

**Screening Assessment for the Challenge**

**Benzene, (chloromethyl)-  
(Benzyl chloride)**

**Chemical Abstracts Service Registry Number  
100-44-7**

**Environment Canada  
Health Canada**

**November 2009**

## Synopsis

Pursuant to section 74 of the *Canadian Environmental Protection Act, 1999* (CEPA 1999), the Ministers of the Environment and of Health have conducted a screening assessment of benzene, (chloromethyl)-, also known as benzyl chloride, Chemical Abstracts Service Registry Number 100-44-7. This substance was identified in the categorization of the Domestic Substances List (DSL) as a high priority for action under the Challenge. Benzyl chloride was identified as presenting greatest potential for exposure of individuals in Canada and had been classified by other agencies on the basis of carcinogenicity and genotoxicity. Although the substance met the categorization criteria for persistence, it did not meet the criteria for bioaccumulation potential or inherent toxicity to aquatic organisms; therefore, the focus of this assessment relates primarily to human health aspects.

According to data submitted in response to a Notice issued under section 71 of the Act, no persons in Canada reported manufacturing benzyl chloride in a quantity greater than or equal to the reporting threshold of 100 kg for the 2006 calendar year. However, it was reported that 100 000–1 000 000 kg were imported into Canada in that year. The response to the section 71 notice indicated that benzyl chloride is mainly used in Canada as a chemical intermediate for the synthesis of quaternary ammonium compounds, which are used primarily as hard surface sanitizers, corrosion inhibitors, fungicides in industrial cleaners and bactericides in surfactants in household and personal care products. Based on information presented in the available scientific and technical literature, benzyl chloride is also used as an intermediate in the organic synthesis of benzyl alcohol and benzyl butyl phthalate, which are used in a wide spectrum of applications, including pharmaceuticals, cosmetic formulations, flavour products, solvents, textile dyes and plasticizers in vinyl flooring and other flexible polyvinyl chloride uses, such as food packaging.

Emissions of benzyl chloride into the ambient environment are expected to be primarily from anthropogenic sources where it is used as a chemical intermediate. However, due to its use in captive reactions, such emissions are likely to be low. Benzyl chloride has been detected in stack emissions from waste incineration, and it might also be present in atmospheric emissions from the burning of some fossil fuels. Based on its physical and chemical properties, the principal route of exposure to benzyl chloride for the general population is likely through inhalation. Exposures due to use of products containing residual quantities of benzyl chloride are predicted to be low.

Based principally on weight of evidence–based assessments of international and other national agencies, the critical effect for the characterization of risks to human health from exposure to benzyl chloride is carcinogenicity. Increased incidences of tumours at multiple sites, including the forestomach, thyroid, lung, liver and circulatory system, were observed in rats and mice exposed via the oral route. There was also limited evidence of skin tumours in mice dermally exposed to benzyl chloride. In addition, epidemiological studies suggested limited evidence of respiratory and digestive system cancers in occupationally exposed populations. Benzyl chloride was genotoxic in a wide

range of *in vitro* studies as well as in some *in vivo* studies. Although the mode of induction of tumours by benzyl chloride has not been elucidated, it cannot be precluded that the tumours observed in experimental animals resulted from direct interaction with genetic material. On the basis of the carcinogenic potential of benzyl chloride, for which there may be a probability of harm at any exposure level, it is concluded that benzyl chloride 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.

Benzyl chloride meets the criterion for persistence in air but not the bioaccumulation criteria as set out in the *Persistence and Bioaccumulation Regulations*. Furthermore, it is expected to have a moderate potential for toxicity to aquatic organisms. Based on this information and the expected low environmental concentrations, it is concluded that benzyl chloride 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.

This substance will be included in the Domestic Substances List inventory update initiative. 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, it is concluded that benzyl chloride meets one or more of the criteria set out in section 64 of CEPA 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 to human health.

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

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

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

The substance benzyl chloride was identified as a high priority for assessment of human health risk because it was considered to present GPE and had been classified by other agencies on the basis of carcinogenicity.

The Challenge for benzyl chloride was published in the *Canada Gazette* on May 31, 2008 (Canada 2008). 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 benzyl chloride was determined to be a high priority for assessment with respect to human health and also met the ecological categorization criteria for persistence, it did not meet the criteria for bioaccumulation potential or inherent toxicity to aquatic organisms. Therefore, this assessment focuses principally on information relevant to the evaluation of risks to human health.

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 CEPA 1999. 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 and stakeholder research reports and from recent literature searches, up to December 2008 for the health effects and exposure sections of the document. 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 of 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. The ecological and human health portions of this assessment have 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 Dr. Lynne Haber (TERA), Dr. Michael Jayjock (The Lifeline Group) and Dr. John Christopher (California Department of Toxic Substances Control). Additionally, the draft of this screening assessment was subject to a 60-day public comment period. Although 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.


The critical information and considerations upon which the assessment is based are summarized below.

### **Substance Identity**

For the purposes of this document, this substance will be referred to as benzyl chloride. Its substance identity information is summarized in Table 1.

**Table 1. Substance identity for benzyl chloride**

<b>CAS RN</b>	100-44-7
<b>DSL name</b>	Benzene, (chloromethyl)-

<b>NCI names</b>	Benzene, (chloromethyl)- (AICS, ASIA-PAC, PICCS, SWISS, TSCA) Benzene, chloromethyl- (PICCS) Benzyl chloride (PICCS, TAIWAN) Benzyl chloride (ENCS) (Chloromethyl)benzene (ECL) $\alpha$ -Chlorotoluene (EINECS)
<b>Other names</b>	1-Chloromethylbenzene; Chloromethylbenzene; Chlorophenylmethane; NSC 8043; Phenylmethyl chloride; Toluene, $\alpha$ -chloro-; Toly chloride; UN 1738; UN 1738 (DOT)
<b>Chemical group (DSL stream)</b>	Discrete organics
<b>Major chemical class or use</b>	Chlorinated organics
<b>Major chemical subclass</b>	Aromatic chlorinated organics
<b>Chemical formula</b>	C <sub>7</sub> H <sub>7</sub> Cl
<b>Chemical structure</b>	
<b>SMILES</b>	c(ccc1)(c1)CCl
<b>Molecular mass</b>	126.59 g/mol

Abbreviations: AICS, Australian Inventory of Chemical Substances; ASIA-PAC, Asia-Pacific Substances Lists; CAS RN, Chemical Abstracts Service Registry Number; DSL, Domestic Substances List; ECL, Korean Existing Chemicals List; EINECS, European Inventory of Existing Commercial Chemical Substances; ENCS, Japanese Existing and New Chemical Substances; PICCS, Philippine Inventory of Chemicals and Chemical Substances; SWISS, Swiss Giftlist 1 and Inventory of Notified New Substances; SMILES, simplified molecular input line entry specification; TAIWAN, Taiwan Toxic Chemical Substances List; TSCA, Toxic Substances Control Act Chemical Substance Inventory.

Source: NCI (2006)

## Physical and Chemical Properties

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

**Table 2. Physical and chemical properties of benzyl chloride**

Property	Type	Value <sup>1</sup>	Rating	Reference
Melting point (°C)	Experimental	-45	-	CRC 2008
Boiling point (°C)	Experimental	179	-	CRC 2008
Density (g/mL at 20°C)	Experimental	1.10	-	Merck Index 2006
Vapour pressure (Pa at 25°C)	Experimental	163.9 (1.23 mmHg)	High	Lide and Milne 1994
Henry's Law constant (Pa·m <sup>3</sup> /mol)	Modelled	41.8 (4.12 × 10 <sup>-4</sup> atm·m <sup>3</sup> /mol)	Moderate	PhysProp 2006
Water solubility (mg/L at 25°C)	Experimental	525	Moderate	Ohnishi and Tanabe 1971
Log K <sub>ow</sub> (dimensionless)	Experimental	2.30	Low	Howard 1989
Log K <sub>oc</sub> (dimensionless)	Modelled	2.71	Moderate	PCKOCWIN 2000

Abbreviations: K<sub>oc</sub>, organic carbon partition coefficient; K<sub>ow</sub>, octanol–water partition coefficient.

<sup>1</sup> The values in parentheses are the values originally reported in the references.

## Sources

Benzyl chloride is not found to occur naturally. According to data submitted in response to a section 71 notice under CEPA 1999, no companies in Canada reported manufacturing benzyl chloride in a quantity greater than or equal to the reporting threshold of 100 kg for the 2006 calendar year. However, it was reported that this substance was imported into Canada in the range of 100 000–1 000 000 kg in the same year (Environment Canada 2008a).

## Uses

According to data submitted under section 71 of CEPA 1999, benzyl chloride is reported to be used in Canada only as a chemical intermediate for the synthesis of benzalkonium chloride, which belongs to the group of quaternary ammonium compounds. End-use applications of quaternary ammonium compounds are as an active ingredient in pest control products or as a surfactant in numerous products (e.g., hard surface sanitizers, corrosion inhibitors, industrial and institutional cleaners, and household and personal care products) (CNS 2008). Quaternary ammonium compounds also function as bactericides

in hair care products and as surfactants in machine dishwashing detergents, architectural paints and coatings for marine yachts and industrial steel (Seper 2001; Davis and Yokose 2007; Environment Canada 2008a). The total quantity of benzyl chloride reported under section 71 to be used during the year 2006 was in the range of 100 000–1 000 000 kg.

Based on information identified in other available scientific and technical literature, benzyl chloride may also be used as an intermediate in the organic synthesis of benzyl alcohol and benzyl butyl phthalate. Benzyl alcohol is used in a wide spectrum of applications, such as in pharmaceuticals; natural health products, both as medicinal (mostly in anorectal, topical anaesthetic/analgesic/antipruritic and throat lozenge products) and as non-medicinal ingredients (as antimicrobial preservative, flavouring agent and solvent); in cosmetic formulations as a fragrance; and in flavour products, solvents and textile dyes (Seper 2001). Benzyl butyl phthalate is used mainly as a plasticizer in vinyl flooring and other flexible polyvinyl chloride (PVC), such as food packaging (Seper 2001; Davis and Yokose 2007; HSDB 2008). In the United States, benzyl alcohol is no longer produced from benzyl chloride but rather is produced from the hydrogenation of benzaldehyde (Davis and Yokose 2007).

Benzyl chloride may also be used in the manufacture of photographic developer and gasoline gum inhibitors (Lewis 2001).

This substance has not been reported in the cosmetic notification system and is therefore not deliberately added to cosmetics in Canada (CNS 2008); however, this substance is not currently listed on Health Canada's Cosmetic Ingredient Hotlist, which are intended to be prohibited or restricted for use in cosmetics, including many personal care products under Canadian legislation (Health Canada 2007). In Canada, benzyl chloride is listed as a List 2 formulant in one commercial class of pest control products, but it is not registered as an active ingredient under the *Pest Control Products Act* (PMRA 2007, 2008). Trace amounts of benzyl chloride may be present as manufacturing impurities in some pest control products containing quaternary ammonium compounds as active ingredients (2009 email from Pest Management Regulatory Agency, Health Canada, to Existing Substances Division, Health Canada; unreferenced). Benzyl chloride is not listed in the Drug Product Database, Natural Health Products Ingredients Database or Licensed Natural Health Products Database and is therefore unlikely to be present in pharmaceutical or natural health products as a medicinal or non-medicinal ingredient. However, benzalkonium chloride is a known antimicrobial preservative and is listed in the Natural Health Products Ingredients Database as an acceptable non-medicinal ingredient with specific concentration limits based on the route of administration of the product in which it is a preservative, to mitigate any possible risk to health (2009 emails from Therapeutic Products Directorate and Natural Health Products Directorate, Health Canada, to Existing Substances Division, Health Canada; unreferenced). The *Controlled Products Regulations* established under the *Hazardous Products Act* require this substance to be disclosed on the Material Safety Data Sheet that must accompany workplace chemicals when it is present at a concentration of 1% or greater as specified on the Ingredient Disclosure List (Canada 1988).

## Releases to the Environment

Benzyl chloride is not manufactured in Canada, and its release into the environment may occur from industrial processing of chemical intermediates, product preparation, emission from waste incineration and thermal degradation of PVC. Benzyl chloride is also detected in wastewater from incineration and combustion facilities (US EPA 1993; Lee et al. 1996). Fugitive emission or venting during the handling, transport or storage of benzyl chloride could be a source of emission to the atmosphere. Emissions of benzyl chloride may also occur during burning of fossil fuels (US EPA 1993). However, in studies conducted by the Science and Technology Branch of Environment Canada at coal-fired power plants, iron and steel facilities, landfills, and solid and hazardous waste incinerator sites, it was found that benzyl chloride was not released in any significant quantities (2009 emails from Emission Research and Measurement Section, Environment Canada, to Existing Substances Division, Health Canada; unreferenced). Residual benzyl chloride emitted from floor tile manufactured from benzyl butyl phthalate and from degradation of PVC and rigid urethane foam compound has also been reported (US EPA 1986).

Under the National Pollutant Release Inventory, industrial facilities in Canada reported a release of 5 kg and 1 kg of benzyl chloride to air in the years 2000 and 2006, respectively. No releases to water or land have been reported (NPRI 2006). In recent information gathered under CEPA 1999 through a section 71 notice with respect to benzyl chloride, companies reported no release of this substance in 2006 (Environment Canada 2008a).

## Environmental Fate

Based on its physical and chemical properties (Table 2), the results of Level III fugacity modelling suggest that benzyl chloride will reside predominantly in the compartment to which it is released (Table 3).

**Table 3. Results of Level III fugacity modelling (EQC 2003)**

Substance released to:	Fraction of substance partitioning to each medium (%)			
	Air	Water	Soil	Sediment
Air (100%)	91.8	6.28	1.92	0.04
Water (100%)	7.80	91.5	0.16	0.54
Soil (100%)	4.02	3.83	92.1	0.02

A high vapour pressure of 163.9 Pa indicates that benzyl chloride is volatile; if released to air, it will exist solely as a vapour in the ambient atmosphere (HSDB 2008). Reaction with hydroxyl radicals will be the dominant removal mechanism.

If released into water, benzyl chloride is expected to moderately adsorb to suspended solids and sediment based upon the moderate estimated log  $K_{oc}$  of 2.71. Hydrolysis will

be the dominant removal mechanism, with a hydrolysis half-life of 9.48 hours at pH 7 and 25°C. Volatilization from water surfaces is a possible fate process, based upon this compound's estimated Henry's Law constant (Howard 1989).

If released to soil, benzyl chloride will remain mainly in this compartment, as illustrated by the Level III fugacity modelling result, and will have moderate adsorptivity, based upon an estimated log  $K_{oc}$  of 2.71. Mobility in soil may be mitigated based on the hydrolysis of benzyl chloride in water. However, benzyl chloride may volatilize from dry soil surfaces based upon its high vapour pressure (HSDB 2008).

## Persistence and Bioaccumulation Potential

### Environmental Persistence

Table 4 presents the empirical degradation data for benzyl chloride. The biodegradation datum (MITI 1992) shows 71% biodegradation over 28 days in a ready-biodegradation test for benzyl chloride, indicating that the ultimate degradation half-life in water is “days or weeks”—much shorter than 182 days—and that the substance is unlikely to persist in that environmental compartment. In addition, there is evidence that benzyl chloride rapidly hydrolyses; the hydrolysis half-life at pH 7 and 25°C is reported to be 9.48 hours (OECD 1998). The hydrolysis product, benzyl alcohol is in turn relatively easy biodegraded (Howard 1989). The photodegradation datum indicates a half-life (reaction with hydroxyl radicals) of 3.69 days in air, indicating that the substance is likely to persist in that environmental compartment.

The characteristic travel distance for this substance is estimated to be 1105 km (TaPL3 2000). This indicates that benzyl chloride is expected to be transported through the atmosphere to areas moderately far from its emission source.

**Table 4. Empirical data for persistence**

Medium	Fate process	Degradation value	Endpoint/units	Reference
Air	Photodegradation	3.69	Half-life, days	Atkinson 1989
Water	Biodegradation	71	% BOD/28 days	MITI 1992
Water	Hydrolysis	9.48	Half-life, hours	OECD 1998

Abbreviation: BOD = biological oxygen demand.

This empirical biodegradation information is supported by results of available quantitative structure–activity relationship (QSAR) models for biodegradation in water (BIOWIN 2000; TOPKAT 2004; CATABOL c2004–2008). The overall conclusion from BIOWIN (2000) is that benzyl chloride is readily biodegradable. Other ultimate degradation models (TOPKAT 2004; CATABOL c2004–2008) also predict that benzyl chloride undergoes relatively rapid mineralization.

The empirical and modelled data indicate that the ultimate degradation half-life of benzyl chloride in water is much less than 182 days and strongly suggest that it is less than 90 days. Using an extrapolation ratio of 1:1:4 for water:soil:sediment biodegradation half-lives (Boethling et al. 1995), the half-life in soil is also expected to be less than 182 days, and the half-life in sediments is expected to be less than 365 days, based on a half-life in water of less than 90 days. This indicates that benzyl chloride is not expected to be persistent in soil or sediment.

Based on the empirical (see Table 4) and modelled data, benzyl chloride does not meet the persistence criteria in water, soil or sediment (half-lives in soil and water  $\geq 182$  days and half-life in sediment  $\geq 365$  days), but it does meet the criterion for air (half-life in air  $\geq 2$  days) as set out in the *Persistence and Bioaccumulation Regulations* (Canada 2000).

### Potential for Bioaccumulation

Experimental log  $K_{ow}$  values for benzyl chloride suggest that this chemical has a relatively low potential to bioaccumulate in the environment (see Table 2).

As no experimental data on bioaccumulation factors (BAFs) or bioconcentration factors (BCFs) for benzyl chloride were available, a predictive approach was applied using the BAF and BCF models shown in Table 5. Information on the metabolism of benzyl chloride in fish was not available, nor was it considered in the bioaccumulation models.

**Table 5. Modelled data for bioaccumulation of benzyl chloride**

Test organism	Endpoint	Value (L/kg wet weight)	Reference
Fish	BAF	13.58	Arnot and Gobas 2003
Fish	BCF	11.12	Arnot and Gobas 2003
Fish	BCF	63	BBM 2008
Fish	BCF	11.75	BCFWIN 2000

The modified Gobas BAF middle trophic level model for fish predicted a BAF of 13.58 L/kg, indicating that benzyl chloride does not have the potential to bioconcentrate and biomagnify in the environment. The results of BCF model calculations also support the low bioconcentration potential of the substance.

Based on the available empirical and kinetic-based modelled values, benzyl chloride does not meet the bioaccumulation criteria (BCF, BAF  $\geq 5000$ ) as set out in the *Persistence and Bioaccumulation Regulations* (Canada 2000).

### Potential to Cause Ecological Harm

There are experimental aquatic toxicity data for benzyl chloride. Representative values from the Organisation for Economic Co-operation and Development (OECD) Screening Information Dataset Initial Assessment Report (OECD 1998) and data from other sources are presented in Tables 6a and 6b. Some of the experimental and modelled data indicate

that benzyl chloride can harm aquatic organisms at low to moderate concentrations; the modelled results may overestimate toxicity (especially to fish), as they do not account for the rapid hydrolysis of the substance to the less toxic benzyl alcohol (OECD 1998). The experimental and modelled data show that benzyl chloride has moderate acute toxicity to aquatic organisms.

**Table 6a. Empirical data for aquatic toxicity**

Test organism	Type of test	Endpoint	Value (mg/L)	Reference
<i>Daphnia magna</i> (water flea)	Acute (24 h)	LC <sub>50</sub>	8.40	Brinkmann and Kuhn 1982
<i>Daphnia magna</i> (water flea)	Acute (24h)	EC <sub>50</sub>	1.30	Brinkmann and Kuhn 1982
<i>Pimephales promelas</i> (fathead minnow)	Acute (24 h)	LC <sub>50</sub>	12.50	Curtis et al. 1978
<i>Pimephales promelas</i> (fathead minnow)	Acute (48 h)	LC <sub>50</sub>	7.30	Curtis et al. 1978
<i>Pimephales promelas</i> (fathead minnow)	Acute (96 h)	LC <sub>50</sub>	5.00	Curtis et al. 1978
<i>Poecilia reticulata</i> (guppy)	Acute (14 days)	LC <sub>50</sub>	0.39	Konemann 1981

Abbreviations: EC<sub>50</sub>, the concentration of a substance that is estimated to cause some toxic sublethal effect to 50% of the test organisms; LC<sub>50</sub>, the concentration of a substance that is estimated to be lethal to 50% of the test organisms.

**Table 6b. Modelled data for aquatic toxicity**

Test organism	Type of test	Endpoint	Value (mg/L)	Reference
Fish	Acute (96 h)	LC <sub>50</sub>	0.26	EPIsuite 2007
Fish	Acute (14 days)	LC <sub>50</sub>	0.17	EPIsuite 2007
Green alga	Chronic	Chv	63.74	EPIsuite 2007
Daphnid	Acute (48 h)	LC <sub>50</sub>	16.84	EPIsuite 2007
<i>Pimephales promelas</i> (fathead minnow)	Acute (96 h)	LC <sub>50</sub>	2.70	AIEPS 2003–2007
<i>Daphnia magna</i> (water flea)	Acute (48 h)	EC <sub>50</sub>	6	TOPKAT 2004
Fish	Acute (14 days)	LC <sub>50</sub>	34.86	ECOTOX 2006

Abbreviations: Chv, the concentration of a substance that causes the chronic effect of a decrease in biomass; EC<sub>50</sub>, the concentration of a substance that is estimated to cause some toxic sublethal effect to 50% of the test organisms; LC<sub>50</sub>, the concentration of a substance that is estimated to be lethal to 50% of the test organisms.

One study was found for effects of benzyl chloride on soil-dwelling organisms. The 96-hour LC<sub>60</sub> for *Panagrellus redivivus* (Nematoda) is approximately 126 mg/L (Samoiloff et al. 1980). No studies were found for the effects of benzyl chloride on birds, plants or sediment-dwelling organisms.

A conservative predicted no-effect concentration (PNEC) of benzyl chloride in water was derived using the lowest empirical acute toxicity value identified. The critical toxicity

value for this assessment is the 14-day  $LC_{50}$  of 0.39 mg/L for acute toxicity to the guppy (Table 6a). An application factor of 100 was applied to account for uncertainty in extrapolating from a measure of acute to chronic effects, from laboratory to field conditions and for intraspecies and interspecies variations in sensitivity, giving a PNEC of 0.0039 mg/L.

Available monitoring data are summarized in the exposure assessment section below under “Potential to Cause Harm to Human Health”. However, no monitoring data were identified for concentrations of benzyl chloride in water or soil in Canada.

Benzyl chloride is used in Canada mainly as a chemical intermediate, and high volumes are used at certain facilities. It has the potential to be released to water, and fugacity modelling indicates that once benzyl chloride has been released to water, it tends to remain in that medium. While not persistent in water, there is potential for ongoing or repeated releases. Experimental and modelled data indicate that benzyl chloride has moderate acute toxicity to aquatic organisms. Therefore, an aquatic predicted environmental concentration (PEC) was modelled and the associated risk quotient (PEC/PNEC) was calculated. A number of industrial sites were identified as the sources of potential aquatic releases. One site was selected for evaluation of a worst-case scenario due to the large quantity of benzyl chloride used. At this particular site, the highest possible release amount was estimated as 5% of the quantity used; this is a conservative estimate of the amount that could be released as a result of the cleaning of chemical containers and process equipment. The release amount was then assumed to discharge directly to a local biological sewage treatment plant (STP), which provides a removal rate of 66.5%, as predicted by computer models (SimpleTreat 1997). Benzyl chloride in the STP effluent is further assumed to be released to a receiving water body that has a dilution capacity of 10 times the effluent flow. Based on the highest possible release amount estimated and the above-mentioned assumptions, the highest concentration of benzyl chloride in the receiving water is estimated to be below the PNEC of 0.0039 mg/L. Thus, under a worst-case industrial release scenario, the aquatic risk quotient is estimated to be below 1 (Environment Canada 2008b, c).

Benzyl chloride is most likely released to air. Based on effect levels for non-cancer effects in inhalation studies in experimental mammalian species summarized in the human health assessment (below), the risk to non-human species associated with airborne benzyl chloride is considered to be low.

Benzyl chloride is not predicted to be persistent in water, soil or sediment, but is persistent in air. It is not expected to bioaccumulate in organisms and is expected to have a moderate potential toxicity to aquatic organisms. In considering the current use pattern and release information, it is predicted that benzyl chloride would be released in relatively small quantities, mainly to air, but also to some extent to water. The toxicity data and calculated risk quotient indicate that benzyl chloride is unlikely to cause harmful effects in aquatic organisms. It is concluded that benzyl chloride is not likely causing ecological harm in Canada.

## Uncertainties in Evaluation of Ecological Risk

Most of the uncertainty surrounding the risk characterization of benzyl chloride relates to exposure. Although there are reliable data for current use patterns, there is uncertainty about the quantity released to water. Additionally, there are no monitoring data for concentrations of benzyl chloride in water. Releases of benzyl chloride to water from industrial facilities and the benzyl chloride concentration in industrial effluent were therefore modelled, with inputs from conservative model default values.

## Potential to Cause Harm to Human Health

### Exposure Assessment

Benzyl chloride has been measured in both ambient and indoor air in Canada and the United States. Ambient air samples from National Air Pollution Surveillance (NAPS) sites of selected Canadian cities in the 2001–2003 survey contained levels ranging from 0.002 to 1.17  $\mu\text{g}/\text{m}^3$ , with a mean of 0.022  $\mu\text{g}/\text{m}^3$  (2009 email from Analysis and Air Quality Section, Environment Canada, to Existing Substances Division, Health Canada; unreferenced). More recently, the highest Canadian ambient air concentration reported in Windsor, Ontario, in the summer of 2006 was 0.029  $\mu\text{g}/\text{m}^3$  (mean 0.001  $\mu\text{g}/\text{m}^3$ ), which is similar to the mean value from the NAPS study. Under the Windsor Ontario Exposure Assessment Study, sampling was performed in the winter and summer periods of 2005 and 2006 (Health Canada 2008). Air samples from five sites in Fort Saskatchewan, Alberta, a highly concentrated industrial area, from September 2004 to March 2006 contained maximum levels ranging from 0.010 to 0.018  $\mu\text{g}/\text{m}^3$  (Environment Canada 2006). In earlier studies from the US hazardous air pollutants measurement program conducted in the 1980s, it was reported that ambient air levels in US cities ranged up to 8.28  $\mu\text{g}/\text{m}^3$  (Shah and Singh 1988; Spicer et al. 1996).

With respect to indoor air, a maximum concentration of 0.073  $\mu\text{g}/\text{m}^3$  (mean 0.003  $\mu\text{g}/\text{m}^3$ ) was measured in Windsor, Ontario, homes in the summer of 2006 (Health Canada 2008). There was no correlation between residential structure characteristics (age and heating system) and levels of benzyl chloride in winter–summer indoor air samples of five homes in North Carolina in the 1980s. However, benzyl chloride was detected only in indoor air samples taken during the winter at levels much higher (mean concentration of 32  $\mu\text{g}/\text{m}^3$ ) (Pleil et al. 1986) than those measured more recently in Canadian homes.

No monitoring data for benzyl chloride in drinking water or soil were identified. Concentrations in these media are likely to be negligible, as the substance hydrolyzes rapidly. Benzyl chloride was not detected in water or sediment samples from rivers in Japan or in water samples from the surrounding sea (Japan Ministry of Environment 2004).

There were no available monitoring data for benzyl chloride in food or beverages; however, concentrations in food and beverages are expected to be negligible, based on

the uses and physical and chemical properties of the substance. Incidental contact of fruits packaged in bins coated with primer containing residual benzyl chloride has been identified; however, exposure was considered negligible (2009 email from Food Directorate, Health Canada, to Existing Substances Division, Health Canada; unreferenced). The benzalkonium chloride used in natural health products as an antimicrobial preservative is normally used in low concentrations within the toxicity limits in the Natural Health Products Ingredients Database (2009 email from Natural Health Products Directorate, Health Canada, to Existing Substances Division, Health Canada; unreferenced). Exposure to benzyl chloride present as manufacturing impurities in an identified commercial-class pest control product is likely to be negligible due to the nature of its use and application (2009 email from Pest Management Regulatory Agency, Health Canada, to Existing Substances Division, Health Canada; unreferenced).

The most recent (2006) maximum ambient and indoor air values from Windsor, Ontario, were used to calculate the upper-bounding estimates of daily intake (Appendix 1). The highest concentration reported in the NAPS survey ( $1.17 \mu\text{g}/\text{m}^3$ ) was determined to be an outlier and thus was not used. The estimates calculated for all media range from  $0.01 \mu\text{g}/\text{kg}$  body weight (kg-bw) per day for adults 60+ years of age to  $0.04 \mu\text{g}/\text{kg}$ -bw per day for children aged 6 months to 4 years, with indoor air contributing significantly more than outdoor air.

The use of benzyl chloride as an active ingredient is not identified in the US Household Products Database (HPD 2009). However, based on the available information, benzyl chloride may be present as an impurity in some household products, such as machine dishwashing detergent, and some personal care products, including hair conditioners and shower gels (IPCS 1999; Seper 2001; Environment Canada 2008a). Scenarios in ConsExpo (ConsExpo 2006; RIVM 2006) were used to estimate inhalation and dermal exposures during use of these products, and the results are presented in Appendix 2. As the consumer products for which data are available are used primarily by adults, the estimates of exposure have been derived for adults only. The inhalation and dermal exposures from the use of machine dishwashing detergent were estimated to be negligible; however, the calculation cannot be shown because of the confidentiality of data for the product. Dermal exposure from the use of hair conditioner and shower gel products is based on the assumption that 1% of benzalkonium chloride with benzyl chloride at a maximum residual level of 100 mg/kg (0.01%) is used in these personal care products (Environment Canada 2008a).

The highest predicted airborne concentration during the use of a consumer product (hair conditioner) is  $1.3 \mu\text{g}/\text{m}^3$ , whereas estimated dermal exposure from use of consumer products could range up to  $0.2 \mu\text{g}/\text{kg}$ -bw as an acute dose per event (hair conditioner) and up to  $0.1 \mu\text{g}/\text{kg}$ -bw per day if amortized for chronic exposure (shower gel). Benzyl chloride was also identified as being used in industrial cleaners, architectural paints and primers/coatings for industrial steel and marine yachts; however, use of these products was limited to professional use only and was not considered to be widespread enough to be appropriate for extrapolation to the general population (Environment Canada 2008a;

2009 email from Products Division, Environment Canada, to Existing Substances Division, Health Canada; unreferenced).

Emissions of residual benzyl chloride from vinyl floor tiles containing benzyl butyl phthalate as a plasticizer have been reported. However, the use of benzyl chloride to synthesize this plasticizer (an important application in the United States) has not been identified in Canada. Therefore, vinyl floor tiles are unlikely to represent a source of exposure to benzyl chloride in Canada.

Confidence in the upper-bounding estimate of intakes of benzyl chloride through environmental media is considered to be high, as recent Canadian monitoring data were available for the most relevant media of exposure (i.e., indoor and ambient air). Although no data were available for drinking water, soil or food, it is expected that these media are not significant sources of exposure. Although there is uncertainty associated with the limited information on the presence or concentrations of the substance in products available in Canada, the estimates of exposure from the use of personal care products containing benzyl chloride were based on conservative assumptions and may overestimate actual exposures.

### **Health Effects Assessment**

A summary of the available health effects information for benzyl chloride is presented in Appendix 3.

The European Commission (1999) has classified benzyl chloride as a Category 2 carcinogenic substance (which should be regarded as if it is carcinogenic to humans), whereas the US Environmental Protection Agency (EPA) has classified it as a Group B2 carcinogen (probable human carcinogen) (US EPA 2008), and the International Agency for Research on Cancer (IARC 1999) has classified the chemical as a Group 2A carcinogen (“combined exposures to  $\alpha$ -chlorinated toluenes and benzoyl chloride are probably carcinogenic to humans”). These classifications were based principally on observation of increases in tumour incidences in long-term bioassays in rodents.

Tumours were observed at multiple sites in both rats and mice treated with benzyl chloride. In a 2-year study, rats were orally administered benzyl chloride at a dose of 6.4 or 12.9 mg/kg-bw per day, whereas mice were exposed to 21.4 or 42.9 mg/kg-bw per day. A statistically significant increase in thyroid C-cell adenoma/carcinoma was observed in high-dose female rats, whereas a statistically insignificant increase in the incidence of carcinoma/papilloma was observed in the forestomach of male rats. In mice at the high dose, males had statistically significant increases in the incidences of hemangioma/hemangiosarcoma, forestomach carcinoma and forestomach carcinoma/papilloma, whereas females had statistically significant increases in the incidence of forestomach carcinoma/papilloma and lung alveolar-bronchiolar adenoma/carcinoma. A statistically significant increase in the incidence of hepatocellular carcinoma/adenoma was observed in low-dose male mice, although in the absence of a dose-response relationship (Lijinsky 1986). Epithelial hyperplasia was also observed in

the stomachs of mice at doses at which significant increases in forestomach tumours were also noted (Lijinsky 1986). Several dermal carcinogenicity studies in mice were also identified (Fukuda et al. 1981; Ashby et al. 1982; Coombs 1982a, b), although the results of only one of these studies (Fukuda et al. 1981) provided evidence for carcinogenicity (a slightly increased incidence of squamous cell carcinomas of the skin). No long-term inhalation studies were identified.

Two relevant epidemiological studies were identified. In a cohort mortality study of cancer incidence conducted among 953 British male workers, 163 of whom were exposed to chlorinated toluenes including benzyl chloride, significant increases in the incidence of cancer of the digestive system (five cases, standardized mortality ratio [SMR] = 4.0) as well as the respiratory system (five cases, SMR = 2.8) were reported. However, there was no attempt to determine SMRs for exposure to specific compounds (Sorahan et al. 1983). In another cohort study, seven cases of respiratory system cancer were reported among 697 male workers in the United States who were exposed to benzyl chloride and to one of two other chlorinated toluenes. The respiratory cancer mortality was significantly elevated for each of the three exposure groups (SMR = 2.6) (Wong and Morgan 1984). The IARC working group considered these data as providing “limited evidence in humans for the carcinogenicity” of benzyl chloride.

On the basis of available evidence on mutagenicity, the IARC working group concluded that “Benzyl chloride [is a] bacterial mutagen... it is genotoxic to fungi, *Drosophila melanogaster* and cultured mammalian cells but did not increase the frequency of micronuclei in mice” (IARC 1999). The OECD (1998) stated that benzyl chloride might be weakly genotoxic, whereas the European Commission (1999) did not classify the substance for mutagenicity. A detailed overview of the available genotoxicity studies is presented in Appendix 3; these data are briefly summarized below.

Although there is clear evidence of the genotoxic potential of benzyl chloride in vitro, evidence in vivo is more limited. The chemical tested positive in bacterial mutation assays. In cultured rodent cells, benzyl chloride showed clear evidence of chromosomal aberration, mutation and deoxyribonucleic acid (DNA) damage. In addition, it induced sister chromatid exchanges (SCEs) in Chinese hamster ovary (CHO) cells. However, equivocal results were observed for SCEs and DNA effects in cultured human cells. A chromosomal aberration assay in human peripheral lymphocytes was negative. In an in vivo study, arylated DNA (or DNA adduct, principally N7-benzylguanine) was found in various organ tissues in mice after intravenous injection with benzyl chloride. Although benzyl chloride did not induce micronuclei in the bone marrow of male mice administered a single intraperitoneal injection, it was found to induce somatic mutations and sex-linked recessive lethal mutations in *Drosophila melanogaster*.

Although modes of action for induction of the observed tumours have not been elucidated by other regulatory or assessment agencies, it is noteworthy that benzyl chloride has been demonstrated to bind to DNA in rodents exposed via intravenous injection.

Exposure to benzyl chloride has also induced non-cancer effects in a range of target tissues, including the liver, forestomach and lungs, in experimental animals. Effects on the liver have been observed in subchronic studies in mice and guinea pigs exposed by gavage and inhalation, respectively. In mice, hyperplasia of the liver was observed in males and females at 2.7 mg/kg-bw per day, the lowest dose tested, and above. However, it was not determined if this effect is toxicologically significant (Lijinsky 1986). In guinea pigs exposed by inhalation for 27 weeks, there was an increase in relative liver weights in males at concentrations of 62 mg/m<sup>3</sup> and higher (Monsanto 1984). The forestomach was also a target for non-cancer effects in rodents administered benzyl chloride by gavage. In a 26-week study in rats, hyperkeratosis in the forestomach of the females was observed at 12.9 mg/kg-bw per day (Lijinsky 1986), whereas epithelial hyperplasia of the forestomach was observed in the chronic study in mice at all doses tested (i.e., at 21.4 and 42.9 mg/kg-bw per day) (Lijinsky 1986).

Exposure to benzyl chloride via inhalation resulted in effects on the respiratory system in short-term studies. In a 4-week inhalation study in male guinea pigs, distended alveoli in the lungs were observed at 180 and 530 mg/m<sup>3</sup> (Monsanto 1983). In an inhalation study in male mice (4–14 days), respiratory and olfactory epithelial lesions were observed at 224 mg/m<sup>3</sup> but not at 107 mg/m<sup>3</sup> (Zissu 1995).

No adequate reproductive studies were identified. In the only developmental toxicity study identified, oral administration of benzyl chloride in the diet to female rats resulted in a significant reduction of fetal length at 100 mg/kg-bw per day, but not at 50 mg/kg-bw per day. There was no evidence of maternal toxicity identified in the exposed animals (Skowronski and Abdel-Rahman 1986).

Neurological effects, consisting of an extension of duration of the immobility phase in a concentration-dependent manner, were observed in mice exposed to benzyl chloride at 62 mg/m<sup>3</sup> and above for 4 hours. The authors considered this result to indicate a neurotoxic effect of the substance (de Ceaurriz et al. 1983).

The confidence in the toxicity database for benzyl chloride is considered to be low to moderate, as information was available to identify critical endpoints for risk characterization, although no reproductive toxicity studies were identified and there were only limited in vivo genotoxicity data. In addition, there was a lack of dermal studies for repeated-dose and developmental toxicity and a lack of inhalation studies for carcinogenicity and developmental toxicity. Furthermore, there were only limited epidemiological studies available, and no clinical human toxicity studies were identified.

### **Characterization of Risk to Human Health**

Based principally on the weight of evidence assessments of international and other national agencies (IARC, European Commission and US EPA), a critical effect for characterization of risk to human health for benzyl chloride is carcinogenicity. Increased incidences of tumours of the thyroid, forestomach, lung, liver and circulatory system were observed in a 2-year oral study in rats and mice. Dermal application of benzyl

chloride also induced skin tumours in one study in mice. Also, epidemiological studies provided some limited evidence of respiratory and digestive system cancers in occupationally exposed humans. In light of the clear evidence of genotoxicity in the in vitro assays and mixed results in the in vivo assays and the range of tumours observed in two species of experimental animals for which the modes of induction have not been elucidated, it cannot be precluded that benzyl chloride induces tumours via a mode of action involving direct interaction with genetic material.

With respect to non-cancer effects, the lowest lowest-observed-effect concentration (LOEC) for inhalation exposure (the principal route of exposure for the general population) was 62 mg/m<sup>3</sup>, based on increased relative liver weight in guinea pigs in a 27-week study, whereas the lowest lowest-observed-effect level (LOEL) for orally administered benzyl chloride was 2.7 mg/kg-bw per day for liver hyperplasia in mice exposed by gavage for 26 weeks. Comparison of these effect levels with the highest concentration of benzyl chloride measured in indoor air in Canada (i.e., 0.073 µg/m<sup>3</sup>) and upper-bounding estimates of total daily intake via environmental media (i.e., 0.04 µg/kg-bw per day) results in margins of exposure of approximately 850 000 and 67 500, respectively. However, exposures could be greater during use of consumer products containing residual benzyl chloride, with potential per event airborne concentrations and chronic dermal exposures being conservatively predicted to be up to 1.3 µg/m<sup>3</sup> (hair conditioner) and 0.1 µg/kg-bw per day (shower gel), respectively. Comparison of these values with the lowest inhalation LOEC and oral LOEL (as a very conservative approach in light of the lack of a dermal effect level) results in margins of exposure of approximately 48 000 and 27 000, respectively. In light of the conservative nature of these estimates, these margins are likely sufficient to be protective against the induction of non-cancer effects in the general population in Canada.

### **Uncertainties in Evaluation of Risk to Human Health**

This screening assessment does not include a full analysis of the mode of induction of effects, including cancer, associated with exposure to benzyl chloride, nor does it take into account possible differences between humans and experimental species to effects induced by this substance. The available human data are limited because of small sample sizes, lack of consideration of potentially confounding factors such as cigarette smoking, and the fact that the exposure was to a mixture of chlorinated toluenes. Furthermore, there is a lack of data for long-term inhalation exposure, the most relevant exposure route for the general population, and a lack of comprehensive repeated-dose studies. There were also no adequate reproductive toxicity studies available, and in vivo genotoxicity data were limited.

There is uncertainty due to the limited information on the presence or concentrations of the substance in products available in Canada, as the substance is not used directly in products. The estimates of exposure from the use of personal care products containing residual benzyl chloride were based on conservative assumptions and may overestimate actual exposures. Therefore, more information on concentrations in consumer products

accessible in Canada would permit better characterization of risk of potential adverse health effects associated with the use of products containing benzyl chloride.

### **Conclusion**

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

On the basis of the carcinogenicity of benzyl chloride, for which there may be a probability of harm at any level of exposure, it is concluded that benzyl chloride 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 benzyl chloride meets one or more of the criteria in section 64 of CEPA 1999. Additionally, benzyl chloride meets the criterion for persistence in air but not the bioaccumulation criteria as set out in the *Persistence and Bioaccumulation Regulations* (Canada 2000).

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### Appendix 1: Upper-bounding estimates of daily intake of benzyl chloride by the general population in Canada

Route of exposure	Estimated intake ( $\mu\text{g}/\text{kg}\text{-bw}$ per day) of benzyl chloride by various age groups							
	0–6 months <sup>1,2,3</sup>			0.5–4 years <sup>4</sup>	5–11 years <sup>5</sup>	12–19 years <sup>6</sup>	20–59 years <sup>7</sup>	60+ years <sup>8</sup>
	Breast fed	Formula fed	Not formula fed					
Ambient air <sup>9</sup>	0.001			0.002	0.002	0.001	0.001	0.001
Indoor air <sup>10</sup>	0.018			0.038	0.030	0.017	0.015	0.013
Drinking water <sup>11</sup>	na	na	na	na	na	na	na	na
Food and beverages <sup>12</sup>			na	na	na	na	na	na
Soil <sup>13</sup>	na			na	na	na	na	na
Total intake	0.02	0.02	0.02	0.04	0.03	0.02	0.02	0.01

Abbreviation: na, not available.

- <sup>1</sup> No measured data were identified on the concentration of benzyl chloride in breast milk.
- <sup>2</sup> Assumed to weigh 7.5 kg, to breathe 2.1 m<sup>3</sup> of air per day, to drink 0.8 L of water per day (formula fed) or 0.3 L/day (not formula fed) or 0.74 L of breast milk per day (breast fed) and to ingest 30 mg of soil per day (Health Canada 1998). Breast-fed and formula-fed infants are assumed to consume no other foods.
- <sup>3</sup> For exclusively formula-fed infants, intake from water is synonymous with intake from food. The concentration of benzyl chloride in water used to reconstitute formula was based on available water data. No data on concentrations of benzyl chloride in formula were identified for Canada. Approximately 50% of infants are introduced to solid foods by 4 months of age and 90% by 6 months of age (NHW 1990).
- <sup>4</sup> Assumed to weigh 15.5 kg, to breathe 9.3 m<sup>3</sup> of air per day, to drink 0.7 L of water per day and to ingest 100 mg of soil per day (Health Canada 1998).
- <sup>5</sup> Assumed to weigh 31.0 kg, to breathe 14.5 m<sup>3</sup> of air per day, to drink 1.1 L of water per day and to ingest 65 mg of soil per day (Health Canada 1998).
- <sup>6</sup> Assumed to weigh 59.4 kg, to breathe 15.8 m<sup>3</sup> of air per day, to drink 1.2 L of water per day and to ingest 30 mg of soil per day (Health Canada 1998).
- <sup>7</sup> Assumed to weigh 70.9 kg, to breathe 16.2 m<sup>3</sup> of air per day, to drink 1.5 L of water per day and to ingest 30 mg of soil per day (Health Canada 1998).
- <sup>8</sup> Assumed to weigh 72.0 kg, to breathe 14.3 m<sup>3</sup> of air per day, to drink 1.6 L of water per day and to ingest 30 mg of soil per day (Health Canada 1998).
- <sup>9</sup> The highest concentration of benzyl chloride (0.029  $\mu\text{g}/\text{m}^3$ ) identified in ambient air samples collected outside randomly selected non-smoking homes in Windsor, Ontario (Health Canada 2008), was used to calculate the upper-bounding estimate. It is assumed that Canadians spend 3 h/day outdoors (Health Canada 1998).
- <sup>10</sup> The highest concentration of benzyl chloride (0.073  $\mu\text{g}/\text{m}^3$ ) identified in indoor air samples collected from randomly selected non-smoking homes in Windsor, Ontario (Health Canada 2008), was used to calculate the upper-bounding estimate of exposure. It is assumed that Canadians spend 21 h/day indoors (Health Canada 1998).
- <sup>11</sup> No reported concentrations of benzyl chloride in tap water in Canada or elsewhere were identified.
- <sup>12</sup> No reported concentrations of benzyl chloride in food in Canada or elsewhere were identified.
- <sup>13</sup> No reported concentrations of benzyl chloride in soil in Canada or elsewhere were identified.

**Appendix 2. Estimated exposures to benzyl chloride in consumer products based on ConsExpo version 4.1 (ConsExpo 2006; RIVM 2006)**

<b>Consumer products scenario</b>	<b>Assumptions</b>	<b>Estimated exposure</b>
Hair conditioner	<p>Weight percent of benzyl chloride: 0.0001%</p> <p><b>Inhalation: Exposure to vapour, instantaneous release</b> Applied amount of 14 g, exposure duration of 4 min, room volume of 10 m<sup>3</sup>, ventilation rate of 2.0 L/h (RIVM 2006)</p> <p><b>Dermal absorption: Exposure, instant application</b> Exposed area of 1440 cm<sup>2</sup>, applied amount of 14 g, frequency of 104×/year (RIVM 2006)</p>	<p><b>Inhalation</b> Event concentration <b>1.3 µg/m<sup>3</sup></b></p> <p><b>Dermal</b> Acute applied dose <b>0.2 µg/kg-bw</b></p> <p>Chronic applied dose <b>0.06 µg/kg-bw per day</b></p>
Shower gel	<p>Weight percent of benzyl chloride: 0.0001%</p> <p><b>Inhalation: Exposure to vapour, instantaneous release</b> Applied amount of 8.7 g, exposure duration of 4 min, room volume of 10 m<sup>3</sup>, ventilation rate of 2.0 L/h (RIVM 2006)</p> <p><b>Dermal absorption: Exposure, instant application</b> Exposed area of 1750 cm<sup>2</sup>, applied amount of 8.7 g, frequency of 329×/year (RIVM 2006)</p>	<p><b>Inhalation</b> Event concentration <b>0.8 µg/m<sup>3</sup></b></p> <p><b>Dermal</b> Acute applied dose <b>0.1 µg/kg-bw</b></p> <p>Chronic applied dose <b>0.1 µg/kg-bw per day</b></p>

## Appendix 3. Summary of health effects information for benzyl chloride

Endpoints	Lowest effect levels <sup>1</sup> /Results
<b>Laboratory animals and <i>in vitro</i></b>	
Acute toxicity	<p><b>Lowest oral LD<sub>50</sub></b> (rat) = 440 mg/kg-bw (Bayer 1978)</p> <p><b>Lowest inhalation LC<sub>50</sub></b> (mice, 2 h) = 390 mg/m<sup>3</sup> (Mikhailova 1964)</p> <p><b>Lowest dermal LD<sub>50</sub></b> (rabbit, 24 h) = &gt;145 mg/kg-bw per day (Bayer 1994)</p> <p>[additional studies: Mikhailova 1964; Back et al. 1972; Izmerov et al. 1982]</p>
Short-term repeated-dose toxicity	<p><b>Lowest inhalation LOAEC</b> = 180 mg/m<sup>3</sup> based on distended alveoli in the lungs of male Duncan-Hartley guinea pigs (10 per group) exposed by whole body to benzyl chloride at 0, 60, 180 or 530 mg/m<sup>3</sup>, 6 h/day, for 4 weeks (Monsanto 1983).</p> <p><b>Other inhalation LOAEC</b> = 224 mg/m<sup>3</sup> based on respiratory and olfactory epithelial lesions in male Swiss OF1 mice (10 per group) exposed to benzyl chloride at 0, 107 or 224 mg/m<sup>3</sup>, 6 h/day, for 4, 9 or 14 days. Severity was rated as severe to very severe but not related to exposure duration (Zissu 1995).</p> <p>No oral or dermal studies were identified.</p>
Subchronic toxicity	<p><b>Lowest oral LOEL</b> = 2.7 mg/kg-bw per day based on moderate, occasionally severe, hyperplasia of liver in B6C3F1 mice (10 males and 10 females) exposed by gavage to benzyl chloride at 0, 6.3, 12.5, 25.0, 50.0 or 100.0 mg/kg-bw, 3 times/week (estimated daily doses: 0, 2.7, 5.4, 10.7, 21.4 or 42.9 mg/kg-bw per day), for 26 weeks (Lijinsky 1986).</p> <p><b>Other oral LOAEL</b> = 12.9 mg/kg-bw per day based on hyperkeratosis in the forestomach of female F344 rats (10) exposed by gavage to 0, 15, 30, 62, 125 or 250 mg/kg-bw, 3 times/week (estimated daily doses: 0, 6.4, 12.9, 26.6, 53.6 or 107.1 mg/kg-bw per day), for 26 weeks (Lijinsky 1986).</p> <p><b>Lowest inhalation LOEC</b> = 62 mg/m<sup>3</sup> based on increased relative liver weight in male Duncan-Hartley guinea pigs (30) exposed by whole body to benzyl chloride at 0, 5, 62 or 148 mg/m<sup>3</sup>, 6 h/day, 5 days/week, for 27 weeks (Monsanto 1984).</p> <p>No dermal studies were identified.</p>
Chronic toxicity/carcinogenicity	<p><b>Oral carcinogenicity in rats:</b> Groups of 52 male and 52 female F-344 rats were administered benzyl chloride by gavage at 0, 15 or 30 mg/kg-bw, 3 times/week (estimated to be equivalent to 0, 6.4 or 12.9 mg/kg-bw per day), for 104 weeks. A statistically significant increase was observed in thyroid C-cell adenoma/carcinoma in high-dose females (4/52, 8/51 and 14/52 in the control, low-dose and high-dose groups, respectively). There were statistically insignificant increases in the incidences of carcinoma/papilloma observed in the forestomach of males at the dose of 30 mg/kg-bw. No non-neoplastic lesions were reported (Lijinsky 1986).</p> <p><b>Oral carcinogenicity in mice:</b> Groups of 52 male and 52 female B6C3F1 mice were administered benzyl chloride by gavage at 0, 50 or 100 mg/kg-bw, 3 times/week (estimated to be equivalent to 0, 21.4 or 42.9 mg/kg-bw per day), for 104 weeks. At the high dose, males had a statistically significant increase in the incidences of hemangioma/hemangiosarcoma (0/52, 0/52 and 5/52 in the control, low-dose and high-dose groups, respectively), forestomach carcinoma (0/51, 4/52 and 8/52) and forestomach carcinoma/papilloma (0/52, 4/52 and 32/52). In high-dose females, statistically significant increases in the incidence of forestomach carcinoma/papilloma (0/52, 5/50 and 19/51) and lung alveolar-bronchiolar adenoma/carcinoma (1/52, 2/51 and 6/51) were observed. A statistically significant</p>

Endpoints	Lowest effect levels <sup>1</sup> /Results
	<p>increase in the incidence of hepatocellular carcinoma/adenoma was observed in the low-dose males (17/52, 28/52, 20/51). For non-neoplastic effects, epithelial hyperplasia occurred in the stomachs of those animals without tumours (Lijinsky 1986).</p> <p><b>Dermal carcinogenicity in mice:</b> A group of 20 female ICR mice was administered benzyl chloride (2.5 mg diluted in benzene to a final volume of 25 µL) on skin, twice weekly, for 50 weeks. Three mice in the test group developed squamous cell carcinomas of the skin. No skin tumours in controls (benzene) were observed (Fukuda et al. 1981).</p> <p><b>Other dermal carcinogenicity in mice:</b> Benzyl chloride showed no dermal carcinogenicity in three other low-dose studies in mice (6–10 months) (Ashby et al. 1982; Coombs 1982a, b).</p> <p><b>Non-neoplastic effects:</b></p> <p><b>Lowest oral LOAEL</b> = 21.4 mg/kg-bw per day based on epithelial hyperplasia in the stomachs of mice (Lijinsky 1986).</p> <p>No inhalation studies were identified.</p>
Reproductive toxicity	<p><b>Lowest oral LOAEL</b> = 0.0006 mg/kg-bw per day based on increased embryonal lethality in Wistar rats exposed to benzyl chloride in sunflower oil by gavage at doses of 0, 0.000 06, 0.0006, 0.006 or 208 mg/kg-bw per day on days 1–19 of gestation (Leonskaya 1980). However, only very limited information was available for this study.</p>
Developmental toxicity	<p><b>Lowest oral LOAEL</b> = 100 mg/kg-bw per day (200 mg/kg in diet) based on significantly reduced fetal length in female SD(Crj:CD) rats (numbers not specified) exposed to benzyl chloride in corn oil at 0, 50 or 100 mg/kg-bw per day by gavage on days 6–15 of pregnancy. There were no effects on the number of implantations, resorptions, live fetuses, mean fetal body weight or external appearance or on skeletal or visceral examination. There was no evidence of maternal toxicity (Skowronski and Abdel-Rahman 1986).</p> <p>No inhalation or dermal studies were identified.</p>
Genotoxicity and related endpoints: <i>in vivo</i>	<p><b>Micronucleus test</b></p> <p><b>Negative:</b> Mice (Tuck To, NMRI or CD-1) administered benzyl chloride by intraperitoneal injection of 600 mg/kg-bw or oral administration of 800 or 1750 mg/kg-bw, respectively. No exposure-related increases in micronuclei in bone marrow were observed (Danford and Parry 1982; Hartley-Asp 1982b; Holmstrom et al. 1982).</p> <p><b>DNA adduct test</b></p> <p><b>Positive:</b> Mice (male, outbred albino NMRI) administered benzyl chloride by intravenous injection (dose not specified). DNA adduct formation (arylation) in various organs was observed, with the highest levels being detected (1 h after injection) in the brain and testes, followed by the liver and lung. Chromatographic evidence suggests that the principal adduct was N7-benzylguanine (Solveig Walles 1981).</p> <p><b>Sex-linked recessive lethal test</b></p> <p><b>Positive:</b> Male <i>Drosophila melanogaster</i> larvae were fed benzyl chloride at doses of 0, 0.5, 1.0 or 2.0 mM. Somatic cell mutations were observed at all tested doses, whereas germinal X-chromosome mutations (recessive lethals and visibles) were induced only at the highest tested dose (2.0 mM) (Fahmy and Fahmy 1982).</p>

Endpoints	Lowest effect levels <sup>1</sup> /Results
Genotoxicity and related endpoints: <i>in vitro</i>	<p><b>Mutagenicity in bacteria</b>  <b>Positive</b> in <i>Salmonella typhimurium</i> TA100, with or without metabolic activation (Yasuo et al. 1978; Neudecker et al. 1980; Ashby et al. 1982; Brooks and Gonzalez 1982; Kirkland et al. 1982a; Pour et al. 1982; Varley 1982; Venitt et al. 1982; Watkins and Rickard 1982; Booth et al. 1983; Hemminki et al. 1983).  [A few negative results were also reported: Simmon 1979; Jones and Richold 1982; Ladner 1982; Moore and Chatfield 1982.]</p> <p><b>Negative</b> in <i>Salmonella typhimurium</i> TA98, with or without metabolic activation (Simmon 1979; Brooks and Gonzalez 1982; Hyldig-Nielsen and Hartley-Asp 1982; Jones and Richold 1982; Kirkland et al. 1982a; Ladner 1982; Pour et al. 1982; Sargent and Regnier 1982; Trueman and Callander 1982; Varley 1982; Venitt et al. 1982; Watkins and Rickard 1982; Booth et al. 1983).  [One positive result was reported: Styles and Pritchard 1982.]</p> <p><b>Negative</b> results in <i>Salmonella typhimurium</i> TA1535, TA1537 and TA1538 were also reported (IARC 1999).</p> <p><b>Positive</b> in <i>Escherichia coli</i> WP2uvrA (pKM101), with or without metabolic activation (Yasuo et al. 1978; Kirkland et al. 1982a; Venitt et al. 1982).</p> <p><b>Mammalian cell mutation assay</b>  <b>Positive</b> in mouse lymphoma cells without metabolic activation (McGregor et al. 1988)  <b>Positive</b> in Chinese hamster lung cells (CHL) without metabolic activation (Mirzayans et al. 1982)  <b>Positive</b> in CHL cells with metabolic activation (Lee and Webber 1982)  <b>Positive</b> in Chinese hamster ovary (CHO) cells without metabolic activation (Phillips and James 1982)</p> <p><b>Chromosomal aberration assay</b>  <b>Positive</b> in CHL and CHO cells without metabolic activation (Phillips and James 1982)  <b>Positive</b> in CHL and CHO cells with metabolic activation (JETOC 1997)  <b>Negative</b> in human lymphocytes (Hartley-Asp 1982a; Kirkland et al. 1982b)</p> <p><b>Sister chromatid exchange (SCE) assay</b>  <b>Positive</b> in CHO cells without metabolic activation (Phillips and James 1982; Hemminki et al. 1983)  <b>Positive</b> in human lymphocytes (Kirkland et al. 1982b)  <b>Negative</b> in human lymphocytes (Hartley-Asp 1982a)</p> <p><b>Rodent micronucleus test</b>  <b>Equivocal:</b> “considerably weak” in Syrian hamster embryo fibroblast without metabolic activation (Schmuck et al. 1988)</p> <p><b>Unscheduled DNA synthesis assay</b>  <b>Negative</b> in HeLa S3 cells, with or without metabolic activation (Booth et al. 1983)</p> <p><b>DNA damage and its repair assay</b>  <b>Positive</b> in human A549 cells, with or without metabolic activation (Mirzayans et al. 1982)</p> <p><b>Differential cytotoxicity of a mutant cell assay</b></p>

Endpoints	Lowest effect levels <sup>1</sup> /Results
	<p><b>Positive</b> in <i>Saccharomyces cerevisiae rad</i> mutants, with the extent of the toxicity being dependent on the presence of genes regulating DNA repair (North and Parry 1982)</p> <p><b>Equivocal:</b> slightly mutagenic to the DNA excision repair-deficient strains of CHO cells (Hoy et al. 1984)</p>
Neurotoxicity	<p><b>Lowest inhalation LOAEC</b> = 62 mg/m<sup>3</sup>, identified based on behavioural changes in male Swiss OF1 mice (10 per group) exposed to benzyl chloride by whole-body inhalation at doses of 0, 62, 88, 94 or 114 mg/m<sup>3</sup> for 4 h. Benzyl chloride caused a concentration-dependent extension of duration of the immobility phase by 32, 52, 71 and 84%, compared with the controls, respectively (de Ceaurriz et al. 1983).</p> <p>No oral or dermal studies were identified.</p>
<b>Humans</b>	
Epidemiology	<p>Two human studies were identified.</p> <p>A retrospective cohort study of cancer mortality was conducted among 953 male workers at a British organic chemical factory. Of the 953 workers, 163 were exposed to chlorinated toluenes, including benzyl chloride, whereas 790 were unexposed. The exposure level was 1–10 ppm, with duration of exposure ranging from 6 months to more than 40 years. Average exposure levels and durations were not stated. Of 25 deaths in the group of 163 exposed workers, 5 were due to digestive system cancer and 5 to respiratory cancer, and the remaining 15 were due to non-cancer causes. The data were analyzed by the standardized mortality ratios (SMRs) method using the mortality rates in England and Wales. Significant excesses occurred for cancer of the digestive system (SMR = 4.0, 5/1.2, <math>p &lt; 0.01</math>) and cancer of the respiratory system (SMR = 2.8, 5/1.8, <math>p &lt; 0.05</math>). However, there was no attempt to determine SMRs for specific chlorinated toluenes (Sorahan et al. 1983).</p> <p>A retrospective cohort mortality study of workers exposed to benzyl chloride, benzotrichloride and benzoyl chloride was conducted at a chlorination plant in the United States. The cohort consisted of 697 male workers who had been employed for &lt;1 to &gt;35 years, and almost all subjects held jobs with potential exposure to all three chemicals. Average levels of exposure to three chemicals and durations of employment were not reported. Analysis was based on comparison with US mortality rates for males. There were seven cases of respiratory system cancer (the expected number was 2.69). The respiratory cancer mortality was significantly elevated for each of the three groups (i.e., exposed to benzyl chloride, benzotrichloride or benzoyl chloride): SMR = 2.6 (<math>p &lt; 0.05</math>) for each. A statistically significant increase in respiratory cancer mortality was observed among employees with 15 or more years of employment (SMR = 3.79, <math>p &lt; 0.05</math>), whereas for those with less than 15 years of employment, the increase in respiratory cancer mortality was insignificant (SMR = 1.31) (Wong and Morgan 1984).</p>

<sup>1</sup> LC<sub>50</sub>, median lethal concentration; LD<sub>50</sub>, median lethal dose; LOAEC, lowest-observed-adverse-effect concentration; LOAEL, lowest-observed-adverse-effect level; LOEC, lowest-observed-effect concentration, LOEL, lowest-observed-effect level.