus	Positive	+/-	Jotz and Mitchell 1981
	Gene mutation, mouse lymphoma L5178Y cells, hprt locus	Positive	-	Knaap et al. 1982
	Gene mutation, mouse lymphoma L5178Y cells, ouabain resistance	Positive	-	Amacher and Dunn 1985
	Gene mutation, human HSC172 lung fibroblasts, diphtheria toxin resistance	Negative	+/-	Gupta and Goldstein 1981
	Gene mutation, human epithelial-type EUE cells, diphtheria toxin resistance	Positive	-	Perocco et al. 1983
Sister chromatid exchange	**Positive** Chinese hamster ovary cells (+/-S9) (Evans and Mitchell 1981; Natarajan and van Kesteren-van Leeuwen 1981) Chinese hamster ovary cells (-S9) (Perry and Thomson 1981) Chinese hamster lung V79 cells (+/-S9) (von der Hude et al. 1987) Chinese hamster lung V79 cells (-S9) (Nishi et al. 1984; von der Hude et al. 1991) Human lymphocytes (+/-S9) (White 1980) Human lymphocytes (-S9) (Carbone et al. 1981; Norppa et al. 1981) **Negative** Chinese hamster ovary cells (+S9) (Perry and Thomson 1981)			
Chromosomal aberrations	**Positive** Chinese hamster ovary cells (-S9) (Sasaki et al. 1980; Asita 1989) Chinese hamster ovary cells (+/-S9) (Natarajan and van Kesteren-van Leeuwen 1981) Chinese hamster lung fibroblasts (-S9) (Ishidate et al. 1981) Human lymphocytes (-S9) (Kučerová and Polívková 1976; Šrám et al. 1976; Norppa et al. 1981) **Negative** Rat epithelial-like liver cells (-S9) (Dean and Hodson-Walker 1979)			
DNA binding	**Positive** Calf thymus DNA (covalent binding) (-S9) (Hemminki 1979)			
Gene conversion	**Positive** *Saccharamyces cerevisiae* JD1 (-S9) (Sharp and Parry 1981b) **Negative** *Saccharamyces cerevisiae* D4 (+/-S9) (Jagannath et al. 1981)			
DNA single-strand breaks	**Positive** Rat hepatocytes (-S9) (Sina et al. 1983) Mouse lymphoma L5178Y cells (-S9) (Garberg et al. 1988)			

Genotoxicity and related endpoints-*in vivo*	
Endpoint	**Results and references**
Sister chromatid exchange	**Positive** CBA/J mouse bone marrow (-S9) (Paika et al. 1981) Human lymphocytes from healthy male non-smokers and smokers (Bukvic et al. 2000)
Chromosomal aberrations	**Positive** ICR mouse bone marrow (-S9) (Šrám et al. 1976) **Negative** CD-1 mouse bone marrow (Rossi et al. 1983a) Human lymphocytes from healthy male non-smokers and smokers (Bukvic et al. 2000)
Host-mediated assay	**Positive** *Salmonella typhimurium* TA60, G46 in ICR mouse peritoneal fluid (-S9) (Šrám et al. 1976) **Negative** *Schizosaccharomyces pombe,* in CD1 and C57BL x CD1 mice (-S9) (Rossi et al. 1983c) *Escherichia coli* K12 in NMRI mice (-S9) (Hellmér and Bolcsfoldi 1992)
Micronucleus test	**Negative** ICR mice (-S9) (Kirkhart 1981) B6C3F_1 mice (-S9) (Salamone et al. 1981) CD-1 mice (-S9) (Tsuchimoto and Matter 1981) ddY mice (-S9) (Asita et al. 1992) Human lymphocytes from healthy male non-smokers and smokers (Bukvic et al. 2000)
Dominant lethal test	**Negative** ICR mice (-S9) (Šrám et al. 1976) ICR/Ha Swiss mice (-S9) (Epstein et al. 1972)
Sex-linked recessive lethal mutation	**Positive** *Drosophila melanogaster* (-S9) (Vogel et al. 1981; Knaap et al. 1982) **Negative** *Drosophila melanogaster* (-S9) (Wurgler and Graf 1981)
DNA binding	**Positive** BALB/c mouse and Wistar rat liver, lung, kidney and stomach (-S9) (Prodi et al. 1986)
Sperm morphology	**Positive** Wistar rats (-S9) (Cassidy et al. 1983) **Negative** CBAx BALB/c mouse (-S9) (Topham 1980)
Human studies	
Acute toxicity	Lowest inhalation LO(A)EL (human)= 0.3 mg/m^3, based on changes in the electroencephalogram pattern (Fomin 1966)
Chronic toxicity/ carcinogenicity	US EPA 1994; IARC 1999; NTP 2005; ESIS 2007 examined a number of cohort studies and a case-control study and concluded that the data were insufficient to conclude the carcinogenicity of epichlorohydrin to humans (Bond et al. 1986; Delzell et al. 1989; Barbone et al. 1992, 1994; Tsai et al. 1996; Olsen et al. 1994). Lowest inhalation LO(A)EC for non-cancer effects = 0.064 ± 0.05 ppm (0.24 ± 0.2 mg/m^3 or intake of 0.08 ± 0.07 mg/kg-bw/day), 167 workers in resin manufacturing plant, estimated average duration of exposure = 7.9 ± 3.8 years, based on significantly increased small airway abnormalities (p=0.005). These cohorts had been simultaneously exposed to dimethyl formamide in varying concentrations (Luo et al. 2003). Further observations on the same cohort

	indicate that there may be sensitive human subpopulations for pulmonary function abnormality based on examination of human polymorphisms for glutathione S-transferase gene (Luo et al. 2004).
Genotoxicity and related endpoints	Four studies involving occupational exposure to various concentrations of epichlorohydrin have reported chromosomal aberrations in lymphocytes (Kučerová et al. 1977; Picciano, 1979; Ŝrám et al. 1980). In a cohort study, a significantly increased sister chromatid exchange frequency ($p<0.05$) was observed in male workers (N=85) exposed to 1.1–3.9 ppm (4-15 mg/m^3) of epichlorohydrin. These cohorts had been simultaneously exposed to dimethyl formamide in varying concentrations (Cheng et al. 1999). In a cytogenetic monitoring study, workers occupationally exposed to various concentrations of epichlorohydrin did not show biologically significant differences in the frequencies of chromosomal aberrations compared to control groups. The study authors concluded that the frequency of chromosomal aberrations is not sufficiently sensitive for routine monitoring of cytogenetic effects in workers exposed to low levels of genotoxic compounds (De Jong et al. 1988) No significant differences in the frequency of gaps and combined breaks and exchange-type aberrations were observed in workers occupationally exposed to various concentrations of epichlorohydrin for over 6 years (Van Sitter and De Jong 1985).
Reproductive toxicity	No significant effect on fertility was observed in two cohort studies of male workers occupationally exposed to epichlorohydrin (Venable et al. 1980; Milby and Whorton 1980; Milby et al. 1981)
Sensitization and irritation	Case reports are available reporting contact dermatitis (van Joost 1988) and eye and throat irritation (Schultz 1964) (Additional studies: Hine and Rowe 1963; Rebandel and Rudzki 1990)

LD_{50} = median lethal dose
LC_{50} = median lethal concentration
LO(A)EL = lowest-observed-(adverse)-effect level
LO(A)EC = lowest-observed-(adverse)-effect concentration