Ethyloxirane
(1,2-Epoxybutane)

Chemical Abstracts Service Registry Number

106-88-7

Synopsis

The Ministers of the Environment and of Health have conducted a screening assessment of Oxirane, ethyl-, (ethyloxirane), Chemical Abstracts Service Registry Number (CAS RN) 106-88-7, a substance identified in the categorization of the Domestic Substances List as a high priority for action under the Ministerial Challenge. Ethyloxirane was identified as a high priority as it was considered to pose intermediate potential for exposure to individuals in Canada (IPE) and had been classified by other agencies on the basis of carcinogenicity. While the substance did meet the ecological categorization criteria for persistence, it did not meet the criteria for bioaccumulation or inherently toxic to aquatic organisms. Therefore, the focus of this assessment of ethyloxirane relates to human health aspects.

Ethyloxirane was reported to be imported into Canada in 2006 in a total quantity in the range of 10 000–100 000 kg/yr. It is used principally as a stabilizer in industrial solvents that, in turn, are primarily used for vapour degreasing, as well as in ultrasonic and cleaning solvents.

Population exposure to ethyloxirane in Canada is expected to be predominantly in air, based on its potential releases to this medium and its high vapour pressure. Although no quantitative data on levels of ethyloxirane in environmental media are available, based on the results of fugacity modelling, exposure of the general population is expected to be very low. Consumer exposure is expected to be negligible, as the products in which ethyloxirane is present are used primarily in industrial and occupational settings.

Based principally on weight of evidence based assessments of international agencies, the critical effect for the characterization of risk to human health is carcinogenicity, based on the increased incidence of tumours of the respiratory system in rats exposed via inhalation. Ethyloxirane was also genotoxic in a range of *in vitro* assays and a limited number of *in vivo* assays. Therefore, although the mode of induction of tumours has not been fully elucidated, it cannot be precluded that the tumours observed in experimental animals resulted from direct action with genetic material.

On the basis of the carcinogencity of ethyloxirane, for which there may be a probability of harm at any level of exposure, it is concluded that ethyloxirane is as 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.

On the basis of ecological hazard and reported releases of ethyloxirane, 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. Ethyloxirane meets the criterion for persistence but it does not meet the criterion for bioaccumulation potential as set out in the *Persistence and Bioaccumulation Regulations.*

This substance will be included in the Domestic Substances List inventory update initiative, to be launched in 2009. 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, ethyloxirane 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 includes substances that

- met all of the ecological categorization criteria, including persistence (P), bioaccumulation potential (B) and inherently toxic 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 2006a), 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 the highest priorities.

The substance ethyloxirane was identified as a high priority for assessment of human health risk because it was considered to present IPE and had been classified by other agencies on the basis of carcinogenicity. The Challenge for ethyloxirane was published in the *Canada Gazette* on February 3, 2007 (Canada 2007a). A substance profile was released at the same time. 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 the Challenge, submissions of information were received.

Although ethyloxirane was determined to be a high priority for assessment with respect to human health and it also met the ecological categorization criterion for persistence, it did not meet the criteria for potential for bioaccumulation and 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 May 2007 (hazard) and September 2007 (exposure). 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 Exponent and Gradient Corporation. 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.

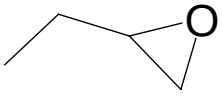
Substance Identity

Common synonyms: 1,2-epoxybutane, butylene oxide

Physical and Chemical Properties

A summary of key physical and chemical properties for ethyloxirane is presented in Table 1. At room temperature, ethyloxirane is a colourless liquid, is highly soluble in water and is highly volatile.

Table 1. Physical and chemical properties of ethyloxirane

Property	Value / Units	Reference
Chemical structure		
Molecular weight	72.11 g/mol	PhysProp 2007
Physical state	Colourless liquid with disagreeable odour	National Fire Protection Association 1986; Lewis 1997
Density	0.83 g/cm^3 (at 20°C)	BASF 1986a
Boiling point (BP)	63.30ºC	PhysProp 2007
Melting point (MP)	-129.5ºC; -150ºC	BASF 1976a; PhysProp 2007
*Vapour pressure (VP)	21.5–22.7 kPa; 24 kPa (180 mm Hg**)	BASF 1976b; Osborn and Scott 1980; BASF 1986b

Henry's Law constant (HLC)	1.732×10^{-4} atm·m^3/mol; 2.118×10^{-4} atm·m^3/mol	HENRYWIN v3.10 2000
*log K_{ow}	0.68	BASF 1988
	0.86 (est.)	KOWWIN v1.67 2000
log Koc	0.65 (est.)	PCKOCWIN v1.66 2000
*Water solubility (WS)	95 g/L	Bogyo et al. 1980

* At 20–25ºC.
** Original values reported in non-SI units.

Sources

Ethyloxirane is prepared commercially from 1-butene utilizing the chlorohydrin process. The process has a potential for emission of ethyloxirane during its separation from the liquid phase but waste water and by-product generation is less probable.

In recent information gathered under CEPA 1999 through a section 71 notice, with respect to ethyloxirane, companies reported the import of this substance in 2006 in a total quantity in the range of 10 000–100 000 kg/yr (Canada 2007b).

Uses

According to recent submissions made under section 71 of CEPA 1999, the Challenge questionnaire submission and other data voluntarily submitted (Canada 2007b), as well as from other sources including the scientific and technical literature, ethyloxirane is used principally as a stabilizer in industrial solvents that, in turn, are primarily used for vapour degreasing, as well as ultrasonic and cleaning solvents (US EPA 1980; HSDB 2006). These types of cleaners are mainly for industrial purposes, being designed to remove oils, lubricants, adhesives, inks and tars from a variety of metal, welded, machined, molded and diecast surfaces as well as reinforced fibreglass and plastics (HSIA 1994). Other applications include its use in the production of pharmaceuticals (US EPA 1980). Ethyloxirane is used by the coating industry to manufacture higher molecular weight polyesters for auto refinish (Canada, 2007b). Also, ethyloxirane may be used as a stabilizer in the production of n-propyl bromide (Canada, 2007b).

Other potential uses of ethyloxirane identified through searches of publicly available scientific and technical literature include its use as a chemical intermediate (non-disperse use) for synthesis in closed systems of fuel additives and defoamers (OECD 2001). Ethyloxirane has also been reported for use as an acid scavenger for chlorine-containing materials and for use as a corrosion inhibitor (HSDB 2006) and may also be used for secondary cleaning in the semiconductor industry (HSIA 1994).

Ethyloxirane was previously a List 2 formulant under the *Pest Control Products Act* and *Pest Control Products Regulations*; however, it was removed from the list in June 2007 (PMRA 2007). Ethyloxirane is included on the Canadian Cosmetic Ingredient Hotlist as a prohibited ingredient not to be used in cosmetics sold in Canada (Health Canada 2007).

Releases to the Environment

Ethyloxirane is not manufactured in Canada and domestic supply is met by imports from the United States. Emissions of ethyloxirane into the environment may occur during formulation and use of the hydrocarbon solvents in which ethyloxirane acts as a stabilizer, or during the use and production of other products that may contain ethyloxirane. Production and processing of ethyloxirane normally occur in closed systems, but no monitoring data on emissions are available.

Fugitive emission or venting during the handling, transport or storage of ethyloxirane could also be a source of emission to the atmosphere. Direct release to the environment from the use of the hydrocarbon solvent is possible; however, only a small fraction of the total production of ethyloxirane would likely be released to the environment from disposal as it is mainly used as a chemical intermediate (US EPA 1980). There are no current NPRI release data for ethyloxirane; the latest report in 2002 indicated releases of zero tonnes (NPRI 2007). In recent information gathered under the CEPA, 1999 through a section 71 notice, with respect to ethyloxirane, companies reported the release of this substance in 2006 in a quantity less than 50 kg, the cut-off quantity for reporting (Canada 2007b).

Environmental Fate

As indicated in Table 1, ethyloxirane is highly soluble in water and has a very low soil-adsorption coefficient, which suggests that if released to water, adsorption of ethyloxirane to sediment and suspended solids is not expected. Volatilization of ethyloxirane from water surfaces would be expected based on the moderate estimated Henry's Law constant. If ethyloxirane is released to soil, it is expected to have low adsorption and thus very high mobility. Volatilization from moist soil and dry soil surfaces is expected, based on its vapour pressure. It is expected that ethyloxirane exists solely as a vapour in ambient atmosphere, based on its very high vapour pressure. Ethyloxirane may also be removed from the atmosphere by wet deposition processes, considering its relatively high water solubility.

The results of a Level III fugacity model, which predict the distribution of ethyloxirane in the environment following release to various media, are summarized in Table 2. It should be noted that the high percentages predicted to partition to soil could be overestimates since the model did not consider fate processes such as volatilization from dry soil and vertical migration in soil. These fate processes are expected to be important for ethyloxirane, based on its physical and chemical properties.

Table 2. Results of the Level III fugacity modelling (EPIWIN V3.12 2004) for ethyloxirane

Substance released to	Fraction of substance partitioning into each compartment (%)			
	Air	Water	Soil	Sediment
Air (100%)	92.4	6.8	0.78	0.01
Water (100%)	6.4	93.4	0.05	0.18
Soil (100%)	11.2	13.5	75.3	0.03
Air, water, soil (33.3% each)	17.5	43.8	38.6	0.09

Persistence and Bioaccumulation Potential

Persistence

The half-life in air is about 5.6 days from the reaction of ethyloxirane with photochemically produced hydroxyl radicals (Table 3), which indicates that this chemical meets the persistence criterion in air (half-life of ≥ 2 days) as set out in the *Persistence and Bioaccumulation Regulations* (Canada 2000). Ethyloxirane is hydrolyzable, with a half-life of 6.5 days, and biodegradable up to 100% degradation and is not expected to persist in water (Table 3). A further model-predicted biodegradation half-life of 15 days in water (BIOWIN 2000, Ultimate Survey) was obtained and used to predict the half-life of this chemical in soil and sediment by applying Boethling's extrapolation factors ($t_{1/2\ water} : t_{1/2\ soil} : t_{1/2\ sediment} = 1: 1: 4$) (Boethling 1995). According to these values, it can be concluded that ethyloxirane does not meet the persistence criteria in water and soil (half-lives ≥ 182 days) and sediments (half-life ≥ 365 days), set out in the *Persistence and Bioaccumulation Regulations* (Canada 2000).

Table 3. Experimental persistence values for ethyloxirane

Fate Process	Degradation value	Degradation endpoint / units	Reference
· OH radical reaction in air	1.9–2.1	Rate constant (10^{-12} cm^3/molecule · sec)	Atkinson 1989
	5.6	Half-life (days)	Atkinson 1989
Hydrolysis*	6.5	Half-life (days)	Gervasi et al. 1985
Biodegradation in water	17; 77–109; 86; 90; 80–90; 100	Biodegradation (%)	BASF 1986c; BASF 1986d; Goodwin 1999; BASF 2000; National Institute of Technology and Evaluation 2002

*At 37°C.

Bioaccumulation

Experimental and modelled log K_{ow} values of 0.68 and 0.86, respectively (Table 1), indicate that the potential for bioaccumulation of ethyloxirane in organisms is likely to be low. Modelled bioaccumulation factor (BAF) and bioconcentration factor (BCF) values of 1 to 17 L/kg (Table

4) indicate that ethyloxirane does not meet the bioaccumulation criteria (BCF/BAF ≥ 5000) as set out in the *Persistence and Bioaccumulation Regulations* (Canada 2000).

Table 4. Predicted bioaccumulation values for ethyloxirane

Test organism	Endpoint / Units	Value	Reference
Fish	BAF (wet weight, L/kg)	1	Modified Gobas BAF T2MTL; Arnot and Gobas 2003
Fish	BCF (wet weight, L/kg)	1–17	OASIS 2005; Modified Gobas BCF 5% T2LTL; Arnot and Gobas 2003; BCFWIN v2.15 2000

* Metabolism information for this substance was not available, nor was it considered in the models.

Potential to Cause Ecological Harm

As indicated earlier, ethyloxirane meets the criterion for persistence but it does not meet the criterion for bioaccumulation as set out in the *Persistence and Bioaccumulation Regulations* (Canada 2000).

Experimental ecotoxicological data for ethyloxirane (OECD 2001) indicate low to moderate toxicity to aquatic organisms. For fish and water flea, acute LC_{50}/EC_{50} values vary within a narrow range of 70-215 mg/L; for algae, toxicity values exceed 500 mg/L, while for bacteria they are close to 5000 mg/L . No toxicity data for non-aquatic non-mammalian organisms were identified.

There are no current NPRI release data for ethyloxirane; the latest report in 2002 indicated releases of zero tonnes. In recent information gathered under section 71 of CEPA 1999, companies reported the release of ethyloxirane in a quantity less than the reporting threshold of 50 kg in 2006. Given the quantity and nature of these releases, they are deemed unlikely to result in significant exposure of organisms in the environment.

Potential to Cause Harm to Human Health

Exposure Assessment

Measured concentrations upon which to base upper-bounding estimates of intake of ethyloxirane were not available for any environmental media in Canada or elsewhere. Based on available information, releases of ethyloxirane to the environment are less than 50 kg/yr, the reporting limit for releases of the substance in the data submission under the section 71 notice of CEPA 1999 (Canada 2007b). Therefore the cut-off value was modelled as a release to air, the expected predominant media of release, and used to predict concentrations for air, water and soil (ChemCAN 2003), which were very low (i.e., predicted concentrations in air, soil and water

were in the range of 10^{-4} ng/m^3, 10^{-8} ng/g and 10^{-6} ng/L, respectively). Thus, based on these very low predicted concentrations, intake of ethyloxirane in environmental media by the general population is likely to be negligible. Confidence in the exposure database is considered to be very low to low, as it is based solely on modelled concentrations of ethyloxirane in air, soil and water. No data were identified on levels of ethyloxirane in food; however, exposure in food is also likely to be negligible, based on the predicted low concentrations of the substance in other environmental media and its low potential to bioaccumulate.

Based upon the information provided by the Canadian companies under the recent section 71 notice issued in accordance with the CEPA 1999, ethlyoxirane is mainly used for industrial applications in closed systems, and thus consumer exposure is expected to be negligible.

Health Effects Assessment

The International Agency for Research on Cancer (IARC 1999) concluded that there were no epidemiological data relevant to the carcinogenicity of ethyloxirane available and "limited evidence" in experimental animals for the carcinogenicity of ethyloxirane. Ethyloxirane was classified as "possibly carcinogenic to humans" (Group 2B), taking into consideration that it is a direct-acting alkylating agent that is mutagenic in a range of test systems. The European Commission has classified ethyloxirane as a Category 3 carcinogen (causes concern for humans owing to possible carcinogenic effects) (European Commission 1994; European Commission 1998; ESIS 2006a). These conclusions were based on the increased incidence of tumours of the respiratory system in male and female rats exposed via inhalation (see Appendix 1 for an overview of the toxicological database). Significant increases in nasal papillary adenomas and combined alveolar/bronchiolar adenomas and carcinomas were observed in male rats exposed to 1200 mg/m^3 ethyloxirane via inhalation for 103 weeks (NTP 1988; Dunnick et al. 1988). There was also a significant positive trend in the incidence of combined alveolar/bronchiolar adenomas and carcinomas. Nasal papillary adenomas were also observed in 2/50 high-dose female rats with none occurring in control or low-dose animals. In mice exposed chronically via inhalation, one male mouse developed a squamous cell papilloma in the nasal cavity (300 mg/m^3) but other tumours were not observed (NTP 1988; Dunnick et al. 1988). Tumours were not observed in mice exposed chronically via dermal exposure (Van Duuren et al. 1967). When trichloroethylene containing 0.8% ethyloxirane was administered orally to mice for up to 35 weeks, followed by 0.4% from weeks 40 to 69, squamous-cell carcinomas of the forestomach occurred in 3/49 males ($p=0.029$, age-adjusted) and 1/48 females at week 106. Trichloroethylene administered alone did not induce these tumours and they were not observed in control animals (Henschler et al. 1984). Two structurally related substances, oxirane (ethylene oxide) and methyloxirane (propylene oxide), which are also direct-acting alkylating agents, have been classified as carcinogenic (European Commission 1999; European Commission 2001; ECB 2002; ESIS 2006b; Canada 2001; IARC 1994a; IARC 1994b; NTP 2005a; NTP 2005b; US EPA 1994).

Ethyloxirane was genotoxic in a number of *in vitro* assays, inducing gene mutation in mammalian and non-mammalian cells, and chromosomal aberrations in mammalian cells

(Appendix 1). Positive results were also observed *in vivo,* including gene mutations and translocations in *Drosophilia melanogaster*. Although an identified study cited negative results in an *in vitro* unscheduled DNA synthesis (UDS) assay and in *in vivo* sperm abnormality, cytogenetic, and dominant lethal and sex-linked recessive lethal (SLRL) mutation assays, which have been attributed to ethyloxirane, it was unclear as to the nature of the test substance used, as CAS 109-99-9 (tetrahydrofuran/ butylene oxide) was cited as the substance tested in the report (McGregor 1981).

The nasal cavity is also the target for critical non-neoplastic effects induced by ethyloxirane. The lowest-observed-(adverse)-effect concentration (LO(A)EC) identified was for chronic exposure to 150 mg/m^3, based upon nasal damage in mice including inflammation, erosion, hyperplasia and squamous metaplasia of the nasal epithelium and atrophy of the olfactory sensory epithelium (NTP 1988; Dunnick et al. 1988). In deriving a Reference Concentration (RfC) for chronic inhalation exposure, the US EPA considered this to be the principal study and the degenerative lesions of the nasal cavity to be the critical effect (US EPA 1992). Similar effects were observed in subchronic studies in both species and in chronic studies in rats at a higher exposure level; however, in both the rat and mouse chronic studies, these effects were observed at the lowest exposure levels tested (NTP 1988; Dunnick et al. 1988).

Although a thorough analysis of the mode of action is beyond the scope of this screening assessment, it is recognized that cellular proliferation may contribute to tumorgenesis. However, a potential role of genetic damage in the development of tumours cannot be discounted.

The confidence in the toxicity database is moderate, since data for acute toxicity, repeated dose toxicity, carcinogenicity, genetic toxicity and reproductive and developmental toxicity in experimental animals are available (although at times limited in nature); however, no studies in exposed human populations are available. The critical non-neoplastic effects observed following chronic exposure occur at the lowest concentrations tested, increasing the uncertainty as to the level at which these effects occur. Although little information was identified concerning the toxicity of ingested ethyloxirane as the majority of the toxicological studies conducted were via inhalation exposure, inhalation is the predicted principal route of human exposure.

Characterization of Risk to Human Health

Based principally on the weight of evidence based assessments of IARC and the EU, a critical effect for characterization of risk to human health for ethyloxirane is carcinogenicity. Although the mode of induction of tumours has not been elucidated, ethyloxirane was genotoxic in *in vitro* and in a limited number of *in vivo* assays; therefore, a mode of action for carcinogenicity involving direct interaction with genetic material cannot be precluded. With respect to non-cancer effects, the margin of exposure between the critical non-neoplastic effect level (i.e., 150 mg/m^3) and the modelled concentration of ethyloxirane in ambient air (i.e., in the range of 10^{-4} ng/m^3 or 10^{-10} mg/m^3) is very large and considered adequate to account for uncertainties in the database.

Uncertainties in Evaluation of Risk to Human Health

The scope of this screening level assessment on ethyloxirane does not take into account possible species differences in sensitivity to effects induced by this substance. However, the respiratory system was a target for ethyloxirane-induced effects in both rodent species tested. As well, the mechanism of tumour induction has not been fully elucidated; however, both genotoxic and non-genotoxic mechanisms may play a role. In addition, there are significant uncertainties with respect to the extent of general population exposure to ethyloxirane. Estimates of exposure through the environment are estimated on the basis of maximum potential releases, as no measured data are available; however, these estimates are conservative, so confidence is high that exposure in the environment is very low.

Conclusion

Based on the available information, it is concluded that ethyloxirane 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 carcinogencity of ethyloxirane, for which there may be a probability of harm at any level of exposure, it is concluded that ethyloxirane 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 ethyloxirane does not meet the criteria in paragraph 64a and 64b of CEPA 1999, but it does meet the criteria in paragraph 64c of CEPA 1999. Additionally, ethyloxirane meets the criterion for persistence but it does not meet the criterion for bioaccumulation potential as set out in the *Persistence and Bioaccumulation Regulations.*

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Appendix 1. Summary of health effects information for ethyloxirane[1]

Endpoint	Lowest effect levels
Laboratory animals and *in vitro*	
Acute toxicity	Lowest **oral LD_{50}** (rat) = 900 mg/kg-bw (BASF 1975) Lowest **inhalation LC_{50}** (mice) ~ 2950 mg/m^3 (NTP 1988) Lowest **dermal LD_{50}** (rabbit) = 1757 mg/kg-bw (Weil et al. 1963) [Additional studies: Smyth et al. 1962; Weil et al. 1963; BASF 1978; NTP 1988]
Short-term repeated-dose toxicity	Lowest **inhalation LO(A)EC** (rabbit) = 750 mg/m^3 for 7 hours/day, 5 days/week for 24 days , based on mortality (lowest concentration tested) (Sikov et al. 1981) [Additional studies: Miller et al. 1981; NTP 1988]
Subchronic toxicity	Lowest **inhalation LO(A)EC** (mice) = 300 mg/m^3 for 6 hours/day, 5 days/week for 13 weeks, based on nasal inflammation (NO(A)EC = 150 mg/m^3) (NTP 1988) [Additional studies: Miller et al. 1981; NTP 1988]
Chronic toxicity/ carcinogenicity	**Inhalation carcinogenicity bioassay in rats:** 0, 600 or 1200 mg/m^3, 6 hours/day, 5 days/week for 103 weeks. Nasal papillary adenomas occurred at 1200 mg/m^3 in 7/50 males (p<0.05) and 2/50 females, but in none of the low-concentration or control animals. The incidences of alveolar/bronchiolar tumours in males were 0/50, 1/50 and 4/49 for carcinomas and 0/50, 1/50 and 1/49 for adenomas, for the control, low- and high-concentration groups, respectively. The combined incidence of these tumours in males exposed to 1200 mg/m^3 was significantly increased (p<0.05) and the trend was also significant (p<0.02). (Dunnick et al. 1988; NTP 1988) **Inhalation carcinogenicity bioassay in mice:** 0, 150 or 300 mg/m^3, 6 hours/day, 5 days/week for 102 weeks. One male in the high-exposure group developed a squamous-cell papilloma in the nasal cavity. Decreased survival of females associated with bacterial infection in ovary and uterus. (Dunnick et al. 1988; NTP 1988) **Dermal carcinogenicity bioassay in mice:** Dermal, 10% in acetone, 3 times/week for 77 weeks. (Control groups receiving 100% acetone or untreated) No tumours observed in any of the groups. (Van Duuren et al. 1967) **Co-exposure oral (gavage) carcinogenicity bioassay in mice:** 1800 (female) or 2400 (male) mg/kg-bw per day corn oil (control) or trichloroethylene or trichloroethylene containing 0.8% ethyloxirane (approximately 14.4 and 19.2 mg/kg-bw per day ethyloxirane in females and males respectively) for up to 35 weeks and then half this dose containing 0.4% ethyloxirane (approximately 7.2 and 9.6 mg/kg-bw per day

[1] Although IARC 1989 and 1999 were used as authoritative sources, for studies cited therein, in some instances the original studies were consulted for additional information

<table>
<tr><td></td><td colspan="4">ethyloxirane in females and males respectively) from week 40 to 69. Experiment terminated at week 106. 3/49 males (p=0.029) and 1/48 females exposed to trichloroethylene plus ethyloxirane developed squamous-cell carcinomas of the forestomach and two of the tumours in males metastasized to the lung, liver or abdominal cavity. (Henschler et al. 1984)

Lowest inhalation LO(A)EC for non-neoplastic effects (mice) = 150 mg/m^3 for 6 hours/day, 5 days/week for 102 weeks based on nasal damage including inflammation, erosion, hyperplasia and squamous metaplasia of the nasal epithelium and atrophy of the olfactory sensory epithelium (lowest concentration tested) (Dunnick et al. 1988; NTP 1988).

[Additional studies: Dunnick et al. 1988; NTP 1988]</td></tr>
<tr><td>Reproductive toxicity</td><td colspan="4">Lowest inhalation LO(A)EC (rats) = 2950 mg/m^3, 7 hours/day, 5 days/week for 3 weeks prior to gestation and 7 hours/day on days 1–19 of gestation based on decreased maternal body weight gain. A slight (statistically non-significant) reduction in the percentage of sperm-positive rats that were pregnant was observed (NO(A)EC = 738 mg/m^3 for reproductive effects) (Sikov et al. 1981)</td></tr>
<tr><td>Developmental toxicity</td><td colspan="4">Lowest inhalation LO(A)EC (rabbits) = 738 mg/m^3 for 7 hours/day, 5 days/week for days 1–24 of gestation based on maternal mortality. At this and higher exposure levels there was an indication of decreased pregnancy rate at term, reduced litter size and embryonic mortality in the presence of maternal toxicity. One surviving fetus at the high exposure level was stunted and had a hypoplastic tail and unilateral renal agenesis (lowest concentration tested) (Sikov et al. 1981).

[Additional studies: Sikov et al. 1981]</td></tr>
<tr><td colspan="5">Genotoxicity and related endpoints: in vitro</td></tr>
<tr><td>Endpoint</td><td colspan="4">Results and reference</td></tr>
<tr><td rowspan="3">Gene mutation</td><td>Species, strain</td><td>Result</td><td>Metabolic activation</td><td>Reference</td></tr>
<tr><td>Salmonella typhimurium TA 98</td><td>Negative</td><td>+</td><td>Simmon 1979a;
De Flora 1981;
Canter et al. 1986;
NTP 1988;
Von der Hude et al. 1990</td></tr>
<tr><td></td><td></td><td>-</td><td>Simmon 1979a;
De Flora 1981;
Gervasi et al. 1985;
Canter et al. 1986;
NTP 1988;
Von der Hude et al. 1990</td></tr>
<tr><td></td><td>Salmonella typhimurium TA100</td><td>Positive</td><td>+</td><td>De Flora 1979;
De Flora 1981;
De Flora et al. 1984;
Canter et al. 1986;
Hughes et al. 1987;
NTP 1988</td></tr>
</table>

			-	McCann et al. 1975; Speck and Rosenkranz 1976; Henschler et al. 1977; De Flora 1979; McMahon et al. 1979; De Flora 1981; De Flora et al. 1984; Gervasi et al. 1985; Canter et al. 1986; NTP 1988; McGregor et al. 1989; Von der Hude et al. 1990
		Negative	+	Simmon 1979a; Dunkel et al. 1984
			-	Simmon 1979a; Dunkel et al. 1984; Rosman et al. 1987
	Salmonella typhimurium TA100-FR1	Positive	-	Rosenkranz and Speck 1975
	Salmonella typhimurium TA102	Positive	+	Hughes et al. 1987
	Salmonella typhimurium TA1530	Positive	-	Chen et al. 1975
	Salmonella typhimurium TA1535	Positive	+	Rosenkranz and Poirier 1979; De Flora 1981; Weinstein et al. 1981; De Flora et al. 1984; Canter et al. 1986; NTP 1988
			-	McCann et al. 1975; Rosenkranz and Poirier 1979; De Flora 1981; Weinstein et al. 1981; De Flora et al. 1984; Canter et al. 1986; Rosman et al. 1987; NTP 1988; McGregor et al. 1989; Von der Hude et al. 1990
		Negative	+/-	Simmon 1979a; Dunkel et al. 1984
	Salmonella typhimurium TA1536	Negative	+/-	Simmon 1979a
	Salmonella typhimurium TA1537	Negative	+	Simmon 1979a; De Flora 1981; Dunkel et al. 1984; Canter et al. 1986;

				NTP 1988; Von der Hude et al. 1990
			-	Simmon 1979a; De Flora 1981; Dunkel et al. 1984; Canter et al. 1986; NTP 1988; Von der Hude et al. 1990
	Salmonella typhimurium TA1538	Negative	+	Simmon 1979b; De Flora 1981; Dunkel et al. 1984
			-	Simmon 1979b; De Flora 1981; Dunkel et al. 1984
	Salmonella typhimurium TA7004	Positive	-	Gee et al. 1998
		Negative	+	Gee et al. 1998
	Salmonella typhimurium TA7001, 7002, 7003, 7005, 7006	Negative	+/-	Gee et al. 1998
	Salmonella typhimurium NM5004	Negative	(+/-GST)	Shimada et al. 1996
	Escherichia coli WP2 *uvr*A	Positive	-	Mcmahon et al. 1979
		Negative	+	Dunkel et al. 1984
			-	Dunkel et al. 1984
	Escherichia coli Sd-4 (-S9)	Positive	-	Hussain 1984
	Klebsiella pneumoniae	Positive	+	Voogd et al. 1981
			-	Voogd et al. 1981; Knaap et al. 1982
	Schizosaccharomyces pombe p1	Positive	+/-	Migliore et al. 1982
	Neurospora crassa	Positive	-	Koelmark and Giles 1955
	Mouse L5178Y cells	Positive	+	McGregor et al. 1987; Mitchell et al. 1988; Myhr and Caspary 1988; NTP 1988
			-	Amacher et al. 1980; Knaap et al. 1982; McGregor et al. 1987; Mitchell et al. 1988; Myhr and Caspary 1988; NTP 1988
Unscheduled DNA synthesis	**Negative results:** Rat hepatocytes (-S9) (Williams et al. 1982)			

Sister chromatid exchange	**Positive results:** Chinese hamster CHO (+/-S9) (NTP 1988; Anderson et al. 1990) Chinese hamster V79 cells (-S9) (Von der Hude et al. 1991) **Negative results:** Rat gliosarcoma 9L cells (-S9) (Bodell 1990)
Chromosomal aberrations	**Positive results:** Chinese hamster CHO (+/-S9) (NTP 1988; Anderson et al. 1990)
DNA damage	**Positive results:** P53R2 gene expression human mammary gland cells (Ohno et al. 2005)
Alkylation	**Positive results:** Deoxyguanosine alkylation (Hemminki et al. 1980; Hemminki et al. 1994) 4-(p-nitrobenzyl)-pyridine alkylation (Kim and Thomas 1992; Hemminki et al. 1994) Calf thymus DNA alkylation (Walles 1974; Hemminki et al. 1994; Kumar et al. 1995)
DNA crosslinking	**Negative results:** Rat gliosarcoma 9L cells (-S9) (Bodell 1990)
Differential toxicity	**Positive results:** *Escherichia coli pol* A (-S9) (Rosenkranz and Poirier 1979; Mccarroll et al. 1981) *Escherichia coli rec* (-S9) (Mccarroll et al. 1981) Chinese hamster CHO repair deficient cells (Hoy et al. 1984)
SOS induction	**Positive results:** *Salmonella typhimurium* TA1535/pSK1002 (+/-S9) (Nakamura et al. 1987; Yasunaga et al. 2004) **Negative results:** *Escherichia coli* PQ37 (+/-S9) (Von der Hude et al. 1990)
Mitotic recombination	**Positive results:** *Saccharomyces cerevisiae* D3 (+/- S9) (Simmon 1979b)
Cell transformation	**Positive results:** Rat embryo cells (-S9) (Price and Mishra 1980; Dunkel et al. 1981) Hamster embryo cells (-S9) (Dunkel et al. 1981; Pienta et al. 1981) Balb/c 3T3 mouse cells (-S9) (Matthews et al. 1993) **Negative results:** Balb/c 3T3 mouse cells (-S9) (Dunkel et al. 1981)
Genotoxicity and related endpoints: *in vivo*	
Endpoint	**Results and reference**
Sex-linked recessive lethal mutations	**Positive results:** *Drosophila melanogaster* (oral) (NTP 1988) (injection) (Knapp et al. 1982) **Weakly positive results:** *Drosophila melanogaster* (injection, vapour) (Vogel and Nivard 1998) (oral) (Vogel and Nivard 1993)
Heritable translocations	**Positive results:** *Drosophila melanogaster* (oral) (NTP 1988)
Micronuclei induction	**Negative results:** Rat (intra-peritoneal) (NTP 1993) – high mortality in higher exposure groups