Methyloxirane
(Propylene oxide)

Chemical Abstracts Service Registry Number

75-56-9

Synopsis

The Ministers of the Environment and of Health have conducted a screening assessment of Oxirane, methyl- (methyloxirane), Chemical Abstracts Service Registry Number (CAS RN) 75-56-9, a substance identified in the categorization of the Domestic Substances List as a high priority for action under the Ministerial Challenge. Methyloxirane was identified as a high priority as it was considered to pose greatest potential for exposure (GPE) to individuals in Canada and had been classified by other agencies on the basis of carcinogenicity and genotoxicity. While the substance did meet the ecological categorization criterion for persistence, it did not meet the criteria for bioaccumulation or inherently toxic to aquatic organisms. Therefore, the focus of this assessment of methyloxirane relates to human health aspects.

Methyloxirane was reported to be imported into Canada in 2006 in a quantity greater than 10 000 000 kg. It is used mainly as a monomer in polymer production of polyether polyols, and to a lesser degree in the production of propylene glycol.

Population exposure to methyloxirane in Canada is expected to be predominantly in air, based on its potential releases to this medium and its high vapour pressure. Based on very limited information on levels in environmental media and the results of fugacity modelling, exposure in the general environment is expected to be low. However, exposure to methyloxirane may be elevated during use of consumer products containing the substance.

Based principally on weight of evidence based assessments by several international and national agencies, a critical effect for the characterization of risk to human health is carcinogenicity, based on the observation of nasal cavity tumours in rats and mice. Methyloxirane was also genotoxic in several *in vitro* and *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 interaction with genetic material. In addition, the upper-bounding estimate of exposure via inhalation during use of consumer products containing methyloxirane may approach or exceed the critical effect level for non-cancer effects in the nasal cavity.

On the basis of the carcinogencity of methyloxirane, for which there may be a probability of harm at any level of exposure, as well as the potential inadequacy of the margin between estimated exposure from products and the critical effect level for non-cancer effects, it is concluded that methyloxirane 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.

On the basis of ecological hazard and reported releases of methyloxirane, 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. Methyloxirane 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, methyloxirane 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 inherently toxic to aquatic organisms (iT), and were believed to be in commerce; and/or
- met the categorization criteria for greatest potential for human 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 the highest priorities.

The substance methyloxirane 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 and genotoxicity. The Challenge for methyloxirane 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 methyloxirane 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 July 2007. 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 John Christopher (California Department of Toxic Substances Control), Michael Jayjock (The Lifeline Group), Donna Vorhees (The Science Collaborative) and Joan Strawson (TERA). Comments on these section were also received from 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.

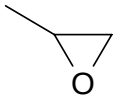
Substance Identity

Common synonyms: propylene oxide, 1,2-epoxypropane, methyl ethylene oxide

Physical and Chemical Properties

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

Table 1. Physical and chemical properties of methyloxirane

Property	Value/Units	Reference
Chemical structure		
Molecular weight	58.08 g/mol	(PhysProp 2003)
Physical state (normal temperature and pressure)	Colourless liquid with a sweet, ether-like odour	(EURAR 2000)
Density	831 kg/m^3 (at 20°C)	BASF 1977a
Boiling point (BP)	33.9–35°C	(American Chemical Society 1952; Jefferson Chemical Company 1960; Plunkett 1987; BASF 1995; PhysProp 2003)
Melting point (MP)	-112.16 to -111ºC	(McDonald et al. 1959; Oetting 1964; Howard 1989; BASF 1995; PhysProp 2003)
Log K_{ow}	0.03; 0.08 ± 0.05	(Deneer et al. 1988; Howard 1989; Hansch et al. 1995)
Log K_{oc}	0.37 (est.)	(PCKOCWIN 2000)
Henry's Law constant (HLC)	1.226×10^{-4} atm·m^3/mol (est.)	(HENRYWIN 2000)
*Vapour pressure (VP)	60.7–71.55 kPa; 59.2 kPa (8.59 PSI**); 70.9–71.7 kPa (532.1-538 mm Hg**)	(American Chemical Society 1952; BASF 1967; Dow 1977; Boublik et al. 1984; Howard 1989; Aldrich Chemical Co. 2003)
*Water solubility (WS)	400–590 g/L	(Bogyo et al. 1980; BASF 1995)

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

Sources

Methyloxirane is not known to occur as a natural product. Peroxidation and chlorohydrination are the two major processes used to manufacture methyloxirane from propylene in large quantities.

Under information reported pursuant to the CEPA 1999 section 71 Notice with respect to methyloxirane, no Canadian companies reported manufacturing this substance in a quantity greater than or equal to 100 kg in 2006. Canadian companies reported importing methyloxirane in a quantity greater than 10 000 000 kg for the 2006 calendar year (Canada 2007b).

Uses

According to submissions made under section 71 of CEPA 1999, from the Challenge questionnaire submission and other data voluntarily submitted (Canada 2007b), as well as from other available scientific and technical literature, methyloxirane is used mainly as a monomer in polymer production of polyether polyols. Polyether polyols are used in the production of polyurethane foams for the furniture and automotive industries. Methyloxirane may also be used in the manufacture of propylene glycol, as a starch modifying agent in food, in potential food contact applications, in cosmetics and personal care products, resins, ink, synthetic lubricants and in the automotive industry as a detergent additive and corrosion inhibitor in motor fuels, gasket removers, cleaners, petroleum

defoamers, fuel additives and adhesives (Dow 1981; Sack et al. 1992; Trent 2001; European Union 2002; Dow 2007). Propylene glycol manufactured from methyloxirane can also be used in the production of unsaturated polyester resin especially in the textile and plastic industries, in pharmaceuticals, and aircraft de-icers (Dow 1981; Trent 2001; European Union 2002; Dow 2007). Propylene glycol is also used in the manufacture of glycol ethers, for use as solvents in paints and varnish (Trent 2001). Methyloxirane itself has no reported uses in Health Canada's Cosmetic Notification Database (Health Canada, Cosmetics Division, Healthy Environments and Consumer Safety Branch, pers. comm., 2008 June 9, unreferenced). However, it is found in paint stripper (Henkel 2008).

Methyloxirane is used for fumigation of dried fruit products and as a fumigant for bulk quantities of several food products such as cocoa, spices, processed nutmeats, starch and gum in the United States (European Union 2002; US EPA 2005). However, the substance is not a registered pesticide in Canada, and food treated in the United States (or elsewhere) and imported into Canada cannot contain more than 0.1 ppm methyloxirane (PMRA 2006).

Methyloxirane is an approved food additive under Health Canada's *Food and Drugs Regulations* (Justice Canada 1985) and is subject to conditions which ensure limited use, precluding human exposure through food consumption. It is included as a preservative substance (antimicrobial) on Health Canada's Natural Health Products non-medicinal ingredient list (HPFB 2007).

Releases to the Environment

Methyloxirane is not manufactured for commercial purposes in quantities greater than 100 kg in Canada (Canada 2007b). Domestic supply is met by imports from the United States. In 1999, the total Canadian supply and consumption of methyloxirane was 51 500 tonnes, but in 2002, only 38 000 tonnes were imported (CPI 2003). The Canadian National Pollutant Release Inventory reported only one emitter in Ontario in 2005. The reported releases were exclusively to air and the volume released decreased steadily from 10.4 tonnes in 1999 to 5.16 tonnes in 2002 and to 0.059 tonnes in 2005 (NPRI 2006). In recent information gathered under a CEPA 1999 section 71 Notice with respect to methyloxirane, companies reported the release of this substance in 2006 in a quantity less than 50 kg, the cut-off quantity for reporting (Canada 2007b).

The major source of release to the environment is through evaporation and vented gases during production of substances where methyloxirane is used as a chemical intermediate, storage, handling, transport and use. Process vents appear to be the most important sources of atmospheric pollution. Methyloxirane releases may also originate from automobile exhaust and combustion exhaust from stationary sources that burn hydrocarbons. Emissions from waste gas are often removed by air scrubbing, with liquid waste being controlled by incineration (IPCS 1985; Ontario MOE 2001).

Environmental Fate

Methyloxirane, with a vapour pressure of 71.5 kPa, is expected to exist solely as a vapour in the ambient atmosphere. Methyloxirane may be reduced from the atmosphere by rain washout, considering the very high water solubility of this chemical (IPCS 1985). In water, methyloxirane hydrolyzes rapidly within 11-22 days (table 3), forming propylene glycol. Degradation is accelerated by the presence of chloride ions, indicating that chemical removal in seawater will be more rapid than in freshwater (European Union 2002). Volatilization from water surfaces, based upon an

estimated Henry's Law constant of 1.23 $\times 10^{-4}$ atm-m^3/mole, is expected to be moderate. Methyloxirane is not expected to adsorb to suspended solid and sediment, based on an estimated log K_{oc} value of 0.37, and will have high mobility in this environmental compartment. Evaporation from soil surfaces is therefore likely to be high (Meylan et al. 1986).

The results of a level III fugacity model, which predicts the distribution of methyloxirane in the environment, 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 methyloxirane based on its physical and chemical properties.

Table 2. Results of the Level III fugacity modelling (EPIWIN 2004) for methyloxirane

Substance released to	Fraction of substance partitioning into each compartment (%)			
	Air	Water	Soil	Sediment
Air (100%)	88.0	10.3	1.6	0.02
Water (100%)	4.5	95.3	0.1	0.18
Soil (100%)	7.6	18.0	74.4	0.03
Air, water, soil (33.3% each)	15.4	44.0	40.6	0.08

Persistence and Bioaccumulation Potential

Persistence

The half-life from the reaction of methyloxirane with photochemically produced hydroxyl radicals in air varies from approximately 7 to 32 days (Table 3), which indicates that this chemical meets the persistence criterion in air (half-life of ≥ 2 days) set out in the *Persistence and Bioaccumulation Regulations* (Canada 2000)

Methyloxirane is hydrolysable, with a half-life of 10.7–21.7 days. Methyloxirane is up to 100% biodegradable and is not persistent in water (Table 3). A further model-predicted biodegradation half-life of 15 days in water (BIOWIN 2000) 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 this chemical does not meet the persistence criteria in water and soil (half-lives ≥ 182 days) and sediments (half-life ≥ 365 days) as set out in the *Persistence and Bioaccumulation Regulations* (Canada 2000).

Table 3. Experimental persistence values for methyloxirane

Fate process	Degradation value	Degradation endpoint/units	Reference
· OH radical reaction in air	0.52–2.4	Rate constant (10^{-12} cm^3/molecule · sec)	Pitts 1979; Winer et al. 1979; Zetsch and Stahl 1981; Edney et al. 1986; Wallington et al. 1988; Atkinson 1989
	6.6 - 32.3	Half-life (days)	
Hydrolysis (at 20–25°C)	0.37–0.75	Rate constant (10^{-6} · s^{-1})	Nichols and Ingham 1955; Koskikallio and Whalley 1959; Mabey and Mill 1978; Sato et al. 1985
	10.7–21.7	Half-life (days)	
Biodegradation in water	12–14; 67; 74; 93–98; 90–100	Biodegradation (%)	Waggy and Payne 1974; BASF 1977b; Dow Deutschland 1978; Miller and Watkinson 1985; Chemicals Inspection and Testing Institute 1992

Bioaccumulation

Experimental and modelled log K_{ow} values of 0.03 and 0.37, respectively, indicate that the potential for bioaccumulation is likely to be low. Modelled bioaccumulation (BAF) and bioconcentration (BCF) factors of 1 to 13 L/kg (Table 4) indicate that methyloxirane 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 methyloxirane

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)	1–13	OASIS Forecast 2005; Modified Gobas BCF 5% T2LTL (Arnot and Gobas 2003) BCFWIN 2000

Potential to Cause Ecological Harm

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

Experimental and modelled ecotoxicological data for methyloxirane indicate low to moderate toxicity to aquatic organisms. Acute experimental LC_{50} values for fish vary from 89 to 219 mg/L (Bridie *et al*., 1979; Crews, 1974). No toxicity data for non-aquatic non-mammalian organisms were identified.

The National Pollutant Release Inventory reports releases of 0.059 tonnes of methyloxirane to air by one emitter in Ontario in 2005 (NPRI 2006). In recent information gathered under section 71 of CEPA 1999, companies reported the release of this substance in 2006 in a quantity less than 50 kg, the cut off quantity for reporting (Canada 2007b). Methyloxirane release may also originate from automobile exhaust and combustion exhaust from stationary sources that burn hydrocarbons (IPCS 1985; Ontario MOE 2001). 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

Very limited information is available on concentrations of methyloxirane in environmental media, on which to base a quantitative estimate of population exposure. In limited studies, methyloxirane was not detected in different media; however, detection limits are available from these studies, i.e., a US pilot study for indoor and outdoor air, as well as surface water and sediment data from a Japanese monitoring study (Sheldon and Jenkins 1990; Japan MOE 1995). Use of detection limits

from the Japanese study as surrogates for drinking water and soil in Canada is considered to be inappropriate for estimating intake. Based on the Canadian uses and release patterns and physical and chemical properties of methyloxirane, its presence in water and soil is expected to be minimal in relation to levels in air, the expected predominant source of exposure. Using the detection limits for indoor and outdoor air in the US study, the upper bounding estimates of exposure to methyloxirane for the general population range from 0.06 µg/kg-bw per day in the 60 + years age group to 0.18 µg/kg-bw per day in the 0.5 to 4 years age group (Appendix 1). In addition, the maximum residue limit of 0.1 ppm methyloxirane in imported fumigated nutmeat was used to calculate the intake estimate from the nuts and seeds category, as no other quantitative data for methyloxirane in food were identified. The calculated intake estimates from food were negligible compared to those from air. In light of the uncertainty associated with the use of detection limits as surrogate concentrations for air and the lack of quantitative information on levels in water and soil in Canada, estimated concentrations for these media were modelled using ChemCan Ver.6.0 (CEMC 2003) based on the release quantity of 50 kg/year, the cutoff quantity for reporting under the recent section 71 notice of CEPA 1999 (Canada 2007b). When modelled as a release to air, the expected predominant medium of release, the predicted concentrations for air, water and soil (Appendix 2) are much lower than those used to estimate the intakes presented in Appendix 1. This further illustrates the conservative nature of these estimates. Although the release quantity of 50 kg/year does not take into account potential releases from products containing methyloxirane, potential releases from these products are expected to be predominantly to air based on the uses of this substance in Canada. Contribution of releases from products to the general environment would likely already be accounted for when using the detection limits in the upper-bounding estimate of exposure outlined above. Confidence in the database on environmental exposure is considered very low, since method detection limits and modelling are used to estimate exposures and because the initial inputs to the exposure models are based solely on theoretical release amounts.

Based on the available information on uses of methyloxirane in Canada, consumer products could represent a source of direct exposure for users. To assess the potential increase in exposure to methyloxirane from use of consumer products containing this substance, estimates of resulting airborne concentrations and daily intake for the Canadian adult population (20–59 years old) were made for paint stripper and acrylic aerosol spray paint (Appendix 3). These products were selected because they represent important product uses of methyloxirane or contain substances in which methyloxirane may be present as a residual. The Canadian adult population is expected to be the principal user of these products. Based on these screening estimates, inhalation from paint stripper could contribute substantially to exposure, while estimated inhalation exposure from acrylic aerosol spray paint is lower. Dermal intake from the use of these consumer products is considered to be negligible based on the high vapour pressure and low log K_{OW} of methyloxirane. Confidence in these estimates of exposure from consumer products is low, however, as they were predicted in the absence of data on actual emissions of methyloxirane from the products.

Health Effects Assessment

On the basis of investigations in experimental animals, methyloxirane has been classified by the International Agency for Research on Cancer (IARC) as Group 2B – "possibly carcinogenic to humans" (IARC 1994), by the European Community as Category 2 Carcinogen – "regarded as if carcinogenic to humans" (European Commission 1999; European Commission 2001; European Union 2002; ESIS 2006), by the US EPA as Group B2 – "probable human carcinogen" (US EPA 1994) and by the National Toxicology Program (NTP) as "reasonably anticipated to be a human

carcinogen" (NTP 2005). These classifications were based on observed nasal cavity epithelial tumours in male and female mice and a low incidence of papillary adenomas in the nasal cavity of both sexes of rats exposed via inhalation to 400 ppm (964 mg/m^3) methyloxirane for 103 weeks (NTP 1985; Renne et al. 1986) (see Appendix 4 for an overview of the toxicological database). In an additional inhalation study, male rats exposed to 300 ppm (723 mg/m^3) methyloxirane for 123–124 weeks had an increased incidence of carcinomas of the respiratory tract and three males exposed to 30 or 300 ppm (72 or 723 mg/m^3) displayed malignant nasal cavity tumours (Kuper et al. 1988). As well, mice exposed via inhalation to 400 ppm (964 mg/m^3) had significantly increased combined incidences of hemangiomas and hemangiosarcomas in the nasal cavity (NTP 1985; Renne et al. 1986). When female rats were exposed orally to 15 or 60 mg/kg-bw methyloxirane twice weekly for 150 weeks, an exposure-dependent increase in the incidence of stomach tumours was observed (no statistical analysis) (Dunkelberg 1982). Studies by Dunkelberg (1979; 1981) and Walpole (1958) demonstrated that methyloxirane can induce local sarcomas at the site of subcutaneous injection in mice and rats, respectively. While in some of the aforementioned studies the incidences of nasal cavity tumour did not reach statistical significance, they were considered to be exposure related in view of the rarity of this tumour in concurrent and historical controls (NTP 1985; Kuper et al. 1988; EU 2002). The only data available from human studies are inadequate to evaluate the carcinogenicity of methyloxirane in humans (IARC 1994; EU 2002).

The European Community has classified methyloxirane as a Category 2 Mutagen – "Regarded as if mutagenic to humans" (European Commission 1999; European Commission 2001; EU 2002; ESIS 2006). This classification was based on the consensus opinion of a panel of specialized experts that there was "clear evidence for mutagenicity of methyloxirane in somatic cells *in vitro* and *in vivo*" (European Commission 1999). Methyloxirane was genotoxic in a number of *in vitro* assays, including tests for gene mutation in mammalian and non-mammalian cells, and chromosomal aberrations and micronucleus induction in mammalian cells (Appendix 4). It also induced DNA strand breaks and formed DNA adducts *in vitro*. Additionally, positive results were observed *in vivo* in rodents and in *Drosophila,* including micronuclei induction, chromosomal aberrations, DNA lesions or the formation of DNA adducts; however some *in vivo* assays for these endpoints were also negative. The results of dominant lethal assays in rodents were negative. A review (EU 2002) of six studies involving occupational exposure noted that no conclusions could be drawn from these studies regarding the mutagenicity of methyloxirane in humans (Theiss et al. 1981; Pero et al. 1982 and 1985; Van Sittert and de Jong, 1985; de Jong et al. 1988; Hogstedt et al. 1990; Viktorova et al. 1994). A recent small pilot study has shown significantly increased blood levels of DNA adducts and sister chromatid exchanges in workers exposed to methyloxirane although confounding factors contributing to cytogenetic effects could not be excluded (Czene et al. 2002).

Although a thorough analysis of the mode of action is beyond the scope of this screening assessment, it is recognized that non-neoplastic cellular proliferation may contribute to tumorgenesis above a certain level of exposure. However, a potential role of genetic damage in the development of tumours cannot be discounted in light of the considerable evidence of genotoxicity. A number of studies have been recently conducted to examine the role of glutathione depletion in methyloxirane related tumourgenesis in both rats and mice (Morris et al. 2004; Lee et al. 2005; Morris and Pottenger 2006). The potential mode of action for induction of tumours by methyloxirane is currently being evaluated by the United States Environmental Protection Agency (US EPA 2005) After an initial review of data submitted by industry, the US EPA has indicated that a threshold mode of action for the carcinogenic effects is "highly plausible"; however, the information is being reviewed further (US EPA 2006). In addition, Albertini and Sweeney (2007) examined the

genotoxicity profile for methyloxirane and concluded that its DNA-reactive genotoxicity may be necessary but not sufficient for carcinogenicity and that a complex mode of action is likely.

In an assessment by the European Union (EU 2002) it was concluded that the carcinogenicity of methyloxirane is primarily confined to the sites of initial contact but that the relative contribution to the carcinogenic process made by irritation, consequential proliferative response, and genotoxicity is unclear based on current scientific knowledge. The EU concluded that due to methyloxirane's direct acting nature and mutagenic activity, the carcinogenic hazard of methyloxirane expressed in animals is considered relevant to humans.

The critical non-neoplastic effects induced by methyloxirane occur in the nasal cavity. The lowest-observed-(adverse)-effect concentration (LO(A)EC) identified was 71 mg/m^3 in rats exposed via inhalation for 123–124 weeks, based on a slight increase in the incidence of "nest-like infolds" in the nasal epithelium of exposed animals (Kuper et al. 1988). The EU (2002) report identifies this value as the 'minimal' LOAEC for nasal epithelial effects. As well, the US EPA (US EPA 1990) considers this effect level a LOAEC for deriving their Reference Concentration (RfC) for chronic inhalation exposure for methyloxirane. Likewise, in terms of a recent reregistration eligibility decision for the use of methyoxirane as a pesticide, the US EPA considered this effect level to be a no-observed-adverse-effects concentration, or NOAEC (US EPA 2005). Similar effects were observed in chronic studies in mice at a higher exposure level of 474 mg/m^3 (NTP 1985; Renne et al. 1986) as well as in both rats and mice exposed for shorter durations at 5- to 15-fold higher concentrations, e.g., 362 mg/m^3 (Eldridge et al. 1995). In chronic studies in both species, these effects were observed at the lowest exposure levels tested.

The confidence in the toxicity database is high, as data for acute toxicity, carcinogenicity, repeated dose toxicity, genetic toxicity and reproductive and developmental toxicity are available, although there is uncertainty in the mode of induction of tumours.

Characterization of Risk to Human Health

Based principally on the weight of evidence based assessments of several international and national agencies (IARC, EU, US EPA and US NTP), a critical effect for characterization of risk to human health for methyloxirane is carcinogenicity, for which a mode of induction involving direct interaction with genetic material cannot be precluded.

With respect to non-cancer effects, comparison of the critical non-neoplastic effect level in chronically exposed experimental animals (i.e., 71 mg/m^3) with the upper bounding estimate of general population exposure via inhalation—the expected principal route of exposure, the estimation of which was based on detection limits in a U.S. study (i.e., 0.31 µg/m^3)—results in a margin of exposure of approximately 229 000. However, if the conservative upper bounding estimate of air-borne concentration during use of consumer products containing methyloxirane is considered (i.e., 200 mg/m^3 in paint stripper), the resulting margin of exposure would be less than 1. If estimated exposure from products is compared to the lowest effect level for short-term repeated exposure (i.e., 362 mg/m^3), which may be more appropriate in light of the infrequent use patterns for such products, the resulting margin of exposure would be approximately 2. Thus, while the margin of exposure for non-neoplastic effects is adequate for exposure in the general environment, the margin for consumer product exposure scenarios (although conservative in nature), may not be adequate to account for uncertainties in the databases on exposure and effects.

Uncertainties in Evaluation of Risk to Human Health

The scope of this screening assessment does not take into account possible differences between humans and experimental species in sensitivity to effects induced by this substance, particularly in light of the limited data available for humans. However, similar effects are observed in both rodent species tested and physiological toxicokinetic modelling (Csandy and Filser 2007) suggests that the toxicokinetics of methyloxriane are similar in humans and rats. In addition, the mechanism of tumour induction has not been fully elucidated; however, the data suggest that both genotoxic and non-genotoxic mechanisms may play a role. As well, there are significant uncertainties with respect to the extent of the exposure of the general population to methyloxirane. However, since the estimates of exposure presented here are conservative, confidence is high that actual exposure levels do not exceed these estimates.

Conclusion

Based on the available information, it is concluded that methyloxirane 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 methyloxirane, for which there may be a probability of harm at any level of exposure, as well as the potential inadequacy of the margin between estimated exposure from products and the critical effect level for non-cancer effects, it is concluded that methyloxirane 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 methyloxirane 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, methyloxirane meets the criterion for persistence but it does not meet the criterion for bioaccumulation potential as set out in the *Persistence and Bioaccumulation Regulations.*

References

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Appendix 1. Upper bounding estimates of daily intake of methyloxirane for the general population in Canada

Route of exposure	Estimated intake (µg/kg-bw per day) of methyloxirane by various age groups						
	0–6 months[1, 2, 3]		0.5–4 years[4]	5–11 years[5]	12–19 years[6]	20–59 years[7]	60+ years[8]
	formula fed	not formula fed					
Ambient air[9]	0.01		0.02	0.02	0.01	0.01	0.01
Indoor air[10]		0.08	0.16	0.13	0.07	0.06	0.05
Drinking water[11]	--	--	--	--	--	--	--
Food and beverages[12]		NA	0.0007	0.001	0.0008	0.001	0.0006
Soil[13]		ID	ID	ID	ID	ID	ID
Total intake	**0.09**	**0.09**	**0.18**	**0.15**	**0.08**	**0.07**	**0.06**

NA = not applicable

ID = no data

1 No data were identified for methyloxirane in breast milk.

2 Assumed to weigh 7.5 kg, to breathe 2.1 m^3 of air per day, to drink 0.8 L of water per day (formula fed) or 0.3 L/day (not formula fed) and to ingest 30 mg of soil per day (EHD 1998).

3 For formula-fed infants, intake from water is synonymous with intake from food. No data on concentrations of methyoxirane in formulae were identified. No data for methyloxirane in water in Canada were identified and a detection limit from a Japanese surface water monitoring study (Japan MOE) was considered inappropriate for use, as, based on the release pattern, physical chemical properties and uses of methyloxirane, its presence in water is expected to be minimal in comparison to levels in air.

4 Assumed to weigh 15.5 kg, to breathe 9.3 m^3 of air per day, to drink 0.7 L of water per day and to ingest 100 mg of soil and 0.1 g of nutmeat per day (EHD 1998).

5 Assumed to weigh 31.0 kg, to breathe 14.5 m^3 of air per day, to drink 1.1 L of water per day and to ingest 65 mg of soil and 0.4 g of nutmeat per day (EHD 1998).

6 Assumed to weigh 59.4 kg, to breathe 15.8 m^3 of air per day, to drink 1.2 L of water per day and to ingest 30 mg of soil and 0.5 g of nutmeat per day (EHD 1998).

7 Assumed to weigh 70.9 kg, to breathe 16.2 m^3 of air per day, to drink 1.5 L of water per day and to ingest 30 mg of soil and 0.8 g of nutmeat per day (EHD 1998).

8 Assumed to weigh 72.0 kg, to breathe 14.3 m^3 of air per day, to drink 1.6 L of water per day and to ingest 30 mg of soil and 0.4 g of nutmeat per day (EHD 1998).

9 No data for methyloxirane in ambient air in Canada were identified. The detection limit of 0.31 µg/m^3 for ambient air from a pilot study of 4 homes in Woodland, California was used to calculate the upper-bounding limit of exposure estimate (Sheldon et al. 1990). Canadians are assumed to spend three hours outdoors each day (EHD 1998).

10 No data for methyloxirane in indoor air in Canada were identified. The detection limit of 0.31µg/m^3 for indoor air from a pilot study of 2 homes in Woodland, California, in which methyloxirane was not detected, was used to calculate the upper-bounding limit of exposure estimate (Sheldon et al. 1990). Canadians are assumed to spend 21 hours indoors each day (EHD 1998).

11 No data for methyloxirane in water in Canada were identified. The maximum detection limit of 5 µg/L from a 1980 survey of 36 Japanese surface water sources (Japan MOE, searched July 2007) was considered inappropriate for calculating the upper-bounding limit of exposure estimate or concentrations in reconstituted formula for infants, as, based on the release pattern, physical chemical properties and uses of methyloxirane, its presence in water is expected to be minimal in comparison to levels in air.

12 The general maximum residue limit of 0.1 ppm for residues of methyloxirane in/on imported fumigated almonds, walnuts and pecans was used to calculate the upper-bounding limits of exposure estimate. These are the only nutmeats known to be fumigated with this pesticide; no data on methyloxirane in other food was identified. (PMRA 2006). In a study submitted to the US EPA on treated nutmeats, the highest residue level of methyloxirane, i.e., of 273 ppm, was found in almonds 28 days after fumigation (for treated nutmeats, the current US label requires the fumigators to hold (i.e., off-gas) the treated nutmeat for 28 days before shipment) (US EPA 2005). Since Canada has

not established import MRLs for this pesticide this means that food treated in the US (or elsewhere) coming into Canada cannot contain more than 0.1 ppm of methyl oxirane, as this would be a violation of the *Food and DrugsRegulations* (PMRA 2006). Consumption of nut and seeds from this food group—but excluding peanut butter—was used, as almonds, pecans and walnuts are the only known nutmeats being fumigated. No data of methyloxirane in other food was identified.

[13] No data for methyloxirane in soil in Canada were identified. The detection limit of 2 µg/kg found in 12 sediment samples from a Japanese monitoring study in 1980 (Japan MOE) was considered inappropriate for calculating the upper bounding limit of exposure estimate (similar to water above) as, based on the release pattern, physical chemical properties and uses of methyloxirane, its presence in soil is expected to be minimal in comparison to levels in air.

Appendix 2. Predicted concentrations[1] of methyloxirane in environmental media

Media	Air	Water	Soil
Concentration [2]	5.4×10^{-7} µg/m^3	1.8×10^{-5} µg/L	1.2×10^{-9} ng/g

[1] Concentrations predicted using Chemcan (version 6.0) (CEMC 2003)

[2] Model predictions were based on 100% release to air in Southern Ontario of a quantity of 50 kg/year, the cut-off reporting quantity from the recent section 71 notice under CEPA 1999 (Canada 2007).

Appendix 3. Estimates of exposure to methyloxirane from consumer products by adults [a]

Consumer product type	Assumptions	Estimated exposure
	Inhalation	
Paint stripper	• Used ConsExpo model version 4.1, exposure to vapour: evaporation as mode of release, area of release increase over time (RIVM 2007a).[b] • Based on the maximum reported weight fraction of 0.01 for methyloxirane in paint stripper (Henkel Technologies 2008) • Assume amount of product used is 1000 g/event to remove the paint from a door for a surface area of 2 m^2, an application duration and exposure duration of 60 minutes, a room volume of 20 m^3, a ventilation rate of 0.6 /hr, a mass transfer rate based on Langmuirs method and a molecular weight matrix of 84 g/mol [c] (RIVM 2007b).	Mean event concentration = 200 mg/m^3
Acrylic aerosol spray paint	• Used ConsExpo model version 4.1, exposure to vapour: evaporation as mode of release, area of release increase over time (RIVM 2007a). • Based on the voluntary submission by industry, the maximum reported percent of 0.009 in propylene carbonate used in paint spray application (Canada 2007b) • Assume paint spray can of 400 ml is sprayed, density of methyloxirane in the spray can is 0.831 g/cm^3, therefore the product amount sprayed is 332g.(RIVM 2007c) • Assumed an application duration and exposure duration of 20 minutes, a room volume of 20 m^3, a ventilation rate of 0.6 /hr, a mass transfer rate based on Langmuirs method and a molecular weight matrix of 102 g/mol [d] (RIVM 2007c).	Mean event concentration = 1.3 mg/m^3

[a] Since these products are used primarily by adults (20–59 years old), estimated exposures have been derived for this age group only.
[b] ConsExpo model version 4.1, exposure to vapour, constant rate as mode of release (for which chemical is assumed release with a constant rate in a certain time) was estimated for comparison, the exposed mean event concentration is identical at 200 mg/m^3.
[c] Molecular weight matrix is calculated based on the molecular weight of the main solvent, methylene chloride in the paint stripper,
[d] Molecular weight matrix is calculated based on the molecular weight of the main solvent , propylene carbonate in spray paint.

Appendix 4. Summary of health effects information for methyloxirane

Endpoint	Lowest effect levels
Laboratory animals and *in vitro*	
Acute toxicity	Lowest **oral LD_{50}** (rat) = 520 mg/kg-bw (Antonova et al. 1981) Lowest **inhalation LC_{50}** (mice) = 4124 mg/m^3 (Jacobson et al. 1956) Lowest **dermal LD_{50}** (rabbit) = 950–1250 mg/kg-bw (Weil et al. 1963; Smyth et al. 1969) [Additional studies: Smyth et al. 1941; Smyth et al. 1969; Blair and Osborne 1977; Antonova et al. 1981]
Short-term repeated-dose toxicity	**Lowest inhalation lowest-observed-effect concentration (LOEC)** (rat) = 362 mg/m^3 for 6 hours/day, 5 days/week for 1 or 4 weeks, based on olfactory cell proliferation (NOEC = 121 mg/m^3) (Eldridge et al. 1995) [Additional studies: Rowe et al. 1956; Blair and Osborne 1977; NTP 1985; Ohnishi et al. 1988; Rios-Blanco et al. 2003b; Morris et al. 2004; American Chemistry Council 2005; Lee et al. 2005; Morris and Pottenger 2006; Okuda et al. 2006] **Lowest oral lowest-observed-effect level (LOEL)** (rat) = 300 mg/kg-bw/day for 5 days/week for 24 days based on impaired growth, gastric irritation and slight liver damage (NOEL = 200 mg/m^3) (Rowe et al. 1956).
Subchronic toxicity	Lowest **inhalation LOEC** (rat) = 711 mg/m^3 for 6 hours/day, 5 days/week for 13 weeks, based on reduced body weight gain (NOEC = 356 mg/m^3) (Reuzel and Kuper, 1981) [Additional studies: Rowe et al. 1956; NTP 1985; Young et al. 1985]
Chronic toxicity/ carcinogenicity	**Inhalation carcinogenicity bioassays in rats:** Rats were exposed by inhalation to 0, 200 or 400 ppm (0, 482 or 964 mg/m^3) for 6 hours/day, 5 days/week for 103 weeks. In the 400 ppm groups, a low incidence of papillary adenomas was observed in the respiratory epithelium and submucosal glands of the nasal cavity, while no tumours of this type were observed in the 200 ppm or control groups (males: 0/50 control, 0/50 in 200 ppm, 2/50 in 400 ppm $p > 0.05$; females: 0/50 control, 0/50 in 200 ppm, 3/50 in 400 ppm, P=0.037 Cochran-Armitage trend test) (NTP, 1985; Renne et al. 1986). Although the results were not statistically significant, the NTP considered them to provide "*some evidence* of carcinogenicity for F344/N rats" while the European Union (EU 2002/ considered the papillary adenomas to be exposure-related in view of the rarity of this tumour in concurrent and historical controls. Rats were exposed by inhalation to 0, 30, 100 or 300 ppm (0, 72, 241 or 723 mg/m^3) for 6 hours/day, 5 days/week for 123–124 weeks. Significant increases in benign and malignant tumours of the mammary gland (fibroadenoma and adenocarcinoma respectively) were observed in females at the highest concentration (fibroadenomas: 32/69 control vs. 47/70 in 300 ppm, $p<0.04$; adenocarcinomas: 3/69 control vs. 8/70 at 300 ppm, $p<0.01$). However, these data are in the range of historical controls. Four males exposed to the highest concentration displayed carcinomas of the respiratory tract and three exposed male rats displayed malignant nasal cavity tumours (1 ameloblastic fibrosarcoma in 30 ppm group, 1 squamous cell carcinoma each in the 30 and 300 ppm groups), while none were observed in the control males or in any of the female groups. (Kuper et al. 1988)

	[Additional studies: Lynch et al. 1984a – results were confounded by *Mycoplasma* infection] **Inhalation carcinogenicity bioassay in mice:** Mice were exposed by inhalation to 0, 200 or 400 ppm (0, 482 or 964 mg/m^3) for 6 hours/day, 5 days/week for 103 weeks. Combined incidences of hemangiomas and hemangiosarcomas in the nasal cavity were significantly increased at 400 ppm compared to control and 200 ppm groups (males: 0/50 control, 0/50 in 200 ppm, 10/50 in 400 ppm (P=0.001); females: 0/50 in control, 0/50 in 200 ppm, 5/50 in 400 ppm (P=0.028)). Nasal cavity epithelial tumours were also observed in males and females of the 400 ppm group (males: 1 papilloma and 1 squamous cell carcinoma; females: 2 adenocarcinomas). Nasal epithelial tumours were not observed in the control or 200 ppm groups for this study, not were they observed in historical controls of B6C3F$_1$ mice (1615 males, 1668 females). Though no tests for statistical significance were provided, the National Toxicology Program considered these tumours to be related to methyl oxirane exposure (NTP, 1985; Renne et al. 1986). **Oral (gavage) carcinogenicity bioassay in rats:** Female rats were exposed by oral gavage to 0 (naive), 0 (vehicle – vegetable oil), 15 or 60 mg/kg-bw methyloxirane twice weekly for 150 weeks. A dose-dependent increase in the incidence of stomach tumours and other reactive changes of the stomach epithelia was observed (no statistical analysis). Squamous cell carcinomas of the forestomach (0/50 vehicle, 0/50 naive, 2/50 low dose, 19/50 high dose) adenocarcinomas of the pylorus (0/50 vehicle, 0/50 untreated, 0/50 low dose, 1/50 high dose) and carcinoma *in situ* of the forestomach (0/50 naive, 0/50 naive, 0/50 low dose, 1/50 high dose) were observed. As well, reactive changes of squamous epithelium (combined hyperkeratosis, hyperplasia, papilloma: 7/50 low dose, 17/50 high dose) occurred (Dunkelberg 1982). **Other exposure routes:** Studies by Dunkelberg (1979; 1981) and Walpole (1958) demonstrated that methyloxirane can induce local sarcomas of the injection site following subcutaneous injection in mice and rats respectively. Lowest **inhalation concentration for non-neoplastic effects** (rats) = 71 mg/m^3 for 6 hours/day, 5 days/week for 123–124 weeks based on a slight increase in the incidence of "nest-like infolds" in the nasal epithelium of exposed animals (lowest concentration tested) (Kuper et al. 1988). [Additional studies: Antonova et al. 1981; Sprinz et al. 1982; Lynch et al. 1984a; NTP 1985; Renne et al. 1986]
Reproductive toxicity	Lowest **inhalation LOEC** (rats) = 1188 mg/m^3, (only concentration tested), 7 hours/day, 5 days/week for 3 weeks prior to gestation and 7 hours/day from 3 weeks before mating to day 16 of pregnancy based on reduced corpora lutea, implantations and surviving live fetuses. These effects occurred in the presence of maternal toxicity (Hackett et al. 1982; Hardin et al. 1983a) [Additional studies: Antonova et al. 1981; Hardin et al. 1983a; Lynch et al. 1984b; Hayes et al. 1985 and 1988; Omura et al. 1994; Okuda et al. 2006]
Developmental toxicity	Lowest **inhalation LOEC** (rats) = 1188 mg/m^3, (only concentration tested), 7 hours/day, 5 days/week for 3 weeks prior to gestation and 7 hours/day from 3 weeks before mating to day 16 of pregnancy based on reduced fetal growth, wavy ribs and reduced ossification of vertebrae and ribs. These effects occurred in the presence of maternal toxicity (Hackett et al. 1982;Hardin et al. 1983a) [Additional studies: Antonova et al. 1981; Hackett et al. 1982; Hardin et al. 1983a; Hayes et al. 1985 and 1988; Harris et al. 1989; Okuda et al. 2006]

Genotoxicity and related endpoints: *in vitro*				
Endpoint	**Results and reference**			
Gene mutation	**Species, strain**	**Result**	**Metabolic activation**	**Reference**
	Salmonella typhimurium TA 97	Positive	+/-	Canter et al. 1986
		Negative	+/-	Zeiger et al. 1988
	Salmonella typhimurium TA 98	Negative	+	Bootman et al. 1979 Canter et al. 1986 Zeiger et al. 1988
			-	Bootman et al. 1979 McMahon et al. 1979 Pfeiffer and Dunkelberg 1980 Canter et al. 1986 Zeiger et al. 1988
	Salmonella typhimurium TA100	Positive	+	Bootman et al. 1979 Canter et al. 1986 Hughes 1987 Castelain et al. 1993
			-	Wade et al. 1978 Bootman et al. 1979 McMahon et al. 1979 Pfeiffer and Dunkelberg 1980 Simmon 1981 Yamaguchi 1982 Canter et al. 1986 Djuric et al. 1986 Agurell et al. 1991 Castelain et al. 1993
		Negative	+	Zeiger et al. 1988
			-	Hemminki and Falck 1979 Zeiger et al. 1988
	Salmonella typhimurium TA1535	Positive	+	Bootman et al. 1979 Canter et al. 1986 Zeiger et al. 1988 Castelain et al. 1993
			-	Wade et al. 1978 Bootman et al. 1979 McMahon et al. 1979 Pfeiffer and Dunkelberg 1980 Simmon 1981 Canter et al. 1986 Djuric et al. 1986 Agurell et al. 1991 Castelain et al. 1993
		Negative	-	Zeiger et al. 1988
	Salmonella typhimurium TA1537	Negative	+	Bootman et al. 1979 Zeiger et al. 1988
			-	Bootman et al. 1979 McMahon et al. 1979 Pfeiffer and Dunkelberg 1980 Zeiger et al. 1988
		Inconclusive	+/-	Canter et al. 1986
	Salmonella	Negative	+	Dean et al. 1985

	typhimurium TA1538		-	Dean et al. 1985 McMahon et al. 1979
	Salmonella typhimurium YG7108	Positive	Not specified	Emmert et al. 2006
	Salmonella typhimurium G46	Negative	-	McMahon et al. 1979
	Escherichia coli WP2 *uvr*A	Positive	+	Dean et al. 1985
			-	Dean et al. 1985 McMahon et al. 1979
		Negative	-	Hemminki and Falck 1979
	Escherichia coli WP2	Positive	+	Bootman et al. 1979
			-	Bootman et al. 1979 McMahon et al. 1979 Dean et al. 1985
		Negative	+	Dean et al. 1985
	Escherichia coli CM891	Positive	-	Bootman et al. 1979
	Escherichia coli CM871	Positive	-	Bootman et al. 1979
	Escherichia coli B (Arg-) Hs30R	Positive	-	Kohda et al. 1987
	Escherichia coli PQ37	Negative	+/-	Von der Hude et al. 1990
	Klebsiella pneumoniae	Positive	-	Voogd et al. 1981
	Saccharamyces cerevisiae	Positive	-	Agurell et al. 1991
	Schizosaccharomyces pombe p1	Positive	+/-	Migliore et al. 1982
	Neurospora crassa	Positive	-	Kolmark and Giles 1955
	Bacteriophage	Positive	Not specified	Garro and Phillips 1980
		Negative	-	Cookson et al. 1971
	Mouse L5178Y cells	Positive	-	McGregor et al. 1991
	Chinese hamster ovary cells, *hprt* locus	Positive	-	Zamora et al. 1983
Sister chromatid exchange	**Positive:** Chinese hamster CHO (+/-S9) (Gulati et al. 1989) Chinese hamster V79 cells (-S9) (Von der Hude et al. 1991; Von der Hude et al. 1992) Rat liver cells *in vitro* (-S9) (Dean and Hodson-Walker, 1979) Human lymphocytes *in vitro* (Tucker et al. 1986; Agurell et al. 1991)			
Chromosomal aberrations	**Positive:** Chinese hamster CHO (+/-S9) (Gulati et al. 1989) Rat liver cells *in vitro* (-S9) (Dean and Hodson-Walker, 1979; Dean et al. 1985) Human lymphocytes *in vitro* (Bootman et al. 1979)			
Micronucleus induction	**Positive:** Human lymphocytes *in vitro* (Jorritsma et al. 1995)			
DNA strand breaks	**Positive:** Rat hepatocytes *in vitro* (-S9) (Sina et al. 1983) Human diploid fibroblasts (Kolman et al. 1997; Chovanec et al. 1998) Calf thymus DNA (Walles 1974)			
DNA adducts	**Positive:** (Lawley and Jarman 1972; Walles, 1974; Hemminki et al. 1980; Randerath et al. 1981; Djuric et al. 1986; Solomon et al. 1988; Hemminki et al. 1994; Kumar et al. 1995; Plna et al. 1999)			
Differential toxicity	**Positive:** Bacteria (other) (-S9) (Bootman et al. 1979)			
SOS induction	**Positive:** *Salmonella typhimurium* TA1535/pSK1002 (+/-S9) (Ong et al. 1987) *Salmonella typhimurium* TA1535/pSK1002 (-S9) (Yasunaga et al. 2004)			

Gene conversion	**Positive:** *Saccharomyces cerevisiae* (- S9) (Agurell et al. 1991)
Cell transformation	**Positive:** Mouse embryo fibroblasts (Kolman and Duniska 1995) Syrian hamster embryo cells (Kolman and Duniska 1995) BALB/c-3T3 cells (-S9) (Matthews et al. 1993)
Genotoxicity and related endpoints: *in vivo*	
Endpoint	**Results and reference**
Micronucleus induction (bone marrow)	**Positive:** Mouse (i.p.) (Bootman et al. 1979; Farooqi et al. 1993) Rat (i.p) (Wakata et al. 1998) **Negative:** Mouse (oral) (Bootman et al. 1979) Mouse (i.p.) (Shelby et al. 1993)
Micronucleus induction (peripheral blood)	**Positive:** Rat (i.p) (Wakata et al. 1998) **Negative:** Cynomolgus monkeys (inhalation) (Lynch et al. 1984b)
Chromosomal aberrations (bone marrow)	**Positive:** Mouse (i.p.) (Farooqi et al. 1993; NTP database 1989–1993)
Sister chromatid exchange (bone marrow)	**Positive:** Mouse (i.p.) (Farooqi et al. 1993; NTP database 1989)
Sister chromatid exchange (peripheral blood)	**Negative:** Cynomolgus monkeys (inhalation) (Lynch et al. 1984b)
DNA lesions in bone marrow, stomach and colon	**Positive:** Mouse (i.p.) (Tsuda et al. 2000)
Dominant lethal assay	**Negative :** Rat (inhalation) (Hardin et al. 1983b) Mouse (oral) (Bootman et al. 1979)
Sex-linked recessive lethal mutation	**Positive:** *Drosophila* (vapour) (Hardin et al. 1983b; Vogel and Nivard 1997; Vogel and Nivard 1998; Nivard et al. 2003) *Drosophila* (oral) (Foureman et al. 1994)
Reciprocal translocations	**Positive:** *Drosophila* (oral) (Foureman et al. 1994)
DNA adducts	**Positive:** *Drosophila* (vapour) (Nivard et al. 2003) Mouse, rat or dog (inhalation, i.p. or i.v.) (Segerback et al. 1994) Mouse (i.p.) (Svensson et al. 1991) Rats (inhalation) (Snyder and Solomon 1993; Segerback et al. 1998; Plna et al. 1999; Osterman-Golkar et al. 2003; Rios-Blanco et al. 2003a)
Chromosome loss	**Positive:** *Drosophila* (vapour) (Vogel and Nivard, 1998)
Humans	
Chronic toxicity/ Carcinogenicity	IARC, 1994 and EU, 2002 examined a number of occupational cohort studies and an occupational case-control study and concluded that no conclusions with respect to carcinogenicity of methyloxirane could be drawn (Stocker and Thiess 1979; Thiess et al. 1982; Hogstedt et al. 1979, 1986; Hogstedt 1988; Gardner et al. 1989; Ott et al. 1989)
Genotoxicity and related endpoints	EU 2002 reviewed six studies involving occupational exposure and noted that no conclusions could be drawn from these studies regarding the mutagenicity of

	methyloxirane in humans (Theiss et al. 1981; Pero et al. 1982 and 1985; Van Sittert and de Jong 1985; de Jong et al. 1988; Hogstedt et al. 1990; Viktorova et al. 1994) A pilot study of a group of eight workers exposed to methyloxirane for 2 years or more (levels historically < 10 ppm and measured to be up to 7 ppm the day before blood sampling), had significantly increased blood levels of DNA adducts and sister chromatid exchanges when compared to 8 control subjects although confounding factors contributing to cytogenetic effects could not be excluded (Czene et al. 2002)
Sensitization, irritation and other	Case reports of allergic contact dermatitis (Van Ketel 1979; Jensen 1981; Steinkraus and Hausen 1994; Morris et al. 1998) Case report of corneal burns (McLaughlin 1946) Case report of symptoms, including respiratory tract and eye irritation (Gosselin et al. 1984)
Haemoglobin adducts	Increased levels observed in small sample populations; (Osterman-Golkar et al. 1984; Kautiainen and Tornqvist 1991; Boogaard et al. 1999; Czene et al. 2002)