Environment Canada Environnement Canada

Screening Assessment

Acetone

Chemical Abstracts Service Registry Number 67-64-1

Environment Canada
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Canada

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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 acetone (Chemical Abstracts Service Registry Number 67-64-1). Acetone was identified as a priority for assessment on the basis of greatest potential for human exposure.

Acetone has both natural and anthropogenic sources. It is produced by thermal combustion, such as from forest fires; it is an oxidation product of natural humic substances; and it is excreted as a metabolic by-product from many organisms, including mammals, plants and microorganisms. Important anthropogenic sources of acetone in air include chemical manufacturing, solvent use, petroleum production, automobile emissions, tobacco smoke, wood burning, pulping, refuse, plastics combustion and off-gassing from landfill sites. Anthropogenic sources of acetone emissions to the aquatic environment include wastewater discharges from industries and leaching from industrial and municipal landfills.

Acetone is used as a formulating solvent for a variety of paints, inks, resins, varnishes, lacquers, surface coatings, paint removers and automotive care products. The largest applications of acetone globally are solvent uses and for the production of methyl methacrylate and bisphenol A. In 2010, total global production of acetone was estimated to be 5.5 million tonnes.

In Canada, acetone is employed for a variety of uses, including use as an industrial and laboratory solvent, as a cleaner and degreaser, and in paints, dyes, adhesives and coatings. Acetone may be used in Canada in food, food packaging, pharmaceuticals, natural health products, veterinary drugs, cosmetics and pest control products.

Based on the results of a survey conducted under section 71 of CEPA 1999 for the year 2000, approximately 1000 tonnes of acetone was manufactured in Canada as a by-product of industrial processes, and 15 000 tonnes of acetone was imported into Canada, at a concentration higher than 1%. However, a facility that accounted for 98% of Canadian acetone production in the year 2000 stopped manufacturing it in 2002.

Acetone was included in the National Pollutant Release Inventory (NPRI) until 1998. In 1998, facilities across Canada reported on-site environmental releases totalling approximately 3570 tonnes, mostly to air. Since 2009, facilities located in the province of Ontario must again report acetone releases to the NPRI. In 2009, total releases of acetone in Ontario were 1039 tonnes (mainly to air), compared with 1379 tonnes in 1998.

Acetone has been measured in ambient and indoor air, and drinking water in Canada, and in the United States and elsewhere in surface water, groundwater, food, and soil. Acetone has been identified in numerous products and building materials, as well as in

cigarettes and tobacco smoke. Acetone is produced endogenously in the body and has been detected in the blood of individuals living in the United States.

Acetone has an estimated tropospheric half-life of 22 to 23 days and is predicted to be subject to long-range atmospheric transport (> 5000 km); therefore, it is persistent in air. It will biodegrade in soil and water and is therefore not persistent in these media.

Acetone is not expected to bioaccumulate in organisms, based on empirical as well as modelled data. Based on empirical data, acetone at low concentrations is not hazardous to aquatic organisms, terrestrial plants or mammals.

Acetone is predicted to stay mainly in the environmental compartment to which it is released. This is especially true when acetone is released to water (> 99% is predicted to remain in water).

For the ecological portion of this screening assessment, the predicted environmental concentrations in air and surface water did not exceed concentrations associated with effects, even when using very conservative scenarios.

Based on the information presented in this screening assessment, there is low risk of harm to organisms or the broader integrity of the environment from this substance. It is concluded that acetone does not meet the criteria under paragraphs 64(*a*) or (*b*) of CEPA 1999 as it 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.

Consideration of the available information indicates that acetone is not likely to be genotoxic or carcinogenic. Critical health effects associated with repeated exposure to acetone are considered to be hematological changes and kidney effects. The general population of Canada has daily exposure to acetone from environmental media, food and acetone-containing products that are used frequently. The margins of exposure between critical effect levels and the upper-bounding total daily intake estimates are considered to be adequate to address uncertainties in the health effects and exposure databases.

No critical health effects were identified for characterization of risk from acute exposures that are expected to occur from occasional, intermittent use of certain products containing acetone. Effects at exposure levels associated with such uses were considered mild, transient and reversible in nature; therefore, they were not considered adverse.

Based on the information available, it is concluded that acetone does not meet the criteria under paragraph 64(*c*) of CEPA 1999 as is not 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.

Overall Conclusion

Based on available information for environmental and human health considerations, it is concluded that acetone does not meet any of the criteria set out in section 64 of CEPA 1999.

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1 Introduction

This screening assessment report was conducted pursuant to section 74 of the *Canadian Environmental Protection Act, 1999* (CEPA 1999). This section of the Act requires that the Ministers of the Environment and of Health 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.

A screening assessment was undertaken on acetone (Chemical Abstracts Service Registry Number 67-64-1), a substance on the Domestic Substances List (DSL). Acetone was identified during the categorization of substances on the DSL as a priority for assessment as it met the criteria for greatest potential for human exposure. Acetone met the categorization criteria for persistence, but it did not meet the criteria for bioaccumulation potential or inherent toxicity to aquatic organisms.

Screening assessments focus on information critical to determining whether a substance meets the criteria 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.[1]

This screening assessment includes consideration of information on chemical properties and uses of acetone, exposure to acetone and hazards associated with exposure to acetone. Data relevant to the screening assessment of this substance were identified in original literature, review and assessment documents, stakeholder research reports and reports written under contract for Health Canada, as well as from recent literature searches, up to September 2011 for ecological sections of the document and December 2011 for human health sections of the document. In addition, an industry survey was conducted in 2001 through a Canada Gazette Notice issued under the authority of section 71 of CEPA 1999 (Canada 2001); this survey collected data on the Canadian manufacture and import of acetone in the year 2000 (Environment Canada 2004). Key studies were critically evaluated; modelling results were used to reach conclusions.

The approach taken in the ecological screening assessment is to examine various supporting information and develop conclusions based on a weight of evidence approach as required under section 76.1 of CEPA 1999. The screening assessment

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[1] A determination of whether one or more of the criteria of section 64 are met is based upon an assessment of potential risks to the environment and/or to human health associated with exposures in the general environment. For humans, this includes, but is not limited to, exposures from ambient and indoor air, drinking water, foodstuffs and the use of consumer products. A conclusion under CEPA 1999 is not relevant to, nor does it preclude, an assessment against the hazard criteria specified in the *Controlled Products Regulations*, which are part of the regulatory framework for the Workplace Hazardous Materials Information System for products intended for workplace use. Similarly, a conclusion based on the criteria contained in section 64 of CEPA 1999 does not preclude actions being taken under other sections of CEPA 1999 or other Acts.

does not present an exhaustive review of all available data. Instead, it presents the critical studies and lines of evidence supporting the conclusions.

Evaluation of risk to human health involves consideration of data relevant to estimation of exposure of the general population (non-occupational) as well as information on health hazards. 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.

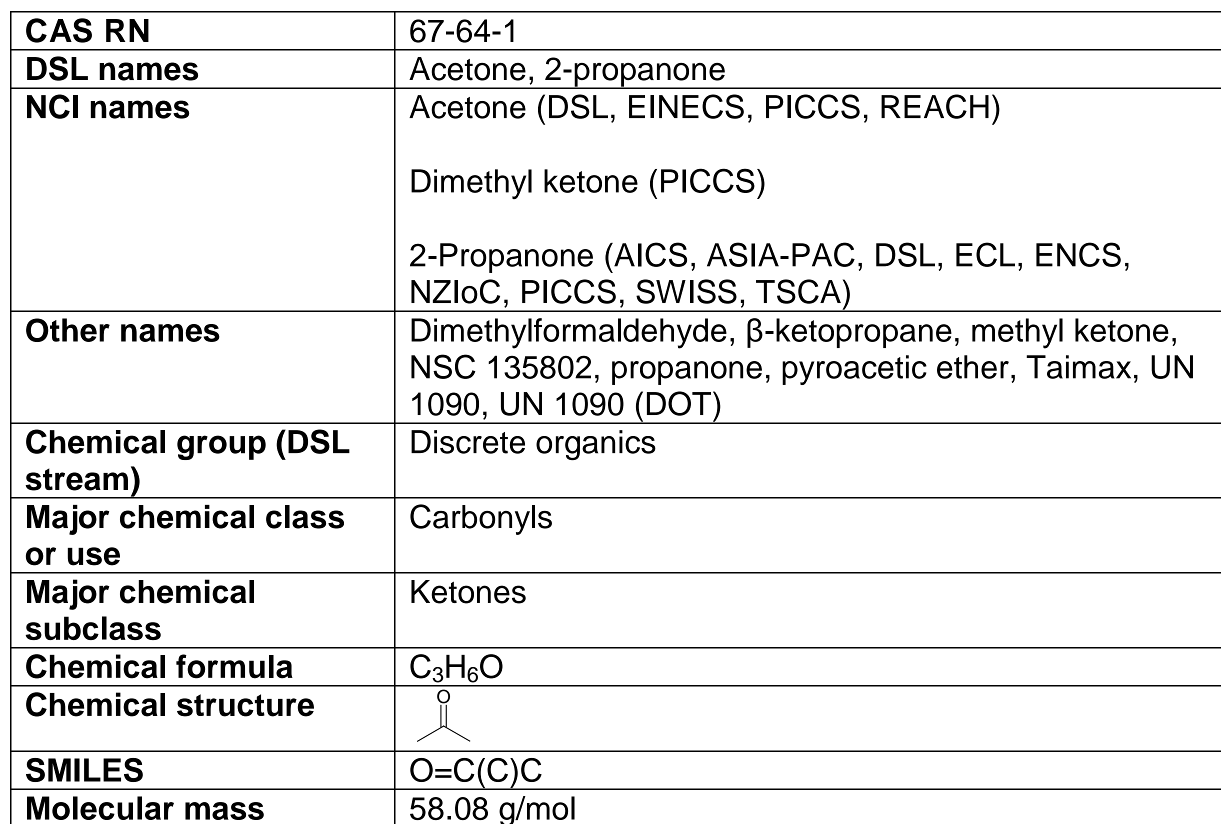
This screening assessment was prepared by staff in the Existing Substances programs at Health Canada and Environment Canada, and the content was reviewed by senior staff for adequacy of data coverage and defensibility of the evaluation. The ecological and health assessments have undergone external written peer review and/or consultation. Comments on the technical portions relevant to human health assessment were received from scientific experts selected and directed by Gradient Consulting. 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 assessment remain the responsibility of Health Canada and Environment Canada.

The critical information and considerations upon which the screening assessment is based are summarized in the following sections.

2 Substance Identity

For the purposes of this document, this substance will be referred to as acetone, a common name for the substance. Information relevant to the identity of the substance is presented in Table 2-1.

Table 2-1: Substance identity for acetone



CAS RN	67-64-1
DSL names	Acetone, 2-propanone
NCI names	Acetone (DSL, EINECS, PICCS, REACH) Dimethyl ketone (PICCS) 2-Propanone (AICS, ASIA-PAC, DSL, ECL, ENCS, NZIoC, PICCS, SWISS, TSCA)
Other names	Dimethylformaldehyde, β-ketopropane, methyl ketone, NSC 135802, propanone, pyroacetic ether, Taimax, UN 1090, UN 1090 (DOT)
Chemical group (DSL stream)	Discrete organics
Major chemical class or use	Carbonyls
Major chemical subclass	Ketones
Chemical formula	C_3H_6O
Chemical structure	
SMILES	O=C(C)C
Molecular mass	58.08 g/mol

Abbreviations: AICS, Australian Inventory of Chemical Substances; ASIA-PAC, Asia-Pacific Substances Lists; CAS RN, Chemical Abstracts Service Registry Number; DOT, Department of Transportation (US); DSL, Domestic Substances List; ECL, Korean Existing Chemicals List; EINECS, European Inventory of Existing Commercial Chemical Substances; ENCS, Japanese Existing and New Chemical Substances; NCI, National Chemical Inventories; NZIoC, New Zealand Inventory of Chemicals; PICCS, Philippine Inventory of Chemicals and Chemical Substances; REACH, Registration, Evaluation, Authorisation and Restriction of Chemical Substances; SMILES, Simplified Molecular Input Line Entry Specification; SWISS, Swiss Giftliste 1 and Inventory of Notified New Substances; TSCA, *Toxic Substances Control Act* Chemical Substance Inventory
Source: NCI (2006)

3 Physical and Chemical Properties

Acetone is a clear, colourless liquid with a strong “fruity” odour that is highly flammable and is miscible with water and organic solvents, such as ether, methanol, ethanol and esters (WHO 1998). Reagent-grade acetone can contain up to 0.5% water as well as small amounts of other polar solvents (OECD 1999). Selected physical and chemical properties of acetone are presented in Table 3-1.

Table 3-1: Physical and chemical properties of acetone

Property	Type	Value	Temperature (°C)	Reference
Melting point (°C)	Experimental	−94	—	Windholz 1989
Boiling point (°C)	Experimental	56.2	—	Weast and Lide 1989
Density (g/mL)	Experimental	0.7899	20	Weast and Lide 1989
Vapour pressure (kPa)	Experimental	24.7	20	Howard 2011
Vapour pressure (kPa)	Experimental	30.8	25	Riddick et al. 1986
Henry's Law constant (Pa·m^3/mol)	Experimental	4.32 (4.26×10^{-5} atm·m^3/g·mol)[a]	25.2	Rathbun and Tai 1987
Henry's Law constant (Pa·m^3/mol)	Experimental	3.55	25	Benkelberg et al. 1995
Log K_{ow} (dimensionless)	Experimental	−0.24	—	Collander 1951
Log K_{oc} (dimensionless)	Experimental	0.99	—	KOCWIN 2010
Water solubility (mg/L)	Experimental	Miscible with water	20	Windholz 1989
Water solubility (mg/L)	Experimental	Infinite	—	Riddick et al. 1986
Water solubility (mg/L)	Modelled	2.7×10^5	25	WATERNT (2010)
pK_a (dimensionless)	Experimental	20	—	Serjeant and Dempsey 1979

Abbreviations: K_{oc}, organic carbon–water partition coefficient; K_{ow}, octanol–water partition coefficient; pK_a, acid dissociation constant

[a] There is a typographical error in the original reference; the value is given as 4.26×10^5 atm·m^3/g·mol in Rathbun and Tai (1987).

The very high acid dissociation constant (pK_a value) of 20 indicates that acetone will be present in an un-ionized form in the natural environment.

4 Sources

Atmospheric emissions of acetone occur from both natural and anthropogenic sources. Natural sources of emission include forest fires and volcanic eruptions. Acetone is also produced endogenously as a metabolic by-product in humans and other animals, microorganisms and plants and is expired as a component of expired air from mammals (Graedel et al. 1986). It is formed in the atmosphere from the photochemical oxidation

of propane and possibly propylene oxide and epichlorohydrin (ATSDR 1994). Acetone is released as a biodegradation product of sewage, solid wastes and alcohols and as an oxidation product of natural humic substances (WHO 1998). Important anthropogenic sources of acetone in air include chemical manufacturing, solvent use, petroleum production, automobile emissions, tobacco smoke, wood burning, pulping, refuse, plastics combustion and off-gassing from landfill sites (WHO 1998). Acetone is manufactured mainly by cumene peroxidation, as a co-product with phenol (SRI 2011).

Anthropogenic sources of acetone emissions to the aquatic environment include wastewater discharges from industries and leaching from industrial and municipal landfills (WHO 1998). Acetone is released into surface water as a component of wastewater from a variety of manufacturing processes and industries, including paper, plastics, pharmaceuticals, specialty cleaning and polishing products, paint and allied products, gum and wood chemicals, industrial organic chemicals, gypsum products, paperboard products and energy-related industries, such as coal gasification and oil shale processing (ATSDR 1994; WHO 1998). The principal sources of acetone emissions to subsurface soil are releases from municipal and industrial discharges in landfills (US EPA 1988). Acetone can also leach from landfills into groundwater (ATSDR 1994).

A survey conducted pursuant to section 71 of CEPA 1999 indicated that in Canada, during the year 2000, approximately 1000 tonnes of acetone was manufactured at a concentration higher than 1% by weight and about 15 000 tonnes was imported at a concentration higher than 1% by weight (Environment Canada 2004). In addition, 16 companies reported either importing or manufacturing acetone at a concentration lower than 1% and in a quantity meeting the reporting threshold of 10 000 kg (Environment Canada 2004). Companies manufacturing acetone in Canada indicated that it was formed as a by-product of their operations (Environment Canada 2004). One of these facilities, which accounted for 977 tonnes (or 98%) of Canadian acetone production in the year 2000, shut down the process that was producing acetone in 2002. The two other companies that reported manufacturing acetone were pulp and paper plants (Environment Canada 2004).

5 Uses

Acetone is the simplest aliphatic ketone and the most commercially important. Total global production in 2010 was estimated to be 5.5 million tonnes (SRI 2011). Total global acetone consumption in 2010 was estimated to have increased by 5% from 2009, and it is expected to increase on average by 4.0% per year from 2010 to 2015, slowing to 2.4% per year from 2015 to 2020 (SRI 2011). Based on 2008 estimates, the largest volume applications of acetone globally are solvent uses (1.82 million tonnes), methyl methacrylate production (1.44 million tonnes) and bisphenol A production (1.23 million tonnes) (Sifniades et al. 2011). These three categories consumed approximately 80% of global acetone consumption in 2010; other applications for acetone include acetone cyanohydrin and isopropyl alcohol production (SRI 2011).

Worldwide, major end uses of acetone can be divided into three separate categories. These include uses as chemical feedstock, a formulating solvent for commercial products and an industrial process solvent (OECD 1999). Several chemicals, such as methyl isobutyl ketone, methyl isobutyl carbinol, isophorone and diacetone alcohol, are also prepared directly from nascent acetone (OECD 1999). Acetone is used as a formulating solvent for a variety of paints, inks, resins, varnishes, lacquers, surface coatings, paint removers and automotive care products. As an industrial process solvent, acetone is used to manufacture cellulose acetate yarn, polyurethane foam, vitamin C and smokeless gun powder (OECD 1999). Acetone is also used in small volume applications for the creation of functional compounds such as antioxidants, herbicides, larger ketones, condensates with formaldehyde or diphenylamine, and vitamin intermediates (Howard 2011).

Uses of acetone in Canada are consistent with international use patterns. In Canada, acetone is employed for a variety of uses, including as an industrial solvent, cleaner, in paints, adhesives and coatings (e.g., automotive finishing coatings) and in laboratories (Environment Canada 2004). Many of these uses were reported to be “dispersive uses where the substance is released into the environment,” including use as a solvent, industrial cleaner, and spray-on adhesive.

Acetone is excluded from the volatile organic compound (VOC) definition under Schedule 1 of CEPA 1999. As such, acetone may be used in formulations of products regulated under the Volatile Organic Compound (VOC) Concentration Limits for Architectural Coatings Regulations (2009) (Canada 2009a) and the Volatile Organic Compound (VOC) Concentration Limits for Automotive Refinishing Products Regulations (2009) (Canada 2009b). Environment Canada is also looking at opportunities for the further reduction of VOC emissions from products. As a result, it is possible that acetone usage in Canada may increase should companies substitute acetone for VOCs in their products.

Acetone is used in food preparation as an extraction solvent for fats and oils and as a flavouring agent (FAO/WHO 1998). It is permitted for use as a food additive in Canada under the *Food and Drug Regulations*, as a carrier or extraction solvent (e.g., spice extracts, meat and egg marking inks), at maximum levels of use specified by the *List of Permitted Carrier or Extraction Solvents* (Health Canada 2012a). These uses must meet all of the conditions specified in that list as incorporated by reference into the *Marketing Authorization for Food Additives That May Be Used as Carrier or Extraction Solvents* (Health Canada 2012a). Acetone may be used as a solvent for many applications related to food packaging and may be found as a residual impurity in some food packaging matterials such as polyethylene and polypropylene resins as a result of manufacturing process (2013 email from Food Directorate, Health Canada, to Risk Management Bureau, Health Canada; unreferenced).

Acetone is listed in the Natural Health Products Ingredients Database (NHPID) with a medical ingredient role, as it meets the criteria under Schedule 1, item 2 (an isolate), of the *Natural Health Products Regulations* (Canada 2006; NHPID 2011). It is also listed in

the NHPID with a non-medicinal ingredient role as a denaturant, flavour enhancer and solvent in natural health products (NHPID 2011). Acetone is listed in the Licensed Natural Health Products Database (LNHPD) as a medicinal and non-medicinal ingredient in currently licensed natural health products (LNHPD 2011). Acetone is not listed in the Drug Product Database as an active ingredient in pharmaceuticals (human/veterinary) (DPD 2011); however, it forms part of the name (as "acetone-precipitated") of certain allergenic extracts administered to humans that are regulated under Schedule D (biological products) of the *Food and Drug Regulations* (Canada 1986). Acetone is listed as a Class 3 residual solvent (i.e., solvent that should be limited by Good Manufacturing Practices) in the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Guideline Q3C (R4) (ICH 2009), which is adopted by the Therapeutic Products Directorate (Health Canada 1999) and the Natural Health Products Directorate (Health Canada 2007); and the International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products Guideline GL18 (VICH 2000), which is adopted by the Veterinary Drugs Directorate (Health Canada 2003). Acetone is used primarily as an extraction solvent and may be present as a residual in pharmaceutical products, natural health products and veterinary drugs with a specified limit of less than 50 mg/day or 0.5% in any product, in accordance with the respective ICH/VICH guideline.

Acetone is used as a denaturant, fragrance and solvent in cosmetics (Personal Care Products Council 2011). In Canada, acetone is a constituent of cosmetics such as manicure preparation products, hair grooming products, skin cleansers and skin moisturizers (2011 email from Risk Management Bureau, Consumer Product Safety Directorate,Health Canada, to Risk Management Bureau, Safe Environments Directorate, Health Canada; unreferenced).

In Canada, acetone is a formulant in pest control products regulated under the *Pest Control Products Act* at concentrations ranging from just over 0% to 41.2% (2011 email from Risk Management Bureau, Health Canada, to Existing Substances Risk Assessment Bureau, Health Canada; unreferenced). Product types include rodenticides, insecticides, insect repellents, fungicides, wood preservatives, antifouling paints, dog, bear and deer repellents, seed treatments, material preservatives and slimicides.

6 Releases to the Environment

6.1 Global Releases

Natural sources, such as vegetative releases and forest fires, are estimated to account for nearly half (47%) of the estimated annual emissions of acetone (OECD 1999), most of which are to air. According to a study by Jacob et al. (2002), up to 77% of annual acetone emissions are attributable to natural sources, such as terrestrial vegetation, the oceans and biomass burning.

Singh et al. (1995) estimated that 50–66% of global tropospheric acetone results from the tropospheric photooxidation of mostly anthropogenic propane and other alkanes and alkenes, while Jacob et al. (2002) estimated that the atmospheric oxidation of anthropogenic isoalkanes, including propane, isobutane and isopentane, contributes 22% of the total acetone in the atmosphere on a global scale. Goldstein and Schade (2000) estimated, based on acetone to acetylene ratios, that 99% of the anthropogenic acetone (13.9% of total acetone) found in the air of a forested rural area (Sierra Nevada Mountains, California) is from secondary formation during the photochemical aging of polluted air as it is transported downwind from urban areas. The most likely source of this secondarily formed acetone is suggested to be the oxidation of reactive alkenes, such as isobutene and isopentene.

It is estimated that only 1% of the estimated 40 million tonnes of acetone that are released annually to the environment worldwide is released from primary (direct) anthropogenic emissions (Jacob et al. 2002), such as from chemical manufacturers and end users. Goldstein and Schade (2000) further concluded that only 1% of anthropogenic acetone (0.14% of total acetone) found in the air of a rural environment is from primary emissions.

6.2 Canadian Releases

Acetone is released from facilities that manufacture the substance or use it as a solvent or as an intermediate in the production of other chemicals. Acetone was included in the Canada-wide National Pollutant Release Inventory (NPRI) until 1998, and facilities manufacturing, importing or otherwise using more than 10 tonnes of the substance per year reported their releases. In 1997, facilities from across Canada reported to the NPRI on-site environmental releases of acetone totalling 4425 tonnes. Releases to air accounted for 3778.4 tonnes (85.4%), releases to underground injection, 560 tonnes (12.7%), releases to surface water, 85.2 tonnes (1.9%), and releases to land, 1.1 tonnes (< 0.1%). On-site releases in 1998 totalled 3567 tonnes, with 95% going to air, 3.1% to underground injection and 1.6% to water. In addition, 1807.5 tonnes were transferred off-site for disposal, and 1777 tonnes were transferred off-site for recycling (Environment Canada 2011a). The releases to surface water were mainly from two chemical manufacturing facilities (52.4 tonnes), with small releases from six pulp and paper facilities (3.2 tonnes total). There were no reported on-site releases to soil, although some companies reported transfers for disposal to landfill of up to 122 tonnes of acetone per facility (Environment Canada 2011a). In the United States, the amount of acetone released into soil from landfill leachate accounted for approximately 0.1% of the total environmental release of acetone, based on data from the 1990 US Toxics Release Inventory (ATSDR 1994).

Acetone was delisted from the US Toxics Release Inventory in 1993 (US EPA 2012). Following a request by Canadian industry to Environment Canada, an independent review (Ritter 1999) was carried out to evaluate whether acetone should be delisted from the NPRI for the 1999 reporting year. The conclusion reached was that ambient levels of acetone in the atmosphere, even at sites adjacent to the largest releases, were

below the levels of concern for exposure of humans and that acetone was not likely to adversely impact aquatic or terrestrial wildlife based on median lethal concentrations (LC_{50} values) generally greater than 2000 parts per million (ppm) (Ritter 1999). Based on the results of this review, acetone was delisted from the NPRI in 1999. Acetone releases are again being reported to the NPRI since 2009 for facilities located in the province of Ontario only, to fulfil VOC reporting requirements under Ontario Reg. 127/01 under the Ontario *Toxics Reduction Act, 2009* (Ontario 2009).

NPRI release data for Ontario from 1998 and 2009 were compared. In 1998 in Ontario, total releases of acetone were 1379 tonnes, which represented 38.7% of the Canadian total. In 2009, total releases were 1039 tonnes, which is 24.7% lower than 1998 levels, despite acetone being excluded from federal VOC regulations. The lower acetone releases by facilities in Ontario may be attributed to a decline in manufacturing activity in this province.

In 2009, almost all releases in Ontario were to air, the largest release to air being 52 tonnes from a plastic products manufacturer. No facilities reported releases to soil, and only one facility reported releases to water (28 tonnes by a chemical products manufacturer). The total amount disposed of in 2009 was 36 tonnes, and none was sent for off-site recycling, which is a large drop from 1998, when 800 tonnes were disposed of and 1201 tonnes were sent for off-site recycling.

A survey conducted pursuant to section 71 of CEPA 1999 indicated that Canadian companies reported environmental releases totalling approximately 2100 tonnes of acetone during the year 2000. Only companies manufacturing or importing more than 10 tonnes in 2000 were required to report to this survey. Releases were reported from companies representing various industry sectors, including chemical and pulp and paper. The media of release were not specified.

7 Environmental Fate

The environmental partitioning of acetone in the environment was modelled using Level III (steady-state, non-equilibrium) of the Equilibrium Criterion (EQC) model for Type 1 chemicals (Mackay et al. 1996; EQC 2003). Inputs to the model included half-lives in air, water, soil and sediment and emission rates to each environmental compartment.

In all release scenarios in Table 7-1, acetone tends to partition mainly (> 73-97%) to the compartment to which it is released. This is especially true when acetone is released to air or water.

Table 7-1: Level III fugacity modelling for acetone, percent partitioning into each medium for three release scenarios (EQC 2003)[a]

Substance released to:	**Air (%)**	**Water (%)**	**Soil (%)**	**Sediment (%)**
100% to Air	95.5	2.2	2.28	< 0.01

100% to Water	1.98	97.9	0.047	0.036
100% to Soil	6.2	21.1	72.7	< 0.01

[a] Input parameters: aqueous solubility, 2.7 x 10^5 mg/L (WATERNT 2010); vapour pressure, 30.8 kPa; log K_{ow}, −0.24; melting point, −94 ºC. Half-lives are based on data from Tables 4a and 4b below (water, 168 hours; sediments, 672 hours; air, 552 hours; soil, 168 hours, fish, negligible; aerosol, 168 hours. The half-life in sediment was extrapolated from that in water using the ratio 1:4 for water:sediment half-lives (Boethling et al. 1995).

Based on its very low organic carbon–water partition coefficient (log K_{oc} value) of 0.99, acetone will be very mobile in soil. Acetone showed no adsorption to montmorillonite, kaolinite clay or stream sediment (Rathbun et al. 1982; Wolfe et al. 1986). Volatilization of acetone from both moist and dry soil surfaces is expected, given acetone's moderate Henry's Law constant of 4.32 Pa·m^3/mol and its very high vapour pressure of 24.7 kPa.

Volatilization from water surfaces is expected based on the Henry's Law constant. Using this Henry's Law constant and an estimation method, estimated volatilization half-lives for a model river and model lake are 38 and 333 hours, respectively (HSDB 1983). Experimentally determined volatilization half-lives in a shallow stream were measured in the range of 8–18 hours (Rathbun et al. 1988, 1991, 1993). Biodegradation of this compound is expected, but volatilization has been shown to be the primary mechanism for the removal of acetone from water (Rathbun et al. 1988, 1991, 1993).

The Transport and Persistence Level III Model (TaPL3) (TaPL3 2003) was used to assess the long-range transport potential of acetone when it is released into air or water. The model calculates the characteristic distance that a substance will travel in a mobile medium until the concentration decreases to 37% (1/e) of its initial value as a consequence of intermedia partitioning and degradation reactions. Advective losses are not included (Beyer et al. 2000; TaPL3 2003). With a modelled characteristic travel distance (CTD) greater than 8000 km, acetone is predicted to be subject to long-range atmospheric transport to remote regions, such as the Arctic.

The Persistent Organic Pollutants (POPs) Screening Model from the Organisation for Economic Co-operation and Development (OECD) can also be used to help identify chemicals with high persistence and long-range transport potential (Scheringer et al. 2006). The OECD model is a global model that compartmentalizes Earth into air, water and soil. This model is "transport oriented" rather than "target oriented," as it simply identifies the CTD without indicating specifically where a substance may be transported (Fenner et al. 2005). Klasmeier et al. (2006) suggested that a threshold of 5098 km, based on the model's CTD estimate for the polychlorinated biphenyl PCB-180, can be used to identify substances with high long-range transport potential. PCB-180 is empirically known to be found in remote regions. The CTD calculated for acetone using the OECD model is 5394 km, indicating that acetone has potential for long-range atmospheric transport. The OECD POPs Screening Model also calculates the transfer efficiency (TE), which is the percentage of emission flux to air that is deposited to the surface (water and soil) in a remote region (TE % = D/E × 100, where E is the emission flux to air and D is the deposition flux to surface media in a target region). The TE for acetone was calculated to be 13.1%, which is well above the boundary of 2.25% (PCB-28) established based on the model's reference substances empirically known to be

deposited from air to soil or water. The high TE means that acetone will likely be deposited to some degree to Earth's surface in remote regions.

Acetone has been measured in Arctic air at an average concentration of 385 ppt (vol) (approximately 0.3 mg acetone/m^3 air) (Grannas et al. 2002). The dominant sources of acetone at Alert, in the Canadian High Arctic, were modelled to be oxidation of isoalkanes (mainly anthropogenic) and plant decay (Jacob et al. 2002).

8 Environmental Persistence and Bioaccumulation Potential

8.1 Environmental Persistence

Acetone has an estimated tropospheric half-life of 22–23 days (see Table 8-1) and is therefore considered to be persistent in air. Acetone is removed from the atmosphere through reaction with hydroxyl (OH) radicals and photolysis. At low altitudes (< 5 km), the reaction of acetone with OH radicals determines its loss rate. At higher altitudes, the loss via the OH radical reaction decreases due to the lower concentration of OH radicals and the decrease in temperature, and the photolysis reaction controls the loss rate (Gierczak et al. 1998).

Table 8-1: Environmental half-lives and processes for the removal of acetone in air

Media/removal process	Half-life (unless otherwise noted)	Reference
Reaction with OH radicals and photolysis	23 days (in lower troposphere at 40°N)	Gierczak et al. 1998
Reaction with OH radicals and photolysis	22 days (mean in troposphere at 40°N)	Meyrahn et al. 1986
Reaction with OH radicals at 25°C	134 days (0.37 year)[a] (total tropospheric lifetime)	Vasvári et al. 2001
Reaction with OH radicals and photolysis	254 days (0.70 year) (total lifetime in upper troposphere at 50°N)	Arnold et al. 2004

[a] Based on OH concentration of 5×10^5 molecules/cm^3 in the troposphere, a standard value for the northern hemisphere (ECJRC 2003).

Acetone will biodegrade and volatilize in water bodies and soil within a time frame of days to weeks and therefore is not considered to be persistent in water or soil (see Table 8-2). The estimated log K_{oc} value of 0.99 (see Table 2) suggests that adsorption of acetone to sediments and suspended solids is not significant, and this has been shown experimentally (Rathbun et al. 1982).

Many aerobic biological screening studies have examined the biodegradability of acetone and have found it to be readily biodegradable (WHO 1998). Studies with several different strains of anaerobic bacteria from municipal wastewater treatment plants have shown that acetone is completely degraded to carbon dioxide following acetoacetate formation through an initial carboxylation reaction (Platen and Schink

1989). Acetone was 84% and 78% degraded in 20-day and 28-day (OECD Test Guideline 301D) closed bottle biological oxygen demand tests, respectively (Waggy et al. 1994). Acetone was 89% biodegraded after 25 days, as measured by percent theoretical methane recovery, when incubated with a sediment/groundwater mixture from an anoxic aquifer contaminated with municipal landfill leachate (Suflita and Mormile 1993).

Grove and Stein (2005) studied the removal of acetone from post-primary treatment municipal wastewater in microcosm constructed wetlands. The 90% removal of acetone required 5–10 days in summer (daytime/nighttime temperatures of 24°C and 16°C, respectively) and 10–14 days in winter (daytime/nighttime temperatures of 13°C and 7°C, respectively).

DeWalle and Chian (1981) studied the migration of organics, including acetone, from a landfill site in Delaware, USA, through the surrounding soil and into an aquifer. The concentration of acetone in the landfill leachate was 43 700 µg/L. DeWalle and Chian (1981) calculated attenuation factors for the organics through 500 m of soil by dividing the leachate concentration by the concentration measured in a recovery well located 500 m away. The attenuation factor for acetone was 48 560, meaning that the concentration of acetone found in the recovery well was approximately 0.9 µg/L.

Table 8-2: Environmental half-lives and processes for the removal of acetone in water and soil

Media/removal process	Half-life (unless otherwise noted)	Reference
Aqueous biodegradation, laboratory (disappearance of acetone measured)	2.1–21 h, mean = 4.3 h, after lag period of 5–19 h, non-acclimatized bacteria 4.8–38 h, mean = 12 h, after lag period of 1–2 h, acclimatized bacteria	Rathbun et al. 1982
Aqueous biodegradation in natural stream water	Complete disappearance of acetone in 7 days after lag period of 4–5 days	Rathbun et al. 1991
Volatilization, river	2–10 days	Howard et al. 1990
Volatilization, river	18–19 h	Thomas 1982
Volatilization, lake	16–186 days	Howard et al. 1990
Volatilization, pond	9 days	WHO 1998
Aqueous photolysis	40 days	Betterton 1991
Biodegradation in groundwater	2–14 days[a]	Howard et al. 1991
Removal from post-primary treatment municipal wastewater in	90% removal of acetone in 5–10 days in summer (daytime/nighttime temperature of 24/16°C)	Grove and Stein 2005

Media/removal process	Half-life (unless otherwise noted)	Reference
microcosm constructed wetlands	and 10–14 days in winter (daytime/nighttime temperature of 13/7°C)	
Soil biodegradation	1–7 days[a]	Howard et al. 1991

[a] Scientific judgment based on unacclimatized aqueous aerobic biodegradation half-life.

8.2 Bioaccumulation Potential

Acetone has a very low log K_{ow} value of −0.24 (Table 2). Only one bioconcentration study was found for acetone: Rustung et al. (1931) measured a BCF of 0.69 in haddock. The BCF for acetone was estimated to be 3.2 L/kg by the BCFBAF (2008) program, and its middle trophic level BAF was estimated to be 0.96 L/kg (BCFBAF 2008). Based on the above information, acetone is not expected to bioconcentrate, biomagnify or bioaccumulate.

9 Potential to Cause Ecological Harm

9.1 Ecological Exposure Assessment

This section discusses the environmental exposure data for acetone, and the choice of the predicted environmental concentrations (PECs) to be used in the risk quotient (RQ) calculations (see Characterization of Ecological Risk section). Natural background concentrations of acetone are quite low, based on very low or non-detect levels of acetone measured in many instances in air and water samples from locations not in proximity to point sources (Appendix Tables A1 and A2). Therefore, natural background concentrations were not taken into account in the selection of the PECs.

9.1.1 Air

Acetone has been measured extensively in outdoor air in Canada and the United States. Acetone is commonly included in studies analysing VOCs in air. Concentrations of acetone in air are presented in Table A1 of Appendix A.

Acetone is measured and reported as part of Environment Canada's National Air Pollution Surveillance (NAPS) program (Environment Canada 2011b) (see Table A1, Appendix A). Four- and 24-hour concentrations from 22 monitoring stations nationwide are collected in agricultural, rural, wilderness (e.g., Kejimkujik National Park), urban and industrial locations. Acetone concentrations at all locations, from 2000 to 2009, ranged from 0.003 to 80.2 μg/m^3. The maximum acetone concentration was measured at a rural station in Egbert, Ontario, where the median and 95th percentile concentrations were 5.7 μg/m^3 and 18.2 μg/m^3, respectively, in 4-hour samples (Environment Canada 2011b).

Acetone was also measured in outdoor air outside of homes in Windsor and Ottawa, Ontario, Regina, Saskatchewan, and Halifax, Nova Scotia, in four recent Canadian

studies (Zhu et al. 2005; Health Canada 2010a, b, 2011; see Table A1, Appendix A). Outdoor air concentrations in these Canadian studies ranged from 0.015 to 544.1 µg/m^3, with median concentrations ranging from 0.2 to 12.9 µg/m^3 and 95th percentile concentrations from 6.0 to 245.9 µg/m^3, respectively (Zhu et al. 2005; Health Canada 2010a, b, 2011). The highest outdoor air concentrations were measured in Windsor (Health Canada 2010a).

Acetone has been measured in air near an industrial site in the United States. Twenty-four-hour average concentrations measured at the fence-line of the Eastman Chemical Co. in Tennessee ranged from 50 to 500 µg/m^3 (OECD 1999). Acetone has also been measured in municipal landfill gases in the United States; average concentrations were 6838 and 32 500 parts per billion (ppb) by volume (Zimmerman and Goodkind 1981; Lang 1989). This is equivalent to about 16.2 and 77.2 mg/m^3 in the landfill gases at standard temperature and pressure (STP)[2].

The highest 95th percentile outdoor air concentration of acetone measured in Canada (245.9 µg/m^3 measured in Windsor, Ontario; Health Canada 2010a) was used as a predicted environmental concentration (PEC) in the risk quotient (RQ) calculations for terrestrial plants and mammals (see Table 9-1 below).

9.1.2 Water

No Canadian measurements of acetone in surface water or groundwater or in effluent from point sources were identified. Table A2 in Appendix A contains data on concentrations of acetone in surface water, groundwater and drinking water samples as well as in industrial and landfill effluents in the United States.

Based on concentrations found in seawater, lakes and streams (see A2 of Appendix A), it appears that ambient background levels of acetone in natural waters vary from below the limit of detection (LOD) to 68 µg/L.

From 2002 to 2005, the National Water-Quality Assessment (NAWQA) Program of the US Geological Survey (USGS) measured acetone in over 600 groundwater, surface water and finished water samples in 24 selected community water systems in the United States (USGS 2007). The majority of the samples had non-detectable levels of acetone (< 6 or 7 µg/L). Acetone was quantified in two groundwater samples at a maximum concentration of 68 µg/L. Acetone levels ranged from 0.2 to 0.7 µg/L in six residential well waters adjacent to a landfill in Wilmington, Delaware (DeWalle and Chian 1981).

According to the Screening Information Data Set (SIDS) for acetone (OECD 1999), levels of acetone in natural water and industrial monitoring wells rarely exceed 1 mg/L, and levels found in surface water and groundwater samples are highly dependent on

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[2] The conversion factor is based on the molar volume of an ideal gas and is 1 ppm = 2.374 mg/m^3 for acetone at STP.

the type of water sample, such as industrial, commercial, residential, sea, surface, ground or well.

No data on the concentrations of acetone in natural waters in Canada have been identified. Therefore, environmental concentrations have been estimated for a worst-case aquatic industrial release scenario based on NPRI data (Environment Canada 2011a). The largest amount of acetone reported released or transferred for disposal to water in the years 1997–1998 and 2009–2010 at a single site was input into the equation below (Q). This was a transfer of 39 tonnes for disposal to a municipal sewage treatment plant in 1998 by a manufacturer in the Toronto area. These time periods were used because 1997–1998 were the last 2 years in which there was Canada-wide reporting of acetone to the NPRI, and 2009–2010 were the years when data were available for acetone reporting from Ontario to comply with Ontario VOC regulations (see Releases to the Environment section).

The equation used to estimate the aquatic concentration resulting from an industrial release is as follows:

$$\text{Aquatic concentration (mg/L)} = [1000 \times Q \times L \times (1-R)] \div (N \times F \times D)$$

where:

- Q: total substance quantity used annually at an industrial site (39 000 kg/year)
- L: loss to wastewater (fraction), equal to 1
- R: wastewater system removal rate (fraction), equal to 0
- N: number of annual release days (250 days/year)
- F: wastewater system effluent flow (3456 m^3/day)
- D: receiving water dilution factor (dimensionless), equal to 1

The above scenario uses highly conservative assumptions, such as no removal in a wastewater treatment system before discharge, a relatively small effluent flow volume, equal to wastewater treatment plant effluent flow at the 10th percentile (3456 m^3/day) of the wastewater treatment plant effluent discharge rates across Canada, and no dilution in the receiving water. Based on these assumptions, this scenario yields a PEC value of 45.1 mg/L. This PEC value represents the level of exposure in the receiving water near the point of discharge. This PEC is used in the RQ calculation for pelagic organisms and for water ingestion by terrestrial mammals (see Table 9-1 below).

In comparison, the highest concentration of acetone found in industrial wastewater from the United States is 37.7 mg/L (OECD 1999).

9.1.3 Soil

No measured concentrations of acetone in soil in Canada were identified. In the United States, acetone has been detected in 43% of the soil samples from designated waste disposal sites that were tested for acetone (ATSDR 1994). The mean concentration of

acetone in soil from Summit National Site, a Superfund cleanup site in Ohio, was 9484 µg/kg dry weight (US EPA 1988). The maximum value found in soil from another Superfund site in Puerto Rico was 9500 µg/kg (ATSDR 1994) (the mean concentration was not reported).

The concentration of acetone measured in septic tank effluent from a community septic tank serving 97 homes in Tacoma, Washington, USA was 70.3 mg/L (DeWalle et al. 1985). Septic tank effluent is released to the soil surrounding the septic tank, where it is then subject to dispersion, biodegradation and volatilization. There are some small communities in Canada that use communal septic tanks as their sewage disposal method. From federal inventory information for First Nations communities (Environment Canada 2006), there are 14 First Nations communities with communal septic systems serving populations between 100 and 360 people. Ontario Ministry of the Environment data (OMOE 2003) also indicate three communities in Ontario using communal septic systems serving populations of 165–1240 people; however, it is known that the largest of these communities recently built a sewage lagoon.

Given that virtually no releases of acetone to soil were reported to the NPRI in the years 1997–1998 and 2009, except for 1.1 tonnes in 1997, which represented 0.1% of total releases that year (see Releases to the Environment section), a PEC for soil was not developed.

9.2 Ecological Effects Assessment

A large data set of toxicity values is available for microorganisms, aquatic plants, vertebrates, invertebrates and soil organisms. Summaries of acute and chronic toxicity data for algae, aquatic invertebrates, microorganisms, fish, terrestrial plants, insects, birds and mammals are available in OECD (1999), WHO (1998) and, for aquatic organisms, Hutchinson et al. (2006).

The ability of acetone to inhibit cell multiplication has been examined in a wide variety of microorganisms (5 studies involving 11 species) (OECD 1999). No-observed-effect concentrations (NOECs) were greater than 1700 mg/L for exposures lasting from 6 hours to 4 days.

Studies with aquatic plants, including algae and diatoms, are summarized in OECD (1999), WHO (1998) and Hutchinson et al. (2006). More recently, Han et al. (2008) studied the effects of acetone on spore release by the green alga *Ulva pertusa*, and Tsai and Chen (2007) and Cho et al. (2009) studied the acute (48-hour) toxicity of acetone to the green microalga *Pseudokirchneriella subcapitata.* In total, 11 studies involving 20 species of aquatic plants were identified. Toxicity thresholds or median effective concentrations (EC_{50} values) were all higher than 2400 mg/L, except for one lowest-observed-effect concentration (LOEC) of 530 mg/L, obtained with the blue-green alga *Microcystis aeruginosa* in an 8-day study (Bringmann and Kühn 1978).

A large data set of acute toxicity values is available for aquatic organisms (WHO 1998; Hutchinson et al. 2006), including 11 studies involving 10 species of aquatic invertebrates, 8 studies involving 6 fish species and 2 amphibian studies. Acute LC_{50s} ranged from > 100 to 64 300 mg/L (WHO 1998), with one 10 mg/L result, which was obtained with *Daphnia magna* (Dowden and Bennett 1965). This result is an outlier, as the other four LC_{50s} for *D. magna* were over 9000 mg/L.

The following early-life stage studies were identified: Marquis et al. (2006) found no significant effects on common frog (*Rana temporaria*) embryos and larvae at acetone concentrations of 0.001–0.1 mL/L (0.79–79 mg/L) during 96/48-hour exposures. Hallare et al. (2006) found no effects of acetone on the survival of zebrafish (*Danio rerio*) embryos after a 96-hour exposure, even at the highest concentration tested (2.0% volume per volume [v/v]), but found a LOEC of 1.5% v/v (approximately 11 766 mg/L) for developmental effects.

Two chronic toxicity studies were identified with fish, and one was identified with amphibians (Hutchinson et al. 2006). The two fish studies found no significant effects at concentrations of 10 µL/L (about 7.9 mg/L) in a 52 day study with lake trout (*Salvelinus namaycush*) (Mac and Seelye 1981) and at 2000 µL/L (about 1580 mg/L) in a 60 day study with zebrafish (*Danio rerio*) (Weber et al. 2003). Pollard and Adams (1988) found an acceleration of metamorphosis in the southern cricket frog (*Acris gryllus*) at acetone concentrations of 10 and 50 mg/L, as evidenced by acceleration in forelimb development as well as significant decreases in tail length for both treatments and in total body length for the 50 mg/L treatment compared with the control over the 15-day test period. Metamorphosis was completed in 15 days in the acetone treatment groups compared with 25 days for the control group. In the two acetone treatments, the tail length decreased by 25% and 44% over 15 days, respectively, while in the control group, the tail length increased by 20%. Only two concentrations of acetone were tested in this study, and there was no replication. This study was considered to be of low quality and so was not considered for use in the selection of a critical toxicity value (CTV).

Five chronic or early life-stage exposure studies involving three species were found for aquatic invertebrates (Hutchinson et al. 2006). The two studies of acceptable quality that found adverse effects are described as follows: Bluzat et al. (1979) studied the toxicity of acetone at concentrations of 0.1% [] to 0.6% by volume (equivalent to 790 to 4740 mg/L at 20°C) to the freshwater snail *Lymnea stagnalis* over a 10-month period. Acetone did not cause any mortality, even at the highest treatment level. However, there were sublethal adverse effects: 1) all concentrations of acetone (0.1–0.6%) caused a significant decrease in shell mineralization, as measured by a decrease in its weight/size factor ratio, but this effect was not concentration dependent; 2) the overall fecundity was decreased, starting with a weak effect at 0.2% (1578 mg/L) and proportional to concentration; and 3) a teratogenic effect (double or multiple embryos) was observed in all treatment groups, but the effect was most pronounced at the lower concentrations: at 0.1–0.2%, the rate was 10–12 times higher than in the control group, whereas at 0.4% and 0.6%, the rate was only double that of the control group. The

lowest effect value of 0.2% (1578 mg/L) (reduction of fecundity) was used as the CTV for pelagic organisms (see Table 9-1 below). This study was deemed to be of satisfactory quality (Environment Canada 2013).

LeBlanc and Surprenant (1983) studied the survival of *Daphnia magna* over 28 days. The NOEC from this study was 1400 mg/L, and the LOEC was 2800 mg/L. Given the large spread between the NOEC and LOEC, the geometric mean of these two concentrations (1980 mg/L) was calculated, which is often called the maximum acceptable toxicant concentration (MATC).

For soil-dwelling organisms, four acetone toxicity studies were identified—one with plants and three with invertebrates. Gorsuch et al. (1990) tested the effects of acetone exposure on the germination and growth of radish (*Raphanus sativus*), lettuce (*Lactuca sativa*) and perennial ryegrass (*Lolium perenne*). Acetone solution (0.1–100 mg/L) was used to soak paper towels in a cellophane wrapper (growth pouch), which also contained the plant seeds. No effects were observed on the germination, shoot or root growth of any of the plant species at the highest concentration tested (100 mg/L) after exposure for 7 days.

An acute test was conducted with the soil ciliate *Colpoda inflata* (Ciliophora, Protozoa), which inhabits the soil pore water. The EC_{50} was > 3000 mg/L (Berthold and Jakl 2002). A 48-hour contact toxicity test was conducted with the earthworm *Eisenia foetida* (Roberts and Dorough 1984), where the exposure was through contact with moist filter paper to which the test substance had been added. The LC_{50} for acetone was in the range 100–1000 $\mu g/cm^2$ (exact value not given). Using the ECOSAR (2008) program, a 14-day earthworm (*Lumbricus terrestris*) LC_{50} value of 172 mg/L was predicted. Anderson et al. (2004) performed acute (4-hour) toxicity tests with the soil nematode *Caenorhabditis elegans*, with the endpoint being behavioural—the rate of movement compared with control replicates. The EC_{50} (the concentration needed to reduce average worm movement to 50% of control movement) with acetone was 0.65 mM (37.8 mg/L). This value is the lowest soil toxicity value; however, this study received a low reliability score during the evaluation of its quality, mainly due to incomplete reporting of the test methodology (Environment Canada 2013). Therefore, the ECOSAR (2008) modelled 14-day LC_{50} value of 172 mg/L is considered more reliable for evaluating toxicity to soil organisms. A CTV was not derived for soil, however, as this exposure route is considered unlikely.

Only one avian study was identified, summarized as follows: The 5-day LC_{50}s of acetone for Japanese quail (*Coturnix coturnix japonica*) and ring-necked pheasant (*Phasianus colchicus*) following dietary exposures were greater than 40 000 mg/kg (Hill et al. 1975).

No toxicity data for mammalian wildlife were identified; therefore, toxicity data for laboratory mice and rats were used as a surrogate. Mammalian toxicity data are summarized in the Health Effects Assessment section of this report. The CTVs for mammalian exposures through inhalation and drinking water are reported in Table 9-1.

Studies containing the most sensitive values for endpoints of concern (i.e., aquatic organisms, terrestrial plants, wildlife ingestion, wildlife inhalation) were critically reviewed for integrity. The most sensitive values from the studies deemed to be of acceptable quality were selected as CTVs and are listed in Table 9-1 below. Effects on benthic organisms were not considered, as acetone does not partition appreciably to sediment (see Environmental Fate section). The studies used to derive the CTVs for mammalian exposure through air (Mast et al. 1988) and water (Dietz et al. 1991) were evaluated by Health Canada and determined to be the most sensitive acceptable studies for these endpoints (see Health Effects Assessment section).

For terrestrial plant exposure through air, only one study was identified (Schubert et al. 1995), involving exposure of hydrated pollen to acetone vapours to determine whether the germination rate would be affected. The test method is summarized as follows: An amount of 0.5 mg pollen of *Nicotiana tabacum* was placed into 3.5 cm petri dishes and held in a water saturated atmosphere for one hour, followed by application of germination medium. Then the petri dishes were put into small, tightly-sealed glass troughs (325 cm^3 each), into which acetone was injected by syringe, where it evaporated at once. The pollen was exposed to different concentrations (no concentration data provided) of the test compounds in the dark at 22˚C for 2 hours, following which the percentage of germinated pollen was counted by microscopy, and compared to the germination in a control treatment. The effective dose causing a 25% decrease in germination relative to the control treatment (ED_{25}) was calculated as 12 200 mg/m^3 for acetone. The Schubert et al. (1995) study had some deficiencies, particularly the lack of full data reporting from the experiments with acetone (Environment Canada 2013). However, this lack of full reporting was not considered to have affected the results of the study, and therefore, it was still deemed acceptable to use it to derive the CTV, given the lack of other studies of plant exposure to acetone in air.

9.3 Characterization of Ecological Risk

The approach taken in this ecological screening assessment is to examine various supporting information and develop conclusions based on a weight of evidence approach as required under section 76.1 of CEPA 1999. Particular consideration has been given to sources, releases, occurrence in the environment, risk quotient (RQ) analyses, persistence, bioaccumulation and toxicity.

Acetone has natural and anthropogenic sources throughout Canada. It is manufactured in Canada only as a by-product, but is imported and used by a variety of industrial sectors. Releases of acetone to the environment as reported by Canadian industry are primarily to air, with smaller amounts to water and landfill, and virtually none to soil. Acetone tends to stay mainly in the compartment to which it is released. It is persistent in air, but not in water or soil. Acetone is not bioaccumulative and has low toxicity to aquatic organisms and terrestrial plants and mammals.

RQs were developed for key exposure scenarios in media of concern—namely, air and water. Endpoint organisms were selected based on analysis of exposure pathways. For each endpoint organism, a conservative (worst-case) predicted exposure concentration (PEC) and a predicted no-effect concentration (PNEC) have been determined. The PNEC was arrived at by selecting the lowest CTV for the organism of interest and dividing it by an application factor (AF) appropriate to account for the following sources of uncertainty: interspecies and intraspecies variations in sensitivity, extrapolation of results from laboratory to field and the use of short-term studies to model long-term exposure. AFs of 10 were used for long-term (chronic) toxicity values, and AFs of 100 were used for acute values. An RQ (= PEC/PNEC) was calculated for each of the endpoint organisms. A summary of values used for the RQs is presented in Table 9-1. Derivation of PEC values for air and water is described in the Ecological Exposure Assessment section.

RQs for air and water indicate that acetone concentrations likely do not exceed concentrations associated with effects, even using very conservative scenarios and assumptions. Therefore, there is low risk of harm to aquatic or terrestrial organisms from this substance.

Table 9-1: Summary of values used to calculate risk quotients for acetone

Exposure medium	Organism	CTV	AF	PNEC	PEC	RQ
Urban air	Terrestrial plants (*Nicotiana tabacum*)	12 200 mg/m^3	100	122 mg/m^3	0.246 mg/m^3	0.002
Urban air	Terrestrial wildlife: inhalation (rat)	26 100 mg/m^3	100	261 mg/m^3	0.246 mg/m^3	0.001
Water, near industrial discharge	Pelagic organisms (freshwater snail)	1578 mg/L	10	158 mg/L	45.1 mg/L	0.29
Water, near industrial discharge	Terrestrial wildlife: ingestion from water (mink)[a]	9272 mg/kg-bw per day[b]	10	927 mg/kg-bw per day	4.96 mg/kg-bw per day[c]	0.005

[a] CTV for male rat was converted to CTV for mink because mink is a species native to Canada.
[b] bw = body weight. To derive the CTV_{mink}, the CTV_{rat} (1700 mg/kg-bw per day) was multiplied by an interspecies scaling factor for a typical adult female mink (*Mustela vison*), using the equation: $CTV_{mink} = (CTV_{rat} \times BW_{mink})/DWI_{mink}$, where BW_{mink} is body weight (0.6 kg) and DWI_{mink} is daily water intake (0.11 kg/kg-bw per day) (US EPA 1993). This equation assumes that all exposure to the substance is via water and that the substance is completely bioavailable for uptake by the organism.
[c] This value represents the daily dose for a mink and was obtained by multiplying the aquatic PEC of 45.1 mg/L by the daily water ingestion rate of an adult female mink, 0.11 kg/kg bw per day (US EPA 1993).

Based on the information presentedin this screening assessment, it is concluded that acetone does not meet the criteria under paragraph 64(a) or (b) of CEPA 1999, as it 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.

9.4 Uncertainties in Evaluation of Ecological Risk

Uncertainty was associated with the exposure characterization of acetone.

Non-industrial, anthropogenic sources of acetone in the Canadian environment (e.g., from automobiles and other combustion sources), as well as releases from natural sources and natural background concentrations, have not been quantified in Canada. Nevertheless, there were ample Canadian ambient air data from which to select a PEC in air to represent a very conservative or worst-case exposure scenario. The exposure value used for air was the maximum concentration measured in Canada during the period 2000–2009, and no risk was identified for terrestrial plants or mammals.

No measured concentrations of acetone were identified for surface water or groundwater, effluents from industrial sources or soils in Canada. The exposure value used for water was therefore modelled based on a worst-case exposure scenario using the largest amount of acetone reported to be released or transferred to water at a single site during the years 1997, 1998 and 2009, with no treatment prior to discharge or dilution in the receiving water body. No risk was predicted for aquatic organisms or mammals exposed to acetone in water.

Regarding the effects characterization, only one toxicity study involving exposure of terrestrial plants to acetone vapours was found, and this study contained deficiencies, mainly in the reporting of the data; however, it was nevertheless used to derive a CTV, due to the absence of better studies or information. The RQ for exposure of terrestrial plants to atmospheric acetone was several orders of magnitude below 1. A study of the effects of acetone in soil on the germination and growth of terrestrial plants also showed that acetone caused no effects (see Ecological Effects Assessment section).

10 Potential to Cause Harm to Human Health

10.1 Exposure Assessment

10.1.1 Environmental Media and Food

Data pertaining to concentrations of acetone in ambient air, indoor air, personal air, drinking water, food, soil and humans were identified for Canada and elsewhere. Although numerous studies were identified, only those considered most relevant for assessing exposure of the general population of Canada are summarized and presented in Appendix A (Tables A1 to A4).

Upper-bounding estimates of total daily intake of acetone from air, water, food and beverages, and soil for the general population of Canada are summarized in Appendix

B. Total daily intake of acetone ranged from 133 µg/kg-bw per day for breastfed infants to 650 µg/kg-bw per day for children aged 0.5–4 years. Acetone in food, which is primarily naturally occurring, and acetone in air, which is primarily from anthropogenic indoor sources, including household and cosmetic products, were estimated to be the highest contributors to total daily intake of acetone. Acetone is produced endogenously in the body during natural biological processes. The following exposure characterization focuses on external (non-endogenous) sources of acetone from environmental media, food and products.

10.1.1.1 Ambient Air, Indoor Air and Personal Air

Acetone has been measured extensively in ambient (outdoor) and indoor air in Canada and the United States. Acetone is commonly included in studies analyzing VOCs in air. Concentrations of acetone in air are presented in Table A1 of Appendix A.

Acetone is measured and reported as part of Environment Canada's NAPS program. Four- and 24-hour acetone concentration data from 22 monitoring stations nationwide are collected in agricultural, rural, urban and industrial locations. In 3688 24-hour samples collected from 2000 to 2009, acetone concentrations ranged from 0.007 to 35.2 µg/m^3, with a median concentration of 2.9 µg/m^3 and a 95th percentile concentration of 6.6 µg/m^3. Over the same time period, in 5754 4-hour samples, acetone concentrations ranged from 0.003 to 80.2 µg/m^3, with a median concentration of 2.9 µg/m^3 and a 95th percentile concentration of 12.4 µg/m^3. The maximum acetone concentration was measured at an agricultural station in Egbert, Ontario, where median and 95th percentile concentrations were 5.7 µg/m^3 and 18.2 µg/m^3, respectively (Environment Canada 2011b).

Acetone was also measured in ambient and indoor air in four recent Canadian studies. Measurements took place in Windsor, Ontario, Regina, Saskatchewan, Halifax, Nova Scotia, and Ottawa, Ontario, as part of the Windsor Ontario Exposure Assessment Study (Health Canada 2010a), the Regina Indoor Air Quality Study (Health Canada 2010b), the Halifax Indoor Air Quality Study (Health Canada 2011) and the Ottawa Residential Home Study (Zhu et al. 2005). In the Windsor study, 45–48 non-smoking participant homes were monitored between January 2005 and August 2006, with samples collected over 24-hour periods for 5 consecutive days. In the Regina study, 146 homes, of which 34 homes had at least one smoking participant, were monitored in 2007 with 24-hour and 5-day samples. In the Halifax study, 50 homes were recruited in both the winter and the summer of 2009, and acetone concentrations indoors and outdoors for seven consecutive 24-hour periods were collected. In these three studies, active air samplers were deployed concurrently inside and outside the home. The Ottawa study is an earlier study sponsored by Health Canada in which acetone was measured in 75 homes between November 2002 and March 2003. Each home was sampled once, and indoor and outdoor active samplers were deployed, with 10 L of air collected over 100 minutes (Zhu et al. 2005).

Ambient air concentrations in these Canadian studies ranged from 0.015 to 544.1 μg/m^3, with median and 95th percentile concentrations ranging from 0.2 to 12.9 μg/m^3 and from 6.0 to 245.9 μg/m^3, respectively (Zhu et al. 2005; Health Canada 2010a, b, 2011). The maximum ambient air concentration was measured in Windsor (Health Canada 2010a). Indoor air concentrations were generally higher than ambient air concentrations and ranged from 0.01 to 3755.5 μg/m^3, with median and 95th percentile concentrations ranging from 21.8 to 173.8 μg/m^3 and from 101.8 to 647.2 μg/m^3, respectively (Zhu et al. 2005; Health Canada 2010a, b, 2011). Both the lowest and highest indoor air concentrations were measured in Windsor (Health Canada 2010a). Indoor and ambient (outdoor) air concentrations have also been measured in several American studies (Heavner et al. 1996; Girman et al. 1999; NYSDOH 2005; Weisel et al. 2005, 2008). In the United States, reported acetone concentrations in homes ranged from < 0.25 μg/m^3 (NYSDOH 2005) to 664.99 μg/m^3 (Heavner et al. 1996).

Two general trends were observed from these studies: indoor air concentrations of acetone are higher than ambient air concentrations, and concentrations of acetone are higher in the summer than in the winter. In the Windsor study, the indoor/outdoor ratio for acetone was greater than 10, indicating predominately indoor sources for acetone (Stocco et al. 2008).

The presence of acetone in indoor air may be attributed to various anthropogenic sources, including evaporative loss and releases from products and as a by-product from incomplete combustion (gas stove, gas fireplace, smoking). Natural sources may include plants and exhaled air. Solomon et al. (2008) examined diurnal patterns in indoor VOC concentrations in Germany in 2005. That study showed elevated levels of acetone indoors at most times during the day; the authors concluded that this likely was not caused by typical anthropogenic sources, such as off-gassing from the building, but rather was related to the occupants' expired air, a local kitchen and indoor plants (Solomon et al. 2008).

Acetone is a component of cigarettes and tobacco smoke, which are sources of acetone exposure from indoor air. Health Canada requires tobacco companies to report information about 26 chemical constituents found in tobacco and 41 chemical emissions found in tobacco smoke; acetone is on this list (2011 email from Risk Management Bureau, Health Canada, to Existing Substances Risk Assessment Bureau, Health Canada; unreferenced). Median indoor acetone concentrations in smoking and non-smoking households in the Regina Indoor Air Quality Study were similar; however, smoking households had higher maximum concentrations in the winter and lower maximum concentrations in the summer (Health Canada 2010b). Lower acetone concentrations in smoking households during the summer months could be due to increased ventilation in these homes. In a study conducted in New Jersey, concentrations of acetone in indoor air were highest in smoking environments, particularly in workplaces, where concentrations up to 21 083 μg/m^3 were measured (Heavner et al. 1996).

Typically, air concentration data from fixed ambient air monitoring stations and fixed indoor air samplers are used to characterize population air exposures. However, for acetone, several studies, including one Canadian study conducted in Windsor, Ontario, measured concentrations of acetone in personal air in addition to indoor air over a 24-hour period (Weisel et al. 2005; Health Canada 2010a; Geiss et al. 2011). Selected participants in the Windsor study wore backpacks equipped with sampling apparatus over 24-hour periods for 5 consecutive days to measure personal exposure to acetone in air. Participants were asked to wear the sampling equipment during the normal course of a day; however, individuals with expected occupational exposure to acetone were not eligible. The highest concentration reported among Windsor participants wearing personal backpackswas 1871.9 µg/m^3, while the corresponding median and 95th percentile values were 116.1 and 475.9 µg/m^3, respectively (Health Canada 2010a). Personal air data, as opposed to fixed ambient and indoor air data, are considered to be more representative of acetone intake through inhalation, as the sampling apparatus samples the air surrounding the individual, similar to what is present in the breathing zone. This value is expected to provide a conservative estimate of daily intake to acetone from air, as acetone concentrations in indoor and outdoor air in Windsor were higher than in Regina, Halifax and Ottawa, and personal air samples were collected in the summer, when acetone air concentrations are generally higher than in the winter. Note that the 95th percentile concentrations of acetone in personal air, indoor air and outdoor air measured in the summer of 2005 in Windsor were 475.9, 647.2 and 19.8 µg/m^3, respectively. Therefore, the 95th percentile value for the concentration of acetone from personal air sampling from the study conducted in Windsor (475.9 µg/m^3) was used to calculate total daily intake of acetone from air.

In analyzing data collected in Windsor (Health Canada 2010a), Stocco et al. (2008) found that indoor air acetone concentrations were higher than personal concentrations in the summer, but not in the winter. The annual personal/indoor air acetone concentration ratio was 1.01. A mixed effects model indicated that approximately 46% of the variability in personal acetone levels could be accounted for using indoor concentrations, season and air exchange rates. In the Relationships of Indoor, Outdoor, and Personal Air (RIOPA) study conducted in three US cities, the study authors concluded that indoor air concentration accounted for less than 20% of the variance of personal exposure variability for acetone (Weisel et al. 2005; Liu et al. 2007). In addition, personal exposure was significantly higher than residential indoor concentrations. The personal exposure was largely attributed to yard and gardening activities and nail polish hardener/remover use (Liu et al. 2007). In a study conducted in 11 cities across Europe (AIRMEX), median personal air concentrations of acetone were similar to concentrations in private homes, slightly higher than concentrations in public buildings (offices, schools) and much higher than concentrations in outdoor air (2011 email Geiss to Existing Substances Risk Assessment Bureau, unreferenced; Geiss et al. 2011), implicating indoor air as a major contributor to personal air concentrations.

It is recognized that the use of products containing acetone in indoor environments could result in higher peak acetone exposures over a short period; intake estimates resulting from these uses are discussed in the Products section.

10.1.1.2 Drinking Water

Acetone is not routinely measured as part of provincial or municipal drinking water surveillance programs in Canada. Acetone was measured in tap water collected from 71 homes in Ottawa, Ontario, in 2002 and 2003; concentrations ranged from < 2 to 131 µg/L, with a 95th percentile concentration of 48 µg/L and a mean concentration of 11.0 µg/L (2003 personal communication from J. Zhu Health Canada Chemistry Research Division to Existing Substances Risk Assessment Bureau, unreferenced). Acetone was not detected during sampling of 30 potable water treatment facilities across Canada in 1979, but this was likely due to the very high quantification limit (~1000 µg/L) (Otson et al. 1982). In the United States, acetone was detected in drinking water from 10 cities as part of the 1975 National Organics Reconnaissance Survey; however, it was quantified at only one site in Seattle, Washington, at a concentration of 1 µg/L (US EPA 1975). In Texas, a maximum acetone concentration of 10.7 µg/L was reported in water samples taken from eight residences as part of the Lower Rio Grande Valley Environmental Monitoring Study (US EPA 1994). Acetone levels ranged from 0.2 to 0.7 µg/L in six residential wells adjacent to a landfill in Wilmington, Delaware (DeWalle and Chian 1981).

Acetone was measured in over 600 groundwater, surface water and finished water samples from 2002 to 2005 in 24 selected community water systems in the United States (USGS 2007). The majority of the samples had non-detectable levels of acetone (< 6 or 7 µg/L); however, acetone was quantified in seven finished water samples at a maximum concentration of 11.73 µg/L (Carter et al. 2007; USGS 2007). Finished water was defined as water that had passed through all the processes in a water treatment plant and was ready to be delivered to consumers.

A number of Canadian and US studies measured acetone in drinking water; concentrations are presented in Table A2 of Appendix A. The 95th percentile value for the concentration of acetone in 71 samples of tap water from homes in Ottawa, Ontario (48 µg/L), was used to calculate total daily intake of acetone from drinking water.

10.1.1.3 Food and Beverages

Acetone occurs naturally in a wide variety of foods, including fruits, vegetables and dairy products. It has been detected in baked potatoes (Coleman et al. 1981), nectarines (Takeoka et al. 1988), kiwi fruit (Bartley and Schwede 1989), roasted filbert nuts (Kinlin et al. 1972), chicken (Grey and Shrimpton 1967; Shahidi et al. 1986), cured pork (Hinrichsen and Anderson 1994), mutton and beef (Shahidi et al. 1986) and blue cheese (Day and Anderson 1965). Based on the compilation by the Division for Nutrition and Food Research TNO, acetone was also detected in papaya, raspberries, blackberries, ginger, parsley, cocoa, endives, asparagus, sherry and orange juice (van Straten and Maarse 1983; Maarse and Visscher 1989). Acetone has been detected, but

not quantified, in human milk of nursing mothers (Pellizzari et al. 1982; Giroux et al. 1992).

Concentrations of acetone quantified in food are presented in Table A3 of Appendix A. Acetone was measured at concentrations up to 3000 µg/kg in strawberries (van Straten and Maarse 1983), the mean value was 2000 µg/kg in black currants from Sweden (Andersson and von Sydow 1966) and the mean concentration (dry weight) was 600 µg/kg in apples (Feys et al. 1980; Maarse and Visscher 1989) and at trace levels in mangos from Sri Lanka (MacLeod and Pieris 1984). The highest concentration of acetone identified in vegetables was 16 000 µg/kg in tomatoes (van Straten and Maarse 1983), with lower levels found in canned and frozen sweet corn (Bills and Keenan 1968), beans (common, lima and mung beans, soybeans), split peas and lentils (Lovegren et al. 1979), potato chips (Mookherjee et al. 1965) and carrots (Heatherbell et al. 1971; Maarse and Visscher 1989). Acetone was measured at concentrations ranging from 20 to 1700 µg/kg in beer (Rosculet and Rickard 1968; van Straten and Maarse 1983) and from 6 to 200 µg/L in apple cider from Britain (Williams et al. 1980). Acetone was quantified in bread at concentrations up to 10 100 µg/kg (Maarse and Visscher 1989). Although many of the concentrations of acetone in food commodities were measured over 30 years ago, these data are considered relevant today, as it is not anticipated that naturally occurring concentrations of acetone in unprocessed food will have changed significantly over this period.

Acetone is produced endogenously in dairy cattle. Milk from healthy cows typically contains up to 11.6 mg/L (approximately 11 600 µg/L, using a density of 1.03 kg/L for milk) of acetone (ACC 2003). A US Environmental Protection Agency (EPA) study investigated the presence of VOCs in commercially available whole, 1% and 2% milk samples from Las Vegas, Nevada. In all milk samples (whole, 2%, 1%), the average acetone concentration ranged from 0.029 to 0.031 mg/L (from 29 to 30 µg/kg), and the maximum concentration ranged from 0.037 to 0.043 mg/L (from 36 to 42 µg/kg) (Hiatt and Pia 2004). However, high acetone levels have been reported in cow’s milk from cattle under ketotic stress, which occurs in approximately 4–5% of cows due to glucose shortages caused by milk production or metabolic demands associated with later stages of gestation (ACC 2003). In a study involving 10 375 registered Holsteins in southern Ontario dairy herds, the mean and maximum concentrations of acetone in raw milk were 1.32 mg/L (1280 µg/kg raw milk) and 278 mg/L (269 900 µg/kg raw milk), respectively, although only 7% of the samples analyzed contained detectable levels of acetone (detection limit not specified) (Wood et al. 2004). In a study of the diurnal variations of milk production in hyperketonemic Swedish dairy cows, milk acetone levels ranging from 18.6 to 225.6 mg/L (18 000 to 219 000 µg/kg raw milk) were also reported (Andersson and Lundstrom 1984). In other studies involving dairy products, the average concentrations of acetone in cheddar cheese and fresh sweet cream butter samples from the United States were reported to be approximately 8500 µg/kg and 130 µg/kg, respectively (Day et al. 1960; Siek and Lindsay 1970).

Acetone is on the Flavour and Extract Manufacturers Association (FEMA) Generally Recognised as Safe (GRAS) list in the United States when present in beverages, baked

foods, desserts and preserves at concentrations ranging from 5 to 8 mg/L (Oser and Ford 1973). In Canada, acetone is a permitted food additive where it may be used as a carrier or extraction solvent in spice extracts leaving a maximum residue of 30 ppm and in meat/egg marking inks at levels consistent with Good Manufacturing Practices, according to the *List of Permitted Carrier or Extraction Solvents* as incorporated by reference into the *Marketing Authorization for Food Additives That May Be Used as Carrier or Extraction Solvents* (Health Canada 2012a). Additionally, acetone may be used as a solvent for many applications related to food packaging components, and the presence of acetone in food packaging applications is the result of impurities deriving from normal manufacturing and processing practices. In the United States, acetone is permitted at concentrations up to 30 ppb as an extraction residue in spice oleoresins, as an extraction solvent for obtaining paprika oleoresin and turmeric oleoresin, as a diluent in colour additive mixtures for food, as a pH adjusting agent in preparations of the colour additive annatto extract and as an indirect additive in food contact packaging, according to the Everything Added to Food in the United States (EAFUS) database (US FDA 2011). The use of acetone in foods in Canada is consistent with international uses of acetone (FAO/WHO 1998; US FDA 2011). According to Fenaroli's Handbook of Flavor Ingredients, acetone is reported to be used in the following food categories (usual use level; maximum use level): alcoholic beverages (0.37 ppm; 0.37 ppm), baked goods (3.00 ppm; 9.00 ppm), fats and oils (14.00 ppm; 20.00 ppm), frozen dairy (3.00 ppm; 5.00 ppm), gelatins and puddings (0.60 ppm; 0.60 ppm), jams and jellies (0.27 ppm; 0.27 ppm), milk products (1.60 ppm; 1.60 ppm), non-alcoholic beverages (0.57 ppm; 0.57 ppm), snack foods (5.00 ppm; 10.00 ppm), soft candy (0.88 ppm; 5.40 ppm) and sweet sauce (1.30 ppm; 1.30 ppm) (Burdock 2010).

Screening-level (or upper-bounding) dietary intake estimates for acetone were generated using maximum levels reported in the literature and are outlined in Appendix B. Dietary intake was lowest in the 60+ years age group, with an intake estimate of 126 µg/kg-bw per day, and highest in infants aged 0–6 months (not formula fed), at 396 µg/kg-bw per day. Vegetables and cereal products were the primary contributors to dietary intake estimates. However, it is noted that the reported concentrations of acetone in foods were obtained mainly from non-Canadian databases, which may not necessarily represent primary sources of these foods for the Canadian population. Furthermore, use of maximum concentrations may overestimate potential dietary intake to acetone, particularly since concentrations vary widely among published data sets and maximum values were extended to all foods within a food group.

10.1.1.4 Soil and Dust

Only limited data were identified on concentrations of acetone in soil (Table A4 in Appendix A). The mean concentration of acetone in soil from the Summit National Site, a waste disposal site located in Ohio, and the maximum concentration of acetone in soils from the Vega Alta Public Supply well sites in Puerto Rico were 9484 and 9500 ng/g, respectively (US EPA 1988; ATSDR 1994). Acetone was also identified in 43% of the soil samples taken from designated waste disposal sites in the United States (ATSDR 1994). No data were found quantifying acetone concentrations in dust.

10.1.2 Products

Data pertaining to concentrations of acetone in various products in Canada, the United States and Europe were identified and are summarized below.

A survey conducted pursuant to section 71 of CEPA 1999 indicated that a wide range of products contain acetone, including automobile refinishing paints, paints and coatings, automotive care and maintenance products (e.g., air intake cleaners, brake cleaners, carburetor cleaners), and spray-grade contact adhesives with levels of acetone ranging from < 1% to 100% (Environment Canada 2004). The list of products and concentration ranges identified in the above survey were generally consistent with identified uses in the United States. The US Household Products Database lists over 500 products containing acetone, including various paints, glazes and varnishes, paint products (thinners and cleaners), cleaners, arts and craft supplies, sealants, wood fillers and hardeners, pesticide products, adhesives and lubricants. The concentration of acetone in these products ranges from 1% to 100% for all forms (aerosol, gel, liquid and paste) (HPD 1993–). A summary of the types of products and the concentrations of acetone in these products is provided in Table 10-1.

Table 10-1: Summary of products identified by the US Household Products Database (HPD 1993–)

Type of product	Number of products	Concentration range (%)
Paint / glaze / varnish (aerosol)	376	15–60
Paint / glaze / varnish (liquid)	15	< 35–58
Paint thinner (liquid)	3	15–95
Glue / adhesive (aerosol)	10	5–65.5
Glue / adhesive (liquid / paste)	37	0–75
Cleaner (aerosol)	20	1–100
Cleaner (liquid, gel, cream)	25	1–100
Sealant (aerosol)	9	< 5–30
Wood hardener (liquid)	1	72
Wood filler (paste)	4	5–35
Pet deodorizer (aerosol)	1	60–80
Lubricant (aerosol)	3	10–40
Pesticidal spray (aerosol)	5	10–21.5

The US EPA's Source Ranking Database also provided a list of approximately 1300 products that contain acetone, including paint (aerosol and liquid), paint remover, cleaners, stains, varnishes, sealants, furniture and lubricants (SRD 2004). The percentage of acetone contained in these products ranged from < 0.1% to 100%. In studies carried out by the Danish Environmental Protection Agency, acetone was detected in animal care products (Nylén et al. 2004), adult toys (Nilsson et al. 2006), balloons (Nilsson 2007), candles (Eggert et al. 2002), Christmas sprays (Laursen and Trap 2002), creams for treatment of sports injuries (Hansen et al. 2006), electronic

products (Malmgren-Hansen et al. 2003), hairstyle products (Poulsen et al. 2002), hobby adhesives (Nilsson and Staal Jensen 2003), joint sealants (Nilsson et al. 2004), perfume in toys and children's articles (Glensvig and Ports 2006), printed material (Hansen and Eggert 2003), products made of exotic wood (Witterseh 2004), products used in live role play (weapons, masks, etc.) (Vogt-Nielsen and Hagedorn-Rasmussen 2007), proofing sprays (Feilberg et al. 2008), shoe care products (Engelund and Sørensen 2005), spray paint (Nielsen et al. 2003), stain removers (Engelund et al. 2003), tents and tunnels for children (Hansen et al. 2004) and textile colorants (Egmose and Pors 2005). Acetone has also been detected in air fresheners (Steinemann et al. 2011) and flooring materials (European Commission 1997).

Acetone has been reported as an ingredient in approximately 300 cosmetic product formulations notified to Health Canada; a summary of the concentration ranges for the various types of products is presented in Table 10-2. Health Canada has been notified that acetone may be present at concentrations up to 30% by weight in hairspray, eyelash adhesives and eyelash removers and up to 100% by weight in artificial nail and nail polish removers (2011, emails from the Consumer Product Safety Directorate, Health Canada, to the Existing Substances Risk Assessment Bureau, Health Canada; unreferenced). It has also been reported in face mask products, in which acetone may be present at a concentration range of 30–100% by weight (2011, emails from the Consumer Product Safety Directorate, Health Canada, to the Existing Substances Risk Assessment Bureau, Health Canada; unreferenced).

Table 10-2: Summary of cosmetic products notified under the *Cosmetic Regulations* to Health Canada

Type of product	Concentration range (%)
Nail polish remover (liquid / gel)	> 10–100
Artificial nail remover (liquid / gel)	> 10–100
Nail polish	> 0.1–100
Polish thinner (liquid)	> 10–100
Manicure product other (liquid / gel)	> 3–100
Eyelash adhesive (liquid / gel)	> 10–30
Eyelash remover (liquid / gel)	> 10–30
Eyelash products other (liquid / gel)	> 10–100
Hairspray (aerosol)	> 1–30
Hairspray (pump)	> 3–30
Tanning spray (pump)	> 1–10
Anti-wrinkle preparation (lotion)	> 0.3–1
Moisturizer (lotion)	> 0.1–0.3
Cleanser (lotion)	> 0.3–10
Mask (liquid)	> 30–100

Air concentrations and inhalation intake estimates from the use of household and cosmetic products were generated and are presented in Appendix C. The information provided in the US Household Products Database was considered recent and

representative of the Canadian market; concentrations listed in Table 10-2 were used in the estimate of general population intake from the use of household products. Based on the products identified, intake estimates were generated for three scenarios considered to represent highest exposures: inhalation exposure from spray painting, inhalation exposure from sealing a concrete floor in a basement, and dermal and inhalation exposure from use of acetone cleaner as a degreasing agent. In addition, intake estimates were generated for the use of five product categories identified in Table 10-2, including artificial/gel nail removers, hairsprays, face masks, moisturizers and cleansers. Although nail polish and nail polish removers are the most common cosmetic products containing acetone, quantitative intake estimates were not generated, as exposure to acetone is anticipated to be greater from the removal of artificial/gel nails. Intake estimates generated for the nail removal scenario are considered protective of nail polish and polish remover uses. Intake estimates were generated using the American Industrial Hygiene Association (AIHA) Exposure Assessment Strategies Committee Industrial Hygiene Modelversion 0.198 (IHMod) and the AIHA Industrial SkinPerm Model version 1.03 (SkinPerm model) (AIHA 2009a, 2010). IHMod was considered to be a relevant and suitable model for acetone, as it is suitable for substances with low boiling points, it is able to model evaporation from a standing pool and it is able to model a dermal flux for acetone, all of which were required for the infinite dose exposure scenarios. A dermal absorption rate of 100% was assumed for finite dose exposure scenarios. Dermal absorption of acetone has also been shown to occur rapidly in humans. In a Japanese study, when volunteers were exposed to an unspecified dose of acetone via skin for 2 hours/day for 4 days, immediate absorption with peak levels at the end of each application was reported (Fukabori et al. 1979). Acetone is often used as a vehicle for dermal studies of other chemicals, but no studies have quantitatively measured the uptake of acetone via the dermal route.

The spray paint intake estimate was derived based on an individual spraying an entire can of paint, containing 60% acetone, over a 15-minute period in a well-ventilated garage and remaining in the area an additional 5 minutes after the application period was complete. The concrete sealant scenario modelled an individual painting a 37.5 m^2 basement room for 1 hour; typical ventilation rates were utilized, recognizing that ventilation would be limited in a basement, but that the individual would likely make efforts to maximize air exchange. The ventilation rate was assumed to be 2.5 times lower than in the spray paint scenario, and the release of acetone from the product was assumed to be linear over the drying time of the product. For the cleaner/degreaser intake estimate, dermal and inhalation exposures were expected to occur while cleaning objects with acetone (e.g., auto parts). The scenario modelled an individual pouring acetone onto a rag and using this to clean an object. As acetone is highly volatile, it was assumed that acetone would be added to the rag throughout the process to maintain a constant “wetness.” For dermal exposure, it was assumed that one half the surface area of the individual’s hand was in contact with acetone for the duration of the activity and that acetone was absorbed at the maximal rate for this time frame; the mean event concentration was estimated assuming a linear rate of evaporation of acetone from the cloth during the process and that all acetone had evaporated by the end of the activity.

Mean and peak air concentrations of acetone during the event were estimated using the well-mixed room model with constant emission rate algorithm in IHMod.

The artificial nail removal scenario modelled an individual soaking her fingertips in a tray filled with acetone; the individual was exposed to acetone both dermally and via inhalation due to evaporation of acetone from the tray. IHMod was used to estimate a rate of evaporation of acetone from the tray. Air concentrations were estimated using a one-box model (well-mixed room) (AIHA 2009b). The dermal intake estimate for this scenario (soaking fingertips in pure solvent) was based on the maximum flux of dermal absorption for acetone estimated by the SkinPerm model (AIHA 2010). The hairspray, face mask, skin cleanser and moisturizer scenarios were set in a bathroom, and the individual was assumed to remain in the bathroom for a total of 25 minutes. For hairspray, acetone released from an aerosol can was considered to be in the vapour form and available for inhalation intake. In the case of skin cleanser, it was assumed that, after application, the majority (99%) was either rinsed or washed off; the acetone in the fraction remaining on the skin (1%) was100% dermally absorbed. As lotions remain on the skin, the upper-bounding estimate of exposure from use of moisturizer assumes that all of the acetone in the applied product is 100% dermally absorbed. As all of the acetone was assumed to be dermally absorbed in the skin cleanser and moisturizer scenarios, an inhalation exposure estimate was unnecessary.

Peak acetone air concentrations following the use of spray paint, concrete sealant and 100% acetone as a cleaner/degreaser were estimated at 4415, 3830 and 1500 mg/m3, respectively, while 4-hour time-weighted average (TWA) concentrations were estimated at 232, 526 and 32 mg/m3, respectively. Acetone concentrations in air following the use of artificial/gel nail removers, hairsprays and face masks were also generated. Peak air concentrations ranged from 117 to 209 mg/m3, while 4-hour TWA concentrations (per event) ranged from 8 to 15 mg/m3. Total exposure estimates following the use of cosmetic products ranged from 0.03 to 0.95 mg/kg body weight (kg-bw) per event; the highest exposure was following the use of artificial/gel nail removers. These exposure estimates are considered to represent the upper bounds of potential acute exposure from occasional, intermittent use of products containing acetone. These estimates are considered conservative, as they were derived using products with the highest identified acetone concentrations.

Frequent use of household and cosmetic products containing acetone contributes to acetone concentrations measured in personal air samples, which were used to derive the total daily intake estimates, as presented in Appendix B. Therefore, the total daily acetone intake estimates reflect the contribution from frequent use of household and cosmetic products containing acetone.

10.1.3 Biomonitoring Data

Acetone is produced naturally in the body when fats and lipids are metabolized; this occurs primarily in the liver. Acetone is then transported to all tissues and organs of the body, where it can be used as a source of energy. The majority of acetone is eliminated

from the body through expired air, either unchanged or following metabolism, with lesser amounts excreted in urine (ATSDR 1994). Acetone has been measured extensively in a variety of biological media, including blood, exhaled air and urine. As previously stated, the focus of this exposure characterization is the non-endogenous (environmental media, food and products) component of total exposure, described above.

Reference ranges of acetone concentrations in whole blood for the general US population were established based on the analysis of 1062 blood samples from non-occupationally exposed adults as part of the Third National Health and Nutrition Examination Survey (NHANES III) from 1988 to 1994; median, 5th and 95th percentile concentrations of acetone in blood are 1800 ppb (~1.8 mg/L), 640 ppb (~0.6 mg/L) and > 6000 ppb (> 6.0 mg/L), respectively (Ashley et al. 1994). Wu (2006) presented reference intervals for acetone concentrations in blood, which include < 20 mg/L for a healthy individual, < 100 mg/L following occupational exposure and 100–700 mg/L for an individual with diabetic ketoacidosis; > 200 mg/L is considered a toxic concentration. Morgott (2001) presented average concentrations of acetone in normal healthy adults ranging from 0.41 to 4.35 mg/L in plasma samples, from 0.84 to 1.8 mg/L (minimum–maximum: 0.0–17.4 mg/L) in whole blood samples, from 0.76 to 3.02 mg/L (minimum–maximum: 0.13–9.35 mg/L) in urine samples and from 0.71 to 1.52 µg/L (minimum–maximum: 0.02–8.25 µg/L) in expired air samples. Peden (1964) reported average serum levels in infants and children ranging from 12 mg/L in newborns to 9 mg/L in teenagers; concentrations up to 140 mg/L were found in 2- to 5-day-old healthy infants. In studies of occupational exposure to acetone, inhaled acetone concentrations are strongly related to concentrations in expired air and blood (Morgott 2001).

It has been estimated that normal healthy adults produce acetone at levels ranging from 20 to 72 mg/kg-bw per day, with a typical rate of 40.9 mg/kg-bw per day (i.e., 2.9 g/day) (Reichard et al. 1979; Morgott 2001). Endogenous acetone production has normal diurnal variations. Dieting, vigorous physical exercise, high fat consumption, lactation and other physiological states can appreciably increase the body burden of acetone through the process of ketogenesis (ATSDR 1994). For example, infants, pregnant women and exercising humans can have ketone body levels that are 2–20 times higher than normal because of their higher energy requirements (Morgott 2001). Increased acetone production is also associated with certain disease states (i.e., starvation, alcoholism, diabetes mellitus, hypoglycemia), and blood acetone levels in normal healthy adults, fasting adults, moderate diabetics and severe diabetics have been reported to be 11, 44, 90 and 189 mg/L, with corresponding production rates of 41, 105, 81 and 637 mg/kg-bw per day, respectively (Morgott 2001). Because acetone levels in the body are influenced by so many factors, endogenous levels can be expected to vary widely between individuals.

It should be noted that exposure to other chemicals that are metabolized to acetone, such as isopropyl alcohol, or to any chemical that can cause oxidative stress through lipid peroxidation can also lead to elevated blood, expired air or urinary levels of acetone (Morgott 2001).

10.1.4 Confidence in Exposure Database

Overall confidence in the exposure database for determining estimates of acetone intake from environmental media and food is considered moderate. Representative, high-quality Canadian data were available for acetone concentrations in ambient air, indoor air, personal air and drinking water, resulting in high confidence in the upper-bounding intake estimates from these media. Very few data were available quantifying acetone concentrations in soil and dust; however, due to the volatility of acetone, significant concentrations are not anticipated in these media, and soil and dust are considered to be minor contributors to total acetone intake. Although acetone has been detected in breast milk, there are no data quantifying concentrations in breast milk; thus, the contribution from breast milk was not captured in the dietary intake assessment for infants, which is an uncertainty. There are very limited data quantifying concentrations of acetone in different food commodities. The use of maximum concentrations may overestimate potential dietary exposure to acetone, particularly since concentrations vary widely among published data sets and maximum values were extended to all foods within a food group.

Overall confidence in the exposure database for products is low to moderate. The following uncertainties limit the ability to quantify the level of conservatism associated with the estimate of exposure from consumer use of products. Due to the wide range of products that contain acetone at concentrations up to 100%, individual exposures are expected to vary greatly, and not all products and uses may have been identified—for example, the exact use pattern associated with acetone as a household cleaner. In the absence of data on the rate of emission of acetone from concrete sealant, it was assumed to be linear over the drying time of the product; the actual emission rate is unknown and may be higher. While acetone is known to be readily absorbed via the dermal route, the actual flux is unknown; therefore, models were used to estimate dermal absorption for products and scenarios where acetone was the primary formulant. Estimates of exposure from products are considered to be in the upper bounds, because exposure estimates were calculated using the product with the highest identified acetone concentration, and the frequency of use was based on those who perform the activity.

Determining total systemic concentrations of acetone is complicated by its endogenous production; as such, intake estimates were presented separately from endogenous production levels. Intake of acetone from environmental media, food and products is a minor contributor to total acetone levels in the body.

10.2 Health Effects Assessment

Acetone has not been classified by any agency or regulatory body on the basis of its toxicological properties, including genotoxicity and carcinogenicity. WHO (1998) concluded that acetone is not genotoxic, and the US EPA (2003) described acetone as negative in almost all of the available genotoxicity assays, but did not provide an overall weight of evidence evaluation. Numerous authoritative reviews have been published on

acetone. These include assessments by the International Programme on Chemical Safety (WHO 1998), OECD (OECD 1999) and US EPA (US EPA 2003), an earlier assessment and an update by the Agency for Toxic Substances and Disease Registry (ATSDR 1994, 2011), an International Uniform Chemical Information Database (IUCLID) dossier (European Commission ©2000a), a major toxicology review (Morgott 2001), documentation on the Acute Exposure Guidance Limit (AEGL) (NRC 2005) and a submission as part of the US EPA’s Voluntary Children’s Chemical Evaluation Program (ACC 2003). Relevant studies on acetone toxicity and toxicokinetics in animals and humans as well as information on mode of action were identified from these reviews. In addition, information on acetone was obtained from reviews by IUCLID (European Commission ©2000b), the International Agency for Research on Cancer (IARC 1999), WHO (1990) and a Screening Information Data Set (SIDS) dossier (OECD 2002).

The following sections present a summary of the available information on the health effects of acetone in animals and humans. Further details for each study are provided in Appendices D and E.

10.2.1 Toxicokinetics

Acetone is miscible in water and has a high vapour pressure and a high blood/air partition coefficient ($K_{B/A}$). The low K_{ow} indicates that acetone selectively partitions into an aqueous phase rather than a lipid phase; however, acetone is also slightly lipophilic, allowing for some diffusion into tissues. Overall, the physicochemical parameters and related biological factors allow for rapid absorption of acetone via the respiratory and gastrointestinal tracts and also for wide distribution within the body, particularly to the organs with high water content. The toxicokinetics of acetone is similar in humans and rodents.

Rapid absorption via the oral route was demonstrated in human studies in which 65–93% of administered acetone was metabolized and residual material was excreted from the body over a period of 2 hours (Haggard et al. 1944). Case studies of accidental poisonings through ingestion of liquid cement or nail polish or by accidental administration of acetone through a gastric tube also provide evidence of extensive and rapid acetone absorption via the oral route (Ramu et al. 1978; Gamis and Wasserman 1988; Sakata et al. 1989; Herman et al. 1997).

Rodent studies demonstrated that acetone is rapidly absorbed through the inhalation route, with the peak blood concentration occurring rapidly after the onset of inhalation exposure and steady state being reached 2 hours, 6 hours and 3–4 days after exposure to 150 ppm, 500 ppm and 2210 ppm acetone, respectively (Haggard et al. 1944; Geller et al. 1979b; Wigaeus et al. 1982). The increase in time to reach steady state with increasing dose suggests dose-dependent kinetics. Studies conducted on volunteers showed that approximately 40–50% of inhaled acetone is absorbed by the body (DiVincenzo et al. 1973; Wigaeus et al. 1981). The low lipid solubility of acetone is

believed to cause resistance when absorbing acetone from the air in the nasal tissue to the bloodstream, resulting in a lower uptake than expected.

Similar to the oral and inhalation routes, dermal absorption of acetone has also been shown to occur rapidly in humans.

Acetone is widely distributed throughout the body in animals, particularly into organs with high water content, due to its high water solubility. Although no data on acetone distribution in humans were located, it is expected that it would also be widely distributed in humans.

Animal studies indicate that acetone can be found in blood, lung, kidney, liver, brain, pancreas, spleen, thymus, heart, testis, vas deferens, muscle and subcutaneous and intraperitoneal white adipose tissue (Wigaeus et al. 1982). A 24-hour exposure to 500 ppm (1200 mg/m^3) of ^{14}C-labelled acetone caused little or no tissue accumulation, except in brown adipose tissue and liver. ATSDR (1994) suggested that the accumulation of radioactivity in the liver and brown adipose tissue could be the result of high metabolic turnover in these tissues. The conversion of ^{14}C-labelled acetone to glucose, acetyl coenzyme A and other Krebs cycle components can lead to the incorporation of acetone-derived ^{14}C into a variety of cellular macromolecules and components. The concentration of acetone is higher in blood than in other tissues (Bruckner and Peterson 1981a; Wigaeus et al. 1982; Scholl and Iba 1997), reflecting its high water content.

Acetone has been reported in breast milk of some lactating women, although it is not known whether the acetone was from exogenous exposure or was formed endogenously (Pellizzari et al. 1982). Acetone can cross the placenta, based on the observation of acetone in maternal and cord blood (Dowty et al. 1976).

The main route of acetone excretion in humans is via the respiratory tract, regardless of the route of exposure. A small fraction of acetone is eliminated through urine. After inhalation, respiratory excretion is complete within 20 hours, while peak urinary excretion occurs from 1 to 3.5 hours after exposure (Matsushita et al. 1969b; Wigaeus et al. 1981). In exhaled air, acetone is excreted both as unmetabolized acetone and as carbon dioxide following metabolism. The rate and pattern of acetone excretion (respiratory and urinary) following human inhalation exposure are affected by exposure concentration, duration, level of physical activity and possibly the sex of the individual.

In a study of subjects exposed to acetone at 700 or 1300 mg/m^3 with or without exercise, about 20% of the absorbed acetone was exhaled as unmetabolized parent compound. Urinary excretion represented around 1% of the absorbed acetone (Wigaeus et al. 1981). While the alveolar concentration remained constant at around 30–40% of the inhaled acetone concentration, the respiratory excretion increased with higher exposure levels and with exercise, suggesting saturation of acetone metabolism. More specifically, the respiratory and urinary excretion were 16%, 20% and 27% for the low-dose low-exercise, high-dose moderate-exercise and high-dose increasing-exercise

groups, respectively. Half-times for acetone in alveolar air, arterial blood and venous blood averaged 4.3, 3.9 and 6.1 hours, respectively. Urinary concentrations, in contrast, were shown to increase only when workers were exposed to acetone concentrations higher than 15 ppm (36 mg/m^3) (Kawai et al. 1992). Wang et al. (1994) found blood and urinary concentrations at the end of a shift of 23 mg/L and 22 mg/L, respectively, in workers with a mean occupational exposure to acetone of 141.8 ppm (336.8 mg/m^3). Grampella et al. (1987) reported average urinary acetone levels of 93 mg/L and 62 mg/L in workers exposed to TWA concentrations of 948–1048 ppm (2.25×10^3–2489 mg/m^3) and 549–653 ppm (1.30×10^3–1.55×10^3 mg/m^3), respectively.

While total body clearance in rats is independent of dose, the half-time for elimination from blood increased from 2.4 hours to 4.9 hours to 7.2 hours when exposure was 196.1 mg/kg-bw, 784.4 mg/kg-bw and 1961 mg/kg-bw, respectively (Plaa et al. 1982).

10.2.2 Acute Effects

The acute toxicity of acetone is low in laboratory animals following inhalation, oral or dermal exposure. In these animal studies, regardless of the route, death is generally preceded by signs of central nervous system (CNS) depression, including weakness, incoordination and unconsciousness. The lowest inhalation LC_{50} values for acetone were 71 000 mg/m^3 for a 4-hour exposure in rats and 44 000 mg/m^3 for a 4-hour exposure in mice (Safronov et al. 1993). Via the oral route, the lowest median lethal dose (LD_{50}) in rats was identified at 1700 mg/kg-bw in newborns (Kimura et al. 1971), while in adults, the lowest value was 5800 mg/kg-bw (Freeman and Hayes 1985). The only oral acute lethality study identified in mice showed an LD_{50} of 5200 mg/kg-bw (Tanii et al. 1986). However, those animals also received an intraperitoneal injection of olive oil. In rabbits, an oral LD_{50} of 5300 mg/kg-bw was identified (Krasavage et al. 1982). No deaths were observed after dermal application of 15 800 mg/kg-bw to rabbits or 7400 mg/kg-bw to guinea pigs (Smyth et al. 1962; Roudabush et al. 1965).

The potential for acetone to cause irritation has been evaluated in animals following inhalation and dermal exposure. Based on an RD_{50} (concentration estimated to result in a 50% decrease in respiratory rate) of 77 516 ppm (184 136 mg/m^3) in male Swiss Webster mice (four per group) exposed by inhalation for 10 minutes, Kane et al. (1980) considered acetone to be a very weak sensory irritant. A similarly high RD_{50} of 23 480 ppm (55 776 mg/m^3), indicating weak sensory irritation, was observed in male Swiss OF1 mice exposed for 15 minutes to unspecified concentrations (De Ceaurriz et al. 1984). Schaper and Brost (1991) did not observe any changes in respiratory parameters measured in a body plethysmograph (a chamber set to measure changes in pressure with each breath), lung weights or lung pathology in male Swiss Webster mice exposed for 30 minutes to 6000 ppm (1.425×10^4 mg/m^3) of acetone vapour.

Several sensory irritation studies following inhalation exposure are also available in humans. Although Matsushita et al. (1969a) reported very slight irritation at concentrations as low as 240 mg/m^3 in subjects exposed to two 3-hour sessions in 1 day, effects were very mild and inconsistent. For the purpose of this report, 1190 mg/m^3

was considered the most appropriate LOEC because the irritation was more clearly defined and was observed more consistently among the subjects. Throat irritation at an incidence greater than in controls was reported in subjects exposed to 2370 mg/m^3 for 3 or 7.5 hours (Stewart et al. 1975). Other studies reported no subjective effects at 551 mg/m^3 for 2 hours (Ernstgård et al. 1999) and “awareness” but no subjective symptoms following exposure to up to 240 or 1190 mg/m^3 for 2 or 4 hours (DiVincenzo et al. 1973). Based on an exposure of 3–5 minutes, an early study concluded that 475 mg/m^3 was the highest exposure that would be tolerable for an 8-hour exposure, while 713 mg/m^3 was considered slightly irritating (Nelson et al. 1943). Throat irritation was reported in subjects exposed to 2375 mg/m^3 for 4 or 8 hours (Seeber et al. 1992); lower concentrations were not tested in this study. Based on consistency of the observed effects and level of discomfort experienced by the subjects, it appears that the most appropriate lowest-effect level for sensory irritation (irritation to the nose, eyes, throat and trachea) is 1190 mg/m^3 (Matsushita et al. 1969a). Thresholds for the onset of sensory irritation measured among these studies likely reflect a combined effect of odour detection and sensory irritation. Two studies designed to distinguish between odour detection and sensory irritation are presented below. It should be noted that in many of the studies reporting irritation, an increase in the sensory irritation threshold was noted with either increased exposure time or repeated exposures, indicating that adaptation may be occurring.

Well-controlled studies that measured sensory irritation alone (Cometto-Muñiz and Cain 1993; Wysocki et al. 1997) identified sensory irritant thresholds much higher than in the other studies. However, the set of studies identifying the lower threshold are relevant, since they reflect actual response perception under relevant exposure conditions. The interplay between odour and irritancy is important, since perceived sensory irritation in subjective tests has been shown to be affected by the perceived odour of acetone (Dalton et al. 1997). Wysocki et al. (1997) concluded that acetone is a weak sensory irritant and that sensory adaptation is an important factor affecting its overall irritancy. Acetone olfactory detection thresholds were 855 ppm (2031 mg/m^3) in acetone-exposed workers, compared with 41 ppm (97 mg/m^3) in unexposed workers. The sensory irritation threshold (as measured by identifying the concentration at which a subject can distinguish the nostril to which the test chemical has been presented) was 36 669 ppm (87 106 mg/m^3) in acetone-exposed workers and 15 758 ppm (37 433 mg/m^3) in unexposed workers. Cometto-Muñiz and Cain (1993) more specifically measured the acetone thresholds for odour and nasal pungency (physical sensation of irritation, such as burning, stinging and tingling) in four subjects lacking a sense of smell (anosmics) and four age- and sex-matched controls. Acetone was pushed into a nostril using a squeezing bottle in both anosmic and normosmic subjects. The detection threshold in anosmics represented pungency, while detection by normosmics represented the odour threshold. Acetone’s odour threshold was approximately 10 000 ppm (23 755 mg/m^3), and the nasal pungency threshold was 100 000 ppm (237 500 mg/m^3).

In humans, blood parameters were also assessed following acute exposure. DiVincenzo et al. (1973) found no effect on measures of liver and kidney function or on hematological values (hemoglobin, hematocrit and differential count) following exposure

to acetone at 240 or 1190 mg/m^3 for 2 or 4 hours. A temporary decrease in phagocytic activity of neutrophils and a slight increase in eosinophil and leukocyte counts in peripheral blood were reported in subjects exposed to 1190 or 2400 mg/m^3 for two 3-hour sessions in 1 day and were attributed to an inflammatory reaction resulting from irritation (Matsushita et al. 1969a).

Several acute studies in laboratory animals and humans investigated neurological effects using various tests and endpoints. Those studies are presented in the Effects on the Nervous System section.

Taken together, along with the toxicokinetics information, the database on acute effects does not identify critical effects following acute exposure. The majority of acute effects were noted to be mild, transient and reversible in nature and often attributed to odour detection or mild sensory irritation. This is consistent with the AEGLs for hazardous substances published by the US EPA and the US National Research Council, which identified AEGL-2 levels of 11 000 mg/m^3 and 3400 mg/m^3 for 30-minute and 4-hour exposures, respectively (NRC 2005). At concentrations below AEGL-2 levels, “the general population, including susceptible individuals, could experience notable discomfort, irritation, or certain asymptomatic, non-sensory effects. However, the effects are not disabling and are transient and reversible upon cessation of exposure.”

10.2.3 Short-term Effects

A 14-day oral drinking water study conducted in rats and mice by the US National Toxicology Program (NTP 1991) (also referenced as Dietz et al. 1991) is considered the most meaningful short-term acetone study, because it was conducted in two rodent species, exposed animals through a route relevant to human exposure and assessed numerous systemic endpoints. The TWA equivalent doses were 0, 714, 1616, 2559, 4312 and 6942 mg/kg-bw per day for male rats and 0, 751, 1485, 2328, 4350 and 8560 mg/kg-bw per day for female rats. In mice, the acetone intakes were 0, 965, 1579, 3896, 6348 and 10 314 mg/kg-bw per day for males and 0, 1569, 3023, 5481, 8804 and 12 725 mg/kg-bw per day for females. Decreased terminal body weight compared with controls was observed only in the rats and was the critical effect, with a lowest-observed-adverse-effect level (LOAEL) of 4312 mg/kg-bw per day. Changes in relative organ weights were also reported in rats, but were not considered adverse in the absence of supporting data on histopathology or absolute organ weight. Bone marrow hypoplasia was also reported in all of the male rats treated with 6942 mg/kg-bw per day, consistent with the hematological effects seen in the subchronic study. In the mouse study, the LOAEL was 3896 mg/kg-bw per day, considering increased liver weight accompanied by liver hypertrophy to be adverse; less severe changes in increased liver weight in the absence of hypertrophy were considered a lowest-observed-effect level (LOEL).

Repeated short-term exposure studies in humans are available only for the inhalation route. Matsushita et al. (1969b) conducted a follow-up to the single day study described in the above section on acute toxicity. In the follow-up study, subjects were exposed to

250 ppm (590 mg/m^3) (resting or exercising) or 500 ppm (1190 mg/m^3) for 6 hours/day (with a 45-minute break) for 6 days. Subjective scores indicated mucous membrane irritation, but exercising (and the resulting increased minute volume) did not increase the degree of irritation. The degree of reported irritation decreased with exposure time, reflecting adaptation. Neurobehavioural tests (reaction time to a visual stimulus) were also conducted. Although an increased reaction time was reported at the low concentration on the first 2 exposure days, the difference from controls (non-pooled absolute values) was not statistically significant. There was a change of 5% in simple reaction time at 590 mg/m^3 and 10% at 1190 mg/m^3 (as reported in Dick et al. 1989). As in the single day study, a statistically significant increase in white blood cell counts and decrease in phagocytic activity of neutrophils were also observed at 1190 mg/m^3.

Stewart et al. (1975) conducted an extensive evaluation of the effects of short-term inhalation exposure to acetone in healthy male and female adult humans. Groups of four males were exposed on successive weeks (one control exposure followed by 4 days of exposure) to 0, 200, 1000 or 1250 ppm (0, 475, 2370 and 2970 mg/m^3). One group was exposed for 3 hours/day and another for 7.5 hours/day. Additional groups of females were exposed successively to 0 and 1000 ppm (0 and 2370 mg/m^3) for 1 hour/day (two subjects) or 3 or 7.5 hours/day (four subjects per group). The subjects underwent extensive pre-exposure testing and testing during exposure. A number of measurements were conducted on selected days of each exposure week, including spontaneous electroencephalogram recordings and visual evoked response (control and days 2 and 4), pulmonary function testing (day 4), cognitive tests (control and days 2 and 4) and complete blood count (including differential white count) and clinical chemistry (once per week, day not specified). The only effect in these tests was a significant change in amplitude of the visual evoked response test in the male subjects exposed to acetone at 2970 mg/m^3 for 7.5 hours/day, on both the 2nd and 4th days of exposure.

Other short-term studies are presented in the section on Effects on the Nervous System.

10.2.4 Subchronic Effects

Bruckner and Peterson (1981b) exposed male rats to acetone at 0 or 45 100 mg/m^3 in an inhalation chamber 3 hours/day, 5 days/week, for 8 weeks. Body weight gain was slightly, but not significantly, decreased throughout the experiment. Absolute brain weight was decreased after 4 and 8 weeks and returned to within control values after a 2-week recovery. Absolute kidney weight was consistently lower during the exposure period, but the decrease was not statistically significant. No effects on other organ weights, blood chemistry or histopathology of major organs were observed. Hematology was not evaluated. Christoph et al. (2003) conducted a schedule-controlled operant behaviour study with male rats exposed to 0, 2400, 4800 or 9500 mg/m^3 6 hours/day, 5 days/week, for 13 weeks. Exposure to concentrations up to 9500 mg/m^3 in this study did not lead to adverse effects on learning. Buron et al. (2009) examined the effects of acetone on the olfactory function (behaviour and histopathology) of mice. Female mice

were exposed to fresh air or to acetone placed on cotton in the inhalation chamber 5 hours/day, 5 days/week, for 4 weeks. The acetone concentration in the chamber reached approximately 19 000 mg/m^3 after 1.5 hours and remained steady. Changes in several sensitive olfactory markers (number of cells, thickness of epithelium and number of proliferating cell nuclear antigen–positive cells) as well as changes in olfactory sensitivity were observed in exposed mice.

Subchronic toxicity via the oral route has been examined in a series of drinking water studies and an oral gavage study. The drinking water study conducted on rats and mice by the US NTP (NTP 1991) was identified as one of the critical studies in risk characterization. In the rat study, male and female rats were exposed to acetone in drinking water for 13 weeks at equivalent doses of 0, 200, 400, 900, 1700 and 3400 mg/kg-bw per day for males and 0, 300, 600, 1200, 1600 and 3100 mg/kg-bw per day for females (NTP 1991). In females, kidney and liver weights were significantly increased at the middle and high dose levels. In males, only the liver weight increase was statistically significant at the middle dose level, while in the high dose group, the increases were significant for kidney, liver and testis weights. Examination of the kidney tissue revealed increased incidence and severity of nephropathy in male rats, which were considered adverse at the two highest doses.

Several treatment-related changes in hematological parameters that were most prominent in males were observed. The changes were in the order of 10% or less, except for the decrease in reticulocytes, which varied between 68% and 80% (152–179 $\times 10^3$/µL) of the control values, depending on dose. Although some hematological changes occurred beginning at the lowest dose tested in males, doses of 1700 mg/kg-bw per day and above generated a consistent pattern of statistically significant biologically related changes. While effects on splenic red pulp were observed, no changes were noted from the bone marrow examination. Thus, for hematological effects, the LOEL is 200 mg/kg-bw per day, based on a statistically significant increase in mean corpuscular hemoglobin and mean cell volume in males, with effects that were more consistent at 1700 mg/kg-bw per day.

Overall, the study LOAEL is 1700 mg/kg-bw per day, based on biologically significant hematological changes in male rats and the onset of adverse effects on the kidney (increased kidney weight in females and mild nephropathy in males) at the same dose. Some statistically significant effects were observed at lower doses, but these effects are not considered adverse; as the lowest level at which they were observed represents a LOEL, it cannot serve as the critical effect level for the study.

For the mouse portion of the study, male and female mice were exposed to acetone in drinking water for 13 weeks; doses were 0, 380, 611, 1353, 2258 and 4858 mg/kg-bw per day in males and 0, 892, 2007, 4156, 5945 and 11 298 mg/kg-bw per day in females. Changes in several organ weights were reported for females, but not for males. Histopathological findings were limited to minimal hepatocellular hypertrophy in high-dose females. Statistically significant changes in hematological parameters were also observed, but those changes were small and did not parallel changes observed in

rats. Overall, the only significant biological effect observed in mice in this study was the change in liver weight accompanied by a consistent pattern of histopathology; thus, a LOAEL of 11 298 mg/kg-bw per day is identified based on this effect.

Woolhiser et al. (2003) exposed male CD-1 mice (eight per group) to acetone in drinking water at concentrations of 0, 600, 3000 or 6000 mg/L for 28 days (actual TWA doses reported by the authors were 0, 121, 621 and 1144 mg/kg-bw per day, respectively). There were no effects on survival and no clinical signs of toxicity attributable to acetone treatment, and terminal body weight was not affected by acetone treatment. There were no treatment-related effects on hematological parameters (total and differential white blood cell counts, red blood cells, hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration and platelets). The immunotoxicity portion of the study is summarized in the corresponding section below.

Subchronic effects reported for rats and mice in several other drinking water studies are considered unreliable due to their study limitations (Sollman 1921; Spencer et al. 1978; Ladefoged et al. 1989).

American Biogenics Corporation (1986) administered acetone via gavage to male and female rats at a dose of 0, 100, 500 or 2500 mg/kg-bw per day for 90 days. Increased body weights were observed in females in the middle and high dose groups. The increase was not considered toxicologically meaningful based on the absence of a clear dose–response relationship and the absence of an effect on body weight in males. Changes in organ weights were reported for the kidneys, liver, brain and heart. With the exception of the kidneys, these changes were not accompanied by histopathological findings. Accentuation of renal proximal tubule degeneration and intracytoplasmic hyaline droplet accumulation was observed in males at the middle and high doses. In females, effects were limited to the accentuation of renal proximal tubular degeneration in the high-dose group only. The study authors reported a treatment-related increase in the severity and distribution of these kidney effects, which are also associated with aging rats, particularly in male rats through α2u-globulin nephropathy. However, since some of these effects were observed in treated female rats, there is likely another cause for the kidney effects than that mediated by α2u-globulin. Thus, the observed kidney effects are considered relevant. Of the three serum measures related to hepatotoxicity examined, only alanine aminotransferase (ALT) was increased in high-dose males. Effects on serum cholesterol were noted at interim sacrifice only. Changes in several other clinical chemistry parameters were observed, but their toxicological relevance is unclear. Treatment-related changes in hematological parameters (significantly increased red blood cell count) were also observed and were limited to male rats exposed to the highest dose level. However, no effects were noted on the tissues of the spleen and bone marrow.

Overall, effects of acetone treatment were observed on the kidneys, liver and hematology. The study identified a LOAEL of 2500 mg/kg-bw per day, based on increased kidney weight supported by histopathological findings. Toxicologically

significant kidney effects were observed in both sexes at this dose. Liver weight increases were also observed at 500 mg/kg-bw per day, but evidence for an adverse effect became apparent only at the highest dose (2500 mg/kg-bw per day), as indicated by clinical chemistry findings (increased ALT). Statistically significant hematological findings were limited to the highest dose, and generally the magnitude of the changes was small and of unknown clinical significance. This study was not chosen as the basis for risk characterization because the gradual administration from drinking water studies is considered to be a more relevant route of administration from the human exposure perspective.

Two studies were identified in which laboratory animals were exposed to acetone via dermal application. One study observed cataracts in two of eight guinea pigs exposed to 0.5 mL acetone twice daily, 5 days/week, for 8 weeks (Rengstorff et al. 1972). In contrast, three other experiments exposing rabbits or guinea pigs to 0.5 or 1 mL of acetone on the skin 2–5 times per week for up to 6 months did not show evidence of cataracts (Rengstorff et al. 1976; Taylor et al. 1993).

10.2.5 Cancer and Chronic Effects

No studies assessing chronic toxicity or carcinogenicity are available via the oral or inhalation route for acetone. Via the dermal route, the database consists mainly of carcinogenicity studies of various durations in which acetone was used as a vehicle control (Park and Koprowska 1968; Barr-Nea and Wolman 1977; van Duuren et al. 1978; Zakova et al. 1985; Ward et al. 1986; Iversen et al. 1988; DePass et al. 1989; Holden et al. 1998). These studies involve various strains of mice to which acetone was applied dermally for durations ranging from 1 month to a lifetime. Applications were administered from once a day to once a week, and the doses (when specified) varied between 290 and 5300 mg/kg-bw per day. However, many limitations were identified in some of these studies, including the absence of a control group, the lack of a dose–response relationship, the less than chronic duration, the small number of animals and the use of relatively low daily doses. In summary, of the eight studies, six did not observe any signs of tumour, even when, in one study, a chemical initiator was applied to the skin prior to acetone exposure. The remaining two studies are presented below.

In the study by DePass et al. (1989), 2 mice out of 40 were diagnosed with subcutaneous mesenchymal neoplasms after being exposed to approximately 290 mg/kg-bw per day for a lifetime. No skin tumours were observed. The only other effects reported were skin effects at the site of application. No systemic endpoints were evaluated. Ward et al. (1986) conducted a skin painting study in a particularly sensitive strain of mice bred for skin initiation and promotion protocols. In one group of 30 mice, 0.2 mL of formalin solution (37–40% formaldehyde solution in acetone) was applied once to the back at 8 weeks of age. Four weeks later, 0.2 mL (5300 mg/kg-bw[3]) acetone was applied once weekly for 88 weeks (average daily dose of 750 mg/kg-bw

[3] Intakes were calculated according to reference values in Health Canada (1994).

per day). In another group of 30 mice, 0.2 mL of acetone was applied twice weekly (average daily dose of 1520 mg/kg-bw per day) to their backs from 8 weeks of age for 92 weeks. There was no control group in this study. In both groups, neoplastic and non-neoplastic lesions occurred with similar incidence, and survival was similar. The most common neoplastic lesions reported were histiocytic sarcoma, lung tumours and mammary gland tumours. The study authors stated that the incidence of the observed tumours was similar to that in the CD-1 mouse, the parent strain, but did not provide any quantitative supporting evidence. Taking into consideration the sensitivity of the strain, the absence of a control group and the similarity of tumour incidence with historical controls, the relevance of the results cannot be determined.

As mentioned, no chronic studies are available for acetone. Thus, the only data available on chronic effects of acetone come from the carcinogenicity studies noted above. Aside from local dermal effects caused by the application of acetone, two studies reported systemic effects (Barr-Nea and Wolman 1972; Ward et al. 1986). However, the significance of the observations cannot be determined due to limitations in both studies.

Several epidemiological studies of acetone-exposed workers are available, but they are generally limited by confounding exposures that were not accounted for in the statistical analysis, relatively small sample sizes and self-reporting of effects. However, the epidemiological studies qualitatively support the findings of the animal studies and acute human studies—namely, that there is no evidence of increased mortality due to acetone exposure and that acetone is a sensory irritant (Ott et al. 1983a, b, c). While there are some positive findings in neurological tests and subjective reports of CNS symptoms, these findings are limited by study design limitations (Raleigh and McGee 1972; Satoh et al. 1996; Mitran et al. 1997). No clinical chemistry findings indicative of kidney or liver effects were reported at occupational exposure levels, and there were no hematological effects, although the endpoints for which results were most consistent in animal studies (mean corpuscular hemoglobin and mean corpuscular volume) were not evaluated (Grampella et al. 1987; Soden 1993). Summaries of the key epidemiological studies are presented in a later section.

Although acetone has not been adequately tested for carcinogenicity via all routes of exposure, the available information indicates that it is not carcinogenic. This is supported by the use of acetone as a solvent in many types of studies, including carcinogenicity studies, to test other substances. This is further supported by the absence of genotoxicity, as described in the following section.

10.2.6 Genotoxicity

In the only study with positive results, Zimmermann et al. (1985) reported that a concentration of approximately 8% acetone caused aneuploidy in *Saccharomyces cerevisiae*, but did not induce point mutations or mitotic recombinations. All other *in vitro* and *in vivo* assays in an extensive battery of tests had negative results. Acetone was negative for gene mutation in the bacterium *Salmonella typhimurium* (McCann et al.

1975; De Flora et al. 1984; Ishidate et al. 1984; Zeiger et al. 1992), in two species of yeast (Abbondandolo et al. 1980; Yadav et al. 1982) and in mammalian cells (mouse lymphoma and lung fibroblast cells) at several different loci (Lankas 1979; Amacher et al. 1980; Cheng et al. 1981; Friedrich and Nass 1983; McGregor et al. 1988). Acetone was also negative for chromosomal aberrations in Chinese hamster ovary cells and human lymphocytes (Norppa et al. 1981; Tates and Kriek 1981; Ishidate et al. 1984; Loveday et al. 1990) and was negative for the development of micronuclei (a measure of clastogenicity) both *in vitro* in human lymphocytes (Zarani et al. 1999) and *in vivo* in hamsters and mice (Basler 1986; NTP 1991). A variety of measures of deoxyribonucleic acid (DNA) damage were also negative, including prophage induction assays (DeMarini et al. 1991; Rossman et al. 1991), which measure induction of the "SOS" response in bacteria, the SOS chromotest (Nakamura et al. 1987), sister chromatid exchange assays in mammalian cells (e.g., Tates and Kriek 1981; von der Hude et al. 1987; Loveday et al. 1990) and unscheduled DNA synthesis in human skin cells (Lake et al. 1978). A number of studies evaluated cellular transformation, a more integrative assay that evaluates the occurrence of multiple changes in a cell, rather than only genotoxicity. Acetone was also negative in the cell transformation studies (Freeman et al. 1973; Mishra et al. 1978; Pienta 1980; Lillehaug and Djurhuus 1982). The complete list of genotoxicity studies identified for acetone is presented in Appendix D. No *in vivo* studies in humans were identified.

Acetone is commonly used as a vehicle for water-insoluble chemicals in *in vitro* genotoxicity testing (Anderson and MacGregor 1980), consistent with the general conclusion that acetone itself is not genotoxic.

10.2.7 Reproductive Effects

There were no effects on male fertility and no testicular damage in rats administered acetone at 800 mg/kg-bw per day in drinking water for 6 weeks (Larsen et al. 1991), no effects on male fertility, reproductive organ weights or testes histopathology in rats treated with acetone at 1400 mg/kg-bw per day in drinking water for 4 weeks or 700 mg/kg-bw per day in drinking water for 9 weeks (Dalgaard et al. 2000), no effects on the weight or histopathology of reproductive organs in male and female rats treated by gavage with up to 2500 mg/kg-bw per day (American Biogenics Corporation 1986) and no effects on reproductive structure or histopathology in female rats exposed to up to 3100 mg/kg-bw per day in drinking water for 90 days (NTP 1991).

Effects on reproductive organs and sperm parameters were observed in male rats in a 13-week drinking water study as well as in its accompanying 14-day dose range–finding study (NTP 1991). In the 14-day study, the only effect observed was an increase in relative testis weight at 4312 mg/kg-bw per day. In the 13-week study, statistically significant effects were reported in the high-dose group (3400 mg/kg-bw per day). Those effects include increased relative testis weight, decreased caudal epididymal and right epididymal weight, increased percentage of abnormal sperm and decreased sperm motility. The increase in relative testis weight is considered to be secondary to a decrease in body weight (Feron et al. 1973). All of the other effects are consistent with

adverse effects on spermatogenesis. Accordingly, a LOAEL of 3400 mg/kg-bw per day was identified for the effects on reproductive organs and sperm parameters in male rats.

In humans, the database on reproductive toxicity is limited. One clinical study reported premature menstruation, but the significance of the finding is unknown, due mainly to small sample size and the possibility of other factors, such as diabetic status, influencing the results (Stewart et al. 1975). One study found inconsistent effects on sperm parameters in plastics production workers (Jelnes 1988). The co-exposure to styrene, small sample size and use of fertility clinic patients with potential fertility problems as controls are major weaknesses of this study. However, the results are in line with the effects observed on sperm parameters in male rats in the NTP (1991) study. Other studies provided no clear evidence for spontaneous abortions or miscarriages in solvent-exposed workers (Axelsson et al. 1984; Taskinen et al. 1994).

10.2.8 Developmental Effects

Developmental toxicity of acetone has been studied in Sprague-Dawley (CD) rats and Swiss (CD-1) mice via inhalation exposure (Mast et al. 1988[4]). Pregnant rats (32 per dose group) were exposed to acetone vapours at a concentration of 0, 440, 2200 or 11 000 ppm (0, 1045, 5200 or 26 100 mg/m^3, respectively) for 6 hours/day, 7 days/week, during gestation days 6–19. Pregnant mice (32 per dose group) were exposed to acetone vapour at a concentration of 0, 440, 2200 or 6600 ppm (0, 1045, 5200 or 15 670 mg/m^3) for 6 hours/day, 7 days/week, during gestation days 6–17. Each treatment group also included 10 virgin females as controls.

In the rat developmental toxicity portion of the study, at the highest concentration of 26 100 mg/m^3, there were statistically significant decreases (compared with controls) in maternal gestation day 20 body weights (7.5% decrease), extragestational weight gains[5] (34% decrease), uterine weights (19% decrease) and fetal weights (male, female and combined). The fetal weights were approximately 13% lower than the contemporary control values provided, and the decreases were considered treatment related. Non-mated controls also exhibited a decrease in body weight (5.9% decrease), but this was not statistically significant. The percentage of litters with resorptions (77% vs. 50%) and percentage of litters with at least one malformation (11.5% vs. 3.8%) were greater in the high-exposure group, compared with control values. In addition, four malformations were observed in one control litter compared with nine malformations in four high-dose litters. The incidences of fetal malformations, variations and reduced ossifications were not statistically significantly different from control values in any exposure group. However, in the 26 100 mg/m^3 group, these changes were considered biologically significant, because the litter values (number and percent of litters/fetuses with

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[4] Some assessments cite this study as NTP (1988).

[5] Extragestational weight gain is the actual maternal body weight gain during pregnancy and is defined as the maternal body weight at sacrifice minus gravid uterine weight minus maternal body weight on gestation day 0.

malformations) were three times higher than the contemporary control values (1 vs. 3 and 3.8% vs. 11.5%, respectively), and the observed malformations were of a different spectrum than those seen in the control group.

The lowest-observed-adverse-effect concentration (LOAEC) for maternal toxicity in rats was 26 100 mg/m^3, based on significant decreases in body weight gain, extragestational weight gains and uterine weight. The LOAEC for developmental effects in rats was 26 100 mg/m^3, based on a significant decrease in fetal weight, an increase in fetal malformations and increased resorptions. Based on the results of this study, NTP (1988) has concluded that acetone had not caused a teratogenic effect in rats.

In the mouse developmental toxicity portion of the study, the high concentration was initially designed to be 11 000 ppm (26 100 mg/m^3). However, severe narcosis was observed in this group on the 1st day of exposure (gestation day 6), and consequently the concentration for this group was reduced to 6600 ppm (15 670 mg/m^3) for the remainder of the study. Thus, the final exposure levels in the mouse study were 0, 1045, 5200 and 15 670 mg/m^3. There were no clinical signs or deaths at exposures up to the highest level of 15 670 mg/m^3. Incidences of fetal variations when all types were combined were not significantly different from control values; however, the incidence of litters with reduced sternebrae ossification was significantly increased in the 15 670 mg/m^3 group.

The single day of higher exposure in the high-concentration group was not considered to affect the study results, because any adverse developmental outcome at this early stage of gestation would likely have manifested itself as early resorptions. Absolute liver weight and liver to body weight ratio were increased in the dams at 15 670 mg/m^3 (by 21% and 22%, respectively). No other liver endpoints were examined. Increased liver weight alone is generally considered adaptive. However, in light of the magnitude of the change and based on the supporting effects observed in mice in a 14-day study from NTP (1991) in which liver hypertrophy was also observed, the effects on the liver were considered relevant. Developmental effects were limited to the high-concentration group and included an increased percentage of late resorptions, decreased fetal weight and increased incidence of reduced sternebrae ossification. Thus, a LOAEC of 15 670 mg/m^3 has been identified for both maternal and developmental toxicity, based on increased relative liver weight in pregnant mice (maternal toxicity) and decreased fetal weight and an increased percentage incidence of late resorptions and retarded ossification development (developmental toxicity).

10.2.9 Immunological Effects

In a study on immunological effects, CD-1 male mice were exposed to acetone at 0, 121, 621 or 1144 mg/kg-bw per day via drinking water for 28 days (Woolhiser et al. 2003). The sheep red blood cell antibody-forming cell (AFC) assay was performed to measure the T cell–dependent, anti-sheep red blood cell immunoglobulin M response, and hematology and thymus weights were evaluated. Body weights, white blood cell numbers, red blood cell counts and hemoglobin and hematocrit levels showed no

treatment-related effects. Eosinophil percentages were variable, but also showed no dose-related trends. Spleen and thymus weights were not statistically different from controls, and there were no effects on spleen cellularity or AFC response as a result of acetone administration. The AFC responses were not statistically different from those of controls. The no-observed-adverse-effect level (NOAEL) in this study was determined to be 1144 mg/kg-bw per day, the highest dose tested.

No effects on B cells, T cells or ratio of CD4+ to CD8+ T cells were observed when mice were topically treated with 0, 50, 100, 200 or 300 µL of acetone either once or twice weekly for 2 or 4 weeks (average daily applied dose ranging from 187 to 380 mg/kg-bw per day, with a total dose range from 1125 to 2250 mg/kg-bw). The sheep red blood cell assay indicated statistically significant depression in humoral immunity at 300 µL, while results at other doses appeared schedule dependent. Thus, interpretation of some of the immunosuppressive effects was limited by the internally inconsistent results (Singh et al. 1996).

Immunological endpoints examined in systemic toxicity studies were limited to histopathological examination of the spleen and thymus and leukocyte counts (American Biogenics Corporation 1986; NTP 1991). Increases in leukocyte counts were observed in male and female rats in the drinking water study, but not in the mouse drinking water study or in the rat gavage study.

In humans, a temporary decrease in phagocytic activity of neutrophils and a slight increase in eosinophil and leukocyte counts in peripheral blood were reported in subjects exposed to 1190 or 2400 mg/m^3 for two 3-hour sessions in 1 day and were attributed to an inflammatory reaction resulting from irritation (Matsushita et al. 1969a).

10.2.10 Effects on the Nervous System

Several acute studies have also investigated neurobehavioural effects using various endpoints. The lowest LOAEC in the acute animal database is 6129 mg/m^3 for 4 hours based on decreases in mobility time in the behavioural despair swimming test in rats (De Ceaurriz et al. 1984). A no- observed-adverse-effect concentration (NOAEC) of 4827 mg/m^3 was also identified based on the absence of neurobehavioural effects.

In neurotoxicity studies, rats that were repeatedly exposed to high vapour concentrations of acetone showed mild, reversible neurobehavioural changes. When Goldberg et al. (1964) exposed female rats to acetone at 0, 7120, 14 240, 28 480 or 37 975 mg/m^3 for 4 hours/day for 2 weeks, a concentration-dependent increase in inhibition of avoidance behaviour was observed starting at 14 240 mg/m^3. Animals in the two highest dose levels showed ataxia several minutes after a single exposure, but tolerance developed rapidly. Similarly, in more recent performance studies in which rats were exposed to acetone at concentrations up to 9500 mg/m^3 for 13 weeks, the rats did not show any permanent effects (Christoph et al. 2003).

In an acute study, Bruckner and Peterson (1981a) exposed mice to 29 900, 45 100, 60 100 or 120 200 mg/m^3) for up to 3 hours and conducted five tests of unconditioned performance and reflexes. Concentration-dependent increases in depth of CNS depression and rate of depression were reported. While the exposure to 120 200 mg/m^3 was lethal within 2 hours, exposure to 29 900 mg/m^3 led to impaired performance and reflexes. Animals showed normal behaviour approximately 9–21 hours after termination of exposure. Glowa and Dews (1987) observed that a 7130 mg/m^3 concentration caused a 10% decrease in response to food presentation in a fixed interval operant behavioural test after exposing mice to six nominal concentrations of acetone ranging from 100 to 56 000 ppm (240–133 000 mg/m^3) for 1 day. The rate of response to food presentation returned to normal 30 minutes after the end of a serial exposure. Overall, studies are consistent with the presumption that CNS effects are more dependent on the total dose than on the exposure concentration (Mashbitz et al. 1936; Haggard et al. 1944).

Effects were seen in a match-to-sample operant behavioural test in four baboons exposed to 1200 mg/m^3 continuously for 7 days, but the study is useful primarily for hazard characterization, since only one concentration was tested, results were highly variable for each animal and the sample size was small (Geller et al. 1979a).

In an oral neurobehavioural study, Ladefoged et al. (1989) compared the effects of exposure to ethanol, acetone and 2,5-hexanedione alone or in combination for 6 weeks. From the 3rd week on, rats were monitored for nerve conduction velocity and rotarod performance. No effects on nerve conduction velocity or on balance time with the rotarod test were observed in male Wistar rats administered 0.5% acetone in the drinking water.

Two early studies focused on evaluation of the concentration–time relationship of various CNS effects. In the first study, Mashbitz et al. (1936) exposed white mice to acetone at 40 000, 60 000, 80 000, 100 000, 120 000, 133 000 or 200 000 mg/m^3 under static exposure conditions for varying durations up to 4 hours. The time to narcosis was reported as 158, 92, 59, 38, 33, 38 and 34 minutes, respectively. At the four highest concentrations, the first effects observed were drowsiness followed by a period of excitement. Other effects that followed included impaired coordination, deep narcosis and frequent rhythmical clonic movement of the hind legs and abdominal muscles. In the second study, Haggard et al. (1944) exposed rats to acetone at 5000, 10 000, 25 000, 50 000, 100 000, 200 000 or 300 000 mg/m^3 for durations ranging up to 8 hours. “Intoxication” (defined as the first visible evidence of slight incoordination) was dose related and seen at concentrations of 25 000 mg/m^3 and above at durations of 100–250, 40–80, 15–35, 10–15 and 5–7 minutes of exposure, respectively. Exposure to concentrations up to 10 000 mg/m^3 for durations up to 8 hours did not result in any intoxication. Loss of righting reflex (50 000 mg/m^3 and above) and loss of corneal reflex (100 000 mg/m^3 and above) were observed subsequently. The authors determined that slight incoordination was seen at blood concentrations of approximately 1000–2000 mg/L, loss of righting reflex at about 3000 mg/L, loss of corneal reflex at 5000 mg/L and respiratory failure at 9100–9300 mg/L.

Two studies conducted sensitive objective testing of CNS effects following acute inhalation exposures in humans. Dick et al. (1989) reported small but statistically significant changes in two neurobehavioural tests (auditory tone discrimination and anger-hostility scale) in subjects exposed to the only acetone concentration tested, 600 mg/m^3, for 4 hours. The authors suggested that the observed changes may have been an artifact of the large number of statistical tests, but the finding of differences at multiple time points, with the magnitude of the difference from control paralleling the blood acetone level, suggests that this study identified a sensitive effect level. The current report considers that the CNS effect level identified in the Dick et al. (1989) study is inconsistent with the rest of the hazard database, noting that occupational epidemiological studies indicate that workers are often exposed daily to concentrations ranging between 1000 and 2000 mg/m^3 without observing adverse and more permanent systemic effects, aside from the transient sensory irritation-related effects (Oglesby et al. 1949; Raleigh and McGee 1972; Ott et al. 1983a, b, c; Grampella et al. 1987; Soden 1993). Stewart et al. (1975) reported transient dizziness and tiredness, along with one report of vertigo, in subjects exposed to acetone concentrations up to 2970 mg/m^3 for up to 7.5 hours. These effects did not appear to be concentration or duration related, and there were no effects on the two objective neurobehavioural tests. However, the suggestion that exposure to 2970 mg/m^3 for up to 7.5 hours causes sensitive neurological effects is supported by the report in the Stewart et al. (1975) study that there was a significant change in amplitude of the visual evoked response test in male subjects exposed under these conditions for 2 or 4 days; the visual evoked response was not measured on the 1st exposure day. It should be noted that the dose groups from this study are particularly small, 2–4 per group, which considerably limits the interpretation of the data, despite the extensive tests conducted.

The neurotoxicity database for acetone indicates that mild, transient, reversible CNS effects may be noted in individuals acutely exposed to acetone. Dizziness and other symptoms were more common following the initial exposure, while adaptation (reduction in prevalence and severity of effects) was noted in workers exposed to higher concentrations for longer periods of time. The available information indicates that neurological effects are not a critical effect for risk characterization following either single or periodic, intermittent acute exposures to acetone.

10.2.11 Epidemiological Studies

Satoh et al. (1996) conducted a cross-sectional study on 110 Japanese male shift workers who were employed for an average of 18.9 years in an acetate fibre plant and 67 male unexposed shift workers employed for an average of 22.2 years. The age of the exposed workers ranged from 18.7 to 56.8 years (mean 37.6 years), and the length of exposure ranged from 0.5 to 34.5 years (mean 14.9 years). The age of the unexposed workers ranged from 20.7 to 57.5 years (mean 41.9 years). The mean TWA acetone concentration in the breathing zone over the course of a workday was 361 ppm (858 mg/m^3), but individual exposures varied widely, from 5 to 1212 ppm (12 to 2888 mg/m^3). Blood concentrations of acetone ranged from 4 to 220 mg/L (mean 66 mg/L).

The authors reported exposure-related increases in eye irritation, tearing and acetone odour at the end of the workshift and in heavy, vague or faint feeling in the head, nausea, loss of weight and slow healing of an external wound within the previous 6 months. No differences between the exposed and unexposed groups were reported for the Manifest Anxiety Scale or the Self-rating Depression Scale scores, R-R interval variation on electrocardiogram, hematological parameters (hemoglobin, packed cell volume, total and differential white blood cell count) or biochemical parameters (alkaline phosphatase, aspartate aminotransferase [AST], ALT, gamma-glutamyltransferase).

Mitran et al. (1997) examined the neurotoxic effects of acetone in 71 occupationally exposed workers at a coin and medal factory. The mean length of exposure of the workers was 14 years. The acetone concentration over an 8-hour shift ranged from 988 to 2114 mg/m^3. Compared with 86 matched controls, acetone-exposed workers exhibited an increased prevalence of mood disorders, irritability, memory difficulties, sleep disturbances, headache, numbness in hands and feet and upper respiratory tract irritation and significant differences in motor nerve conduction velocity in median, ulna and peroneal nerves. The authors concluded that chronic acetone exposure impaired human performance and elicited neurotoxic effects in these workers, but that the motor nerve conduction results should not be overinterpreted and that the use of standardized psychological and neurobehavioural tests was needed. It is unclear why this study reported neurological effects at such low concentrations, when urinary acetone concentrations (53–101 mg/L) were within a factor of 2 of normal. However, Graham (2000) raised a number of issues about the methods of the Mitran et al. (1997) study, particularly noting that nerve conduction velocity is very sensitive to the temperature at which testing is conducted, and the observed differences could be explained if the controls were tested at warmer ambient temperatures. Other issues noted by Graham (2000) included insufficient information about the number of diabetics in the test and control groups and the surprising consistency in the average age and exposure duration in three different factories, raising questions about how the subjects were selected. In reply, Mitran (2000) noted that the subjects were selected from a much larger pool, but did not specifically address the temperature or diabetes issues.

Ott et al. (1983a, b, c) examined employees of a cellulose fibre plant in which acetone was used as the only solvent. The TWA air concentration of acetone reported by the authors was about 1000 ppm (2400 mg/m^3). There was no significant excess risk of mortality from any cause or of cardiovascular disease or total malignant neoplasms in workers in this study.

Grampella et al. (1987) examined systemic effects including organ damage in 60 volunteers employed for at least 5 years at an acetate fibre manufacturing plant. Based on their level of exposure, workers were divided equally into high and low acetone exposure groups. The TWA acetone concentrations ranged from 948 to 1048 ppm (2300 to 2500 mg/m^3) and from 549 to 653 ppm (1300 to 1600 mg/m^3) in the high- and low-exposure groups, respectively. The reported average urinary acetone levels were 93 mg/L and 62 mg/L for the high- and low-exposure groups, respectively. Another group of 60 subjects that had never been exposed to acetone was included in this

evaluation. Several hematological and biochemical parameters were analyzed. After adjusting for confounding factors, such as smoking, alcohol consumption, age and past medical histories (liver and kidney damage), the authors found no statistically significant differences in hematological parameters or biochemical markers of liver and kidney effects.

Oglesby et al. (1949) examined the effect of acetone vapours on sensory irritation and systemic toxicity (hematology and urinalysis, endpoints evaluated not further specified) in the workplace in 800 acetone-exposed employees. Acetone concentrations at the workplace ranged from 1425 to 5100 mg/m^3. The mean length of exposure was not reported. The secondary source reported a NOEC for human sensory irritation of 3560 mg/m^3, but acetone exposure did not elicit systemic toxicity or adverse health effects.

Soden (1993) evaluated the effects of acetone on hematology and blood chemistry in 150 occupationally exposed workers at a triacetate fibre plant. The workers were exposed to an average 8-hour TWA concentration of 900 ppm (2140 mg/m^3) for an unspecified duration. Compared with 260 non-exposed controls, there were no significant differences in ALT, AST, total bilirubin or hematocrit in the exposed group. The response rates for symptoms such as loss of memory, headache or dizziness were also not different between exposed subjects and controls.

Raleigh and McGee (1972) monitored nine filter press operators involved in removing and replacing filter cloths saturated with cellulose acetate dissolved in acetone. These workers had short-term (about 2–3 hours) exposures to much higher acetone concentrations than those normally present in the work area. The average acetone concentrations of 2300 ppm (5500 mg/m^3) and 300 ppm (710 mg/m^3) were measured in the breathing zone of workers pulling filters and those dressing presses, respectively, for the 1st and 2nd years of the study, compared with 110 ppm (260 mg/m^3) measured in the general air. Exposure caused transient and intermittent eye, throat and nasal irritation as well as headaches and light-headedness in some individuals when exposure exceeded 1000 ppm (2400 mg/m^3). There were no other CNS effects attributable to acetone exposure in this study, as assessed by finger-to-nose test and joint position sense test.

10.2.12 Uncertainties in the Hazard Database

The confidence in the available data set is considered to be high. The effects of acetone following acute and daily exposure are well characterized in animal studies for a range of endpoints and species. The animal data are supported by an extensive database of effects in humans following acute exposure. The long-term effects of acetone exposure have been evaluated in several epidemiological studies; however, most studies had design limitations. Epidemiological studies indicate that effects of repeated exposure are comparable to those observed in shorter-duration studies in humans; therefore, shorter-term studies are relevant to risk characterization for daily exposure of the general population.

The acute human data are adequate for evaluation of a concentration–response relationship. Data from humans and experimental animals support the conclusion that the most sensitive toxicological endpoints for acute exposure are sensory irritation and CNS effects. Chemical-specific data on the concentration–duration–response relationship for extrapolating across exposure durations are limited to animal studies. Also, while animals are known to metabolize acetone through the same pathways as humans, the rates appear to differ, adding some uncertainty to the time-to-effect data from animal studies.

While the mode of action for the critical effects for daily exposure (hematological and renal effects) is not well understood, the pattern of effects is fairly consistent for the identification of the critical effect level. The renal effects in male rats may be due only partially to α2u-globulin nephropathy[6]. Since this α2u-globulin phenomenon cannot fully explain the observed effects, the observed renal effects were assumed to be relevant to humans.

Although acetone has not been adequately tested for carcinogenicity via all routes of exposure, the available information indicates that it is not carcinogenic. Acetone is often used as a solvent in chronic dermal toxicity studies, and it is not genotoxic. Chronic toxicity data are available only via the inhalation route; however, the metabolic pathway is the same regardless of route of exposure.

10.3 Characterization of Risk to Human Health

Upper-bounding estimates of daily intake of acetone for the general population were derived based on concentrations of acetone in air, water, food and beverages and soil. Total daily intake is estimated to range from 133 µg/kg-bw per day for breastfed infants aged 0–6 months to 650 µg/kg-bw per day for children aged 0.5–4 years (Appendix B). Estimates of exposure from exogenous sources are a small fraction of levels of acetone present in the body due to endogenous production.

Two shorter-term animal studies have been identified as critical studies to characterize the risk to human health from daily exposure. These studies are considered relevant, as the human health effects database indicates that the effects observed in clinical studies of shorter duration are comparable in nature and severity to effects observed in epidemiological studies in which occupationally exposed individuals are typically exposed for several years. The first study is a 13-week drinking water study in rats (NTP 1991). The overall LOAEL was 1700 mg/kg-bw per day, based on biologically significant hematological changes and adverse kidney effects (increased kidney weight with mild

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[6] The accumulation of alpha2u-globulin (a2u-g), a low-molecular-weight protein, in the male rat kidney initiates a sequence of events that appears to lead to renal tubule tumor formation

nephropathy) in male rats. The second study is an inhalation developmental toxicity study in rats by Mast et al. (1988). The LOAEC was 11 000 ppm (26 100 mg/m^3, 2300 mg/kg-bw per day), based on decreased fetal body weight and increases in malformations. These developmental effects occurred at maternally toxic doses in rats and occurred at higher levels than the hematological changes and adverse kidney effects observed in the NTP (1991) study. Accordingly, margins of exposure based on the LOAEL (1700 mg/kg-bw per day) reported in the NTP (1991) drinking water study are considered protective of potential developmental effects. These two studies were selected based on the endpoints examined, the quality of the methodology and the identification of the most appropriate lowest LOAEL values.

The margins of exposure between the upper-bounding total daily intake estimate from air, water, food and beverages and soil and critical effect levels from a 13-week drinking water study in rats at 1700 mg/kg-bw per day ranged from 2600 for children aged 0.5–4 years (650 µg/kg-bw per day) to 13 000 for infants aged 0–6 months (133 µg/kg-bw per day). The margin of exposure between the LOAEC of 26 100 mg/m^{3}and upper-bounding concentrations of acetone in air from personal air sampling data of 475.9 µg/m^3 is 55 000. These margins of exposure are considered adequate to address uncertainties in the exposure and health effects databases.

Peak and 4-hour TWA air concentrations of acetone were derived for use of certain household and cosmetic products containing acetone. Peak air concentrations ranged from 117 to 4415 mg/m^3; 4-hour TWA air concentrations were an order of magnitude lower and ranged from 8 to 526 mg/m^3. The effects observed (sensory irritation and mild CNS depression) following acute exposure to acetone within this range of concentrations are mild, transient and reversible once the subject is removed from the exposure source. While the odour threshold (sensory irritation) may be in the range of estimated exposures, which generally starts to be felt at concentrations of approximately 1000 mg/m^3 in humans, irritancy of mucous membranes occurs at concentrations that are orders of magnitude higher than the estimated peak exposures.

In the human health effects literature, CNS effects were generally limited to symptoms such as dizziness and headache. Sensitive measures such as auditory tone discrimination and self-reported anger/hostility were noted by Dick et al. (1989) at a dose as low as 600 mg/m^3 over a 4-hour exposure period. Such effects may be considered adaptable, since several studies of occupationally exposed individuals noted an absence of effects in longer-duration studies in individuals exposed to higher concentrations of acetone. Additionally, CNS effects are more dependent on the total dose than on the exposure concentration; hence, shorter exposure requires a much higher concentration of acetone to exert effects. For a 10-minute exposure, a concentration of 200 000 mg/m^3 was required to induce CNS effects in rats (Haggard et al. 1944).

Overall, no critical health effects were identified for the purpose of the acute risk characterization. This is consistent with outcomes of assessments from other agencies.

OECD (1999) determined that the acute toxicity of acetone is low, and the US EPA (2003) considered acute effects reported in human studies (occupational and volunteer) to be mild and transient (occurring on initial exposure and then dissipating over time).

Based on the information available, it is concluded that acetone does not meet the criteria under paragraph 64(*c*) of CEPA 1999 as it is not 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.

10.4 Uncertainties in Evaluation of Risk to Human Health

No chronic studies in animals have been conducted with acetone; however, epidemiological studies indicate that effects of repeated exposure are similar to effects observed in shorter clinical studies in humans.

Although the available information indicates that acetone is not carcinogenic, the absence of a standard carcinogenicity study by the predominant route of exposure is an uncertainty.

Overall confidence in the acetone total daily intake estimates from environmental media, food, cosmetic products and household products is moderate. Data on acetone concentrations in Canadian environmental media were available for personal air samples and water; however, there were no Canadian data for levels of acetone in food and no data for levels of acetone in breast milk. The use of maximum concentrations may overestimate potential dietary exposure to acetone, particularly since concentrations vary widely among published data sets and maximum values were extended to all foods within a food group. Acetone is used in a wide range of products at concentrations up to 100%; therefore, individual exposures are expected to vary greatly. Additionally, in the absence of data, assumptions were made on the rate and quantity of acetone released from products, and the level of conservatism in these assumptions is not known. However, exposure to acetone from environmental media, food and products is estimated to represent less than 2% of the acetone produced endogenously in the human body and falls within the range of human variability of endogenous acetone production.

11 Conclusion

Based on the information presented in this screening assessment, there is low risk of harm to organisms or the broader integrity of the environment from this substance. It is therefore concluded that acetone does not meet the criteria under paragraph 64(a) or 64(b) of CEPA 1999, as it 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. It is also concluded that acetone does not meet the criteria under paragraph 64(c) of CEPA 1999, as it is not 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.

Based on available information for environmental and human health considerations, it is concluded that acetone does not meet any of the criteria set out in section 64 of CEPA 1999.

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Appendix A: Concentrations of Acetone in Environmental Media and Food

Table A1-1: Ambient, indoor and personal air concentrations of acetone in Canada and elsewhere, Ambient air; National Air Pollution Surveillance (NAPS) Program 2000–2009 (Environment Canada 2011b)

Study, location and type of sample	Sample duration	No. of samples	Concentration Median (µg/m³)	Concentration Range (µg/m³)	Concentration 95th percentile (µg/m³)
Outdoors, all stations	24 h	3688	2.895	0.007 - 35.167	6.55
Outdoors, all stations	4 h	5754	2.931	0.003 - 80.228	12.39
Outdoors, Egbert, ON – agricultural	4 h	494	5.679	0.600 - 80.228	18.2
Outdoors, Windsor, ON – rural	24 h	285	2.829	0.800 - 22.206	6.617
Outdoors, Winnipeg, MB – commercial	24 h	460	3.101	0.025 - 13.678	5.854
Outdoors, Port Moody, Metro Vancouver, BC – industrial	24 h	299	3.873	0.05 - 14.202	8.946

Table A1-2: Ambient, indoor and personal air concentrations of acetone in Canada and elsewhere, Residential homes, non-smoking participants, adults, 2005; Windsor Ontario Exposure Assessment Study (WOEAS) (Health Canada 2010a)

Season	Study, location and type of sample	Sample duration	No. of samples	Concentration Median (µg/m³)	Concentration Range (µg/m³)	Concentration 95th percentile (µg/m³)

Winter	Personal	24 h	225	34.8	9.7 - 814.5	135.8
Winter	Indoor	24 h	232	29.3	5.9 - 673.3	134.5
Winter	Outdoor	24 h	200	3.8	1.5 - 18.3	9.4
Summer	Personal	24 h	206	116.1	18.2 - 1871.9	475.9
Summer	Indoor	24 h	217	173.8	0.01 - 3755.5	647.2
Summer	Outdoor	24 h	216	10.1	3.9 - 51.6	19.8

Table A1-3: Ambient, indoor and personal air concentrations of acetone in Canada and elsewhere, Residential homes, non-smoking participants, children, 2006; Windsor Ontario Exposure Assessment Study (WOEAS) (Health Canada 2010a)

Season	Study, location and type of sample	Sample duration	No. of samples	Concentration Median (µg/m³)	Concentration Range (µg/m³)	Concentration 95th percentile (µg/m³)
Winter	Indoor	24 h	224	48.0	8.6 - 1380.7	194.3
Winter	Outdoor	24 h	215	3.0	1.2 - 27.2	7.4
Summer	Indoor	24 h	211	134.8	9.5 - 1977.5	538.9
Summer	Outdoor	24 h	214	10.4	3.2 - 544.1	71.0

Table A1-4: Ambient, indoor and personal air concentrations of acetone in Canada and elsewhere, residential homes – smoking/non-smoking participants, 2007, Regina Indoor Air Quality Study (RIAQS) (Health Canada 2010b)

Season	Study, location and type of sample	Sample duration	No. of samples	Concentration Median (µg/m³)	Concentration Range (µg/m³)	Concentration 95th percentile (µg/m³)
Winter	Indoor – all houses	24 h	104	36.5	8.6 - 436.9	120.3
Winter	Indoor – all houses	5 days	89	45.2	7.5 - 451.9	127.5
Winter	Indoor –	24 h	21	37.0	11.5 -	113.1

Season	Study, location and type of sample	Sample duration	No. of samples	Concentration Median (µg/m³)	Concentration Range (µg/m³)	Concentration 95th percentile (µg/m³)
	smoker				436.9	
Winter	Indoor – smoker	5 days	19[a]	45.2	10.1 - 451.9	451.9
Winter	Indoor – non-smoker	24 h	83	35.4	8.6 - 192.6	120.3
Winter	Indoor – non-smoker	5 days	70	45.2	7.5 - 202.9	127.5
Winter	Outdoor – all houses	24 h	94	3.4	0.6 - 36.0	9.6
Winter	Outdoor – smoker	24 h	17[a]	3.1	1.2 - 13.8	13.8
Winter	Outdoor – non-smoker	24 h	77	3.5	0.6 - 36.0	9.6
Summer	Indoor – all houses	24 h	105	41.1	11.3 - 1451.7	156.5
Summer	Indoor – all houses	5 days	101	51.7	13.0 - 867.9	318.2
Summer	Indoor – smoker	24 h	13[a]	32.4	14.0 - 101.8	101.8
Summer	Indoor – smoker	5 days	13[a]	52.7	23.5 - 124.1	124.1
Summer	Indoor – non-smoker	24 h	91	42.4	11.3 - 1451.7	241.3
Summer	Indoor – non-smoker	5 days	88	51.7	13.0 - 867.9	327.6
Summer	Outdoor – all houses	24 h	108	8.6	3.0 - 33.0	21.1
Summer	Outdoor – all	5 days	97	11.0	4.7 - 303.4	106.4

Season	Study, location and type of sample	Sample duration	No. of samples	Concentration Median (μg/m³)	Concentration Range (μg/m³)	Concentration 95th percentile (μg/m³)
	houses					
Summer	Outdoor – smoker	24 h	12[a]	7.2	3.4 - 18.4	18.4
Summer	Outdoor – smoker	5 days	14[a]	12.9	4.7 - 245.9	245.9
Summer	Outdoor – non-smoker	24 h	95	8.6	3.0 - 33.0	22.2
Summer	Outdoor – non-smoker	5 days	82	10.8	5.3 - 303.4	102.2

[a] Due to the small sample size (< 20 samples), the derived 95th percentiles are equivalent to the maxiumum values.

Table A1-5: Ambient, indoor and personal air concentrations of acetone in Canada and elsewhere, residential homes –non-smoking participants, 2009, Halifax Indoor Air Quality Study (HIAQS) (Health Canada 2011)

Season	Study, location and type of sample	Sample duration	No. of samples	Concentration Median (μg/m³)	Concentration Range (μg/m³)	Concentration 95th percentile (μg/m³)
Winter	Indoor	24 h	312	21.8	4.0 - 2188.0	108.7
Winter	Outdoor	24 h	286	2.8	1.2 - 25.3	6.0
Summer	Indoor	24 h	331	26.5	<0.06 - 1285.0	288.5
Summer	Outdoor	24 h	324	4.7	2.1 - 50.2	9.9

Table A1-6: Ambient, indoor and personal air concentrations of acetone in Canada and elsewhere, residential homes – smoking/non-smoking, Winter 2002-2003, Ottawa – (Zhu et al. 2005)

Study, location and type of sample	Sample duration	No. of samples	Concentration Median (µg/m³)	Concentration Range (µg/m³)	Concentration 95th percentile (µg/m³)
Indoor	100 min	75	28.5	0.015 - 455.9	90th: 76.4
Outdoor	100 min	74	0.2	0.015 - 15.3	90th: 3.6

Table A1-7: Ambient, indoor and personal air concentrations of acetone in Canada and elsewhere, residential homes, 1999-2001, Texas, Los Angeles, New Jersey – (Relationship of Indoor, Outdoor and Personal Air [RIOPA] study; Weisel et al. 2005)

Study, location and type of sample	Sample duration	No. of samples	Concentration Median (µg/m³)	Concentration Range (µg/m³)	Concentration 95th percentile (µg/m³)
Indoor – passive	48 h	398	8.25	< 0.4 - ns	45.8
Outdoor – passive	48 h	395	4.39	< 0.4 - ns	19.6
Personal – passive, adult	48 h	409	8.36	< 0.4 - ns	57.7
Personal – passive, child (15–19 years)	48 h	169	11.5	< 0.4 - ns	81.0
In-vehicle	55–459 min	115	4.08	< 13.38 - ns	45.0

Abbreviation: ns, not stated

Table A1-8: Ambient, indoor and personal air concentrations of acetone in Canada and elsewhere, residential homes, 1997-2003; New York – (NYSDOH 2005)

Study, location and type of sample	Sample duration	No. of samples	Concentration Median (µg/m³)	Concentration Range (µg/m³)	Concentration 95th percentile (µg/m³)
Indoor	2 h	227	21	< 0.25 - ns	90th: 110
Outdoor	2 h	114	6.4	< 0.25 - ns	90th: 44

Abbreviation: ns, not stated

Table A1-9: Ambient, indoor and personal air concentrations of acetone in Canada and elsewhere, suburban and rural homes, 2003-2006; New Jersey – (Weisel et al. 2008)

Study, location and type of sample	Sample duration	No. of samples	Concentration Median (µg/m³)	Concentration Range (µg/m³)	Concentration 95th percentile (µg/m³)
Indoor (94/100 detected)	24 h	100	34.5	< 12 - 2900	190

Table A1-10: Ambient, indoor and personal air concentrations of acetone in Canada and elsewhere, residential homes and workplaces, fall 1992; New Jersey, Pennsylvania – (Heavner et al. 1996)

Study, location and type of sample	Sample duration	No. of samples	Concentration Median (µg/m³)	Concentration Range (µg/m³)	Concentration 95th percentile (µg/m³)
Indoor – non-smoking home	14 h	60	33.88	2.81 - 389.71	ns
Indoor – smoking home	14 h	29	39.33	19.73 - 664.99	ns
Indoor – non-smoking work	7 h	51	28.53	5.48 - 414.30	ns

Indoor – smoking work	7 h	28	60.53	8.26 - 21 083.81	ns

Abbreviation: ns, not stated

Table A1-11: Ambient, indoor and personal air concentrations of acetone in Canada and elsewhere, Office buildings, 1995–1998 summer and winter; United States – (Building Assessment Survey and Evaluation [BASE] study; Girman et al. 1999)

Study, location and type of sample	Sample duration	No. of samples	Concentration Median ($\mu g/m^3$)	Concentration Range ($\mu g/m^3$)	Concentration 95th percentile ($\mu g/m^3$)
Indoor	8–10 h	56	29	7.1 - 220	ns

Abbreviation: ns, not stated

Table A1-12: Ambient, indoor and personal air concentrations of acetone in Canada and elsewhere, 2003–2008, 11 cities (European Indoor Air Monitoring and Exposure Assessment [AIRMEX] study; 2011 email Geiss 2011to Existing Substances Risk Assessment Bureau, unreferenced; Geiss et al. 2011)

Study, location and type of sample	Sample duration	No. of samples	Concentration Median ($\mu g/m^3$)	Concentration Range ($\mu g/m^3$)	Concentration 95th percentile ($\mu g/m^3$)
Outdoor – passive	7 days	66	4.5	0.3 - 12.8	9.3
Indoor – passive, residential homes	7 days	88	31	10.4 - 165.1	94.2
Indoor – passive, public buildings/schools	7 days	129	19.5	1.4 - 336.8	59.6
Personal – passive	3 days	45	31	11.8 - 225.9	66.7

Table A2-1: Concentrations of acetone in water in Canada and elsewhere, drinking water

Location	Sampling period	No. of samples	Mean (µg/L)	Range (µg/L)	Reference
Ottawa, Ontario	Fall 2002	71	11.0	< 2–131 P95 = 48	2003 personal communication from J. Zhu Health Canada Chemistry Research Division to Existing Substances Risk Assessment Bureau, unreferenced
24 US communities	2002–2005	150	ns	< 6–11.73	USGS 2007
Lower Rio Grande Valley, TX, USA	1993	8	nd	nd–10.7	US EPA 1994
Private and community wells in Wisconsin, USA	1980–1984	ns	nd	< nd	Krill and Sonzogni 1986
Canada (potable water treatment facilities)	1979	30 plants	nd	nd (< 1000)	Otson et al. 1982
Seattle, Washington, USA	1975	ns	ns	Detected – 1	US EPA 1975

Abbreviations: Max, maximum; na, not applicable; nd, not detected; ns, not stated; P95, 95th percentile

Table A2-3: Concentrations of acetone in water in Canada and elsewhere, surface water

Location	Sampling period	No. of sampl es	Mean (µg/L)	Range (µg/L)	Reference
9 US communities	2002–2005	241	—	< 7	USGS 2007
Streams in New York and New Jersey, USA	January 1997	42	2.6 median estimate d	Max: 6.6	O’Brien et al. 1997
Seawater	ns	ns	ns	5–53	Corwin 1969

Storm water runoff, 20 industrial sites, North Carolina, USA	1993–1994	20	ns	< 100 (7 sites) > 100 (2 sites)	Line et al. 1997

Abbreviations: Max, maximum; na, not applicable; nd, not detected; ns, not stated; P95, 95th percentile

Table A2-3: Concentrations of acetone in water in Canada and elsewhere, groundwater

Location	Sampling period	No. of sampl es	Mean (µg/L)	Range (µg/L)	Reference
15 US communities	2002–2005	223	ns	< 6–68.36	USGS 2007
In vicinity of 34 disposal sites from 8 American regions	ns	254	ns	Detected (not quantified)	Plumb 1991
New Jersey, USA	ns	ns	ns	Max: 3000	US EPA 1980
Residential well water in vicinity of a landfill site, Delaware, USA	1977	6	ns	0.2–0.7	DeWalle and Chian 1981
Groundwater from landfill sites in Minnesota, USA, with good water quality	ns	7	ns	nd–25	Sabel and Clark 1984
Groundwater from sites in Minnesota, USA, contaminated with landfill leachate	ns	13	ns	nd–3000	Sabel and Clark 1984

Abbreviations: Max, maximum; na, not applicable; nd, not detected; ns, not stated; P95, 95th percentile

Table A2-4: Concentrations of acetone in water in Canada and elsewhere, wastewater

Location	Sampling period	No. of sampl es	Mean (µg/L)	Range (µg/L)	Reference

Industrial wastewater, 4000 sites, USA	ns	ns	2500 (highest median value, printing and publishing plants)	138–37 709	OECD 1999
Industrial and municipal landfill leachate from sites in the USA	1982, 1984	ns	ns	50–62 000	Brown and Donnelly 1988
Landfill leachate, Delaware, USA	1977	1	43 700	na	DeWalle and Chian 1981
Leachate from sites in Minnesota, USA	ns	6	ns	140–13 000	Sabel and Clark 1984
Septic tank effluent from septic tank serving 97 homes in Tacoma, Washington, USA	1982	7 (24 h composite samples)	70 300 (one measurement only)	ns	DeWalle et al. 1985

Abbreviations: Max, maximum; na, not applicable; nd, not detected; ns, not stated; P95, 95th percentile

Table A3-1: Concentrations of acetone detected in foods in Canada and elsewhere, dairy [a]

Item sampled	Sampling period	No. of samples	Mean concentration (µg/kg)	Concentration range (µg/kg)	Reference
Whole, 1% and 2% commercial milk samples from Las Vegas, Nevada, USA	January – February 2002	19 (whole) 8 (2%) 5 (1%)	29 30 30	5–42 22–36 25–36	Hiatt and Pia 2004
Raw (unpasteurized) milk from cows in southern Ontario dairy herds	January – December 1999	10 375 cows	1280 (raw milk basis)	0–269 900 (raw milk basis)	Wood et al. 2004
Raw milk from hyperketonemic cows in Sweden[b]	26 h	Samples from 8 cows	ns	18 048–219 351	Andersson and Lundstrom 1984
Butter from Oregon, USA	ns	1	130	ns	Siek and Lindsay 1970
Cheddar cheese from USA	ns	3	8500 (approximate)	ns	Day et al. 1960
Cheese	ns	ns	ns	100–8500	Maarse and Visscher 1989
Yoghurt	ns	ns	ns	300–58 000	Maarse and Visscher 1989

Abbreviations: Max, maximum; ns, not stated
[a] Values presented per volume were converted to mass using a density of 1.03 kg/L for milk.
[b] These cows had beyond normal levels of acetone, a condition that can occur in early lactation.

Table A3-2: Concentrations of acetone detected in foods in Canada and elsewhere, fruit

Item sampled	Sampling period	No. of samples	Mean concentration (µg/kg)	Concentration range (µg/kg)	Reference
Strawberries	ns	ns	ns	1300–3000	van Straten and Maarse 1983
Currants	ns	ns	ns	Max: 1200	Maarse and Visscher 1989

Black currants from Sweden	Harvested in 1962; stored until 1964	ns	2000	ns	Andersson and von Sydow 1966
Mangos from Sri Lanka	ns	3 cultivars	Trace	ns	MacLeod and Pieris 1984
Apples from Belgium	ns	ns	600 (dry weight)	ns	Feys et al. 1980
Apples	ns	ns	ns	130	Maarse and Visscher 1989

Abbreviations: Max, maximum; ns, not stated

Table A3-3: Concentrations of acetone detected in foods in Canada and elsewhere, vegetables

Item sampled	Sampling period	No. of samples	Mean concentration (µg/kg)	Concentration range (µg/kg)	Reference
Canned and frozen sweet corn from Oregon, USA	ns	7	1500	300–2400	Bills and Keenan 1968
Carrots from Oregon, USA	1969 growing season	3	240	200–310	Heatherbell et al. 1971
Carrots	ns	ns	ns	100–800	Maarse and Visscher 1989
Common, lima and mung beans and soybeans (country of origin not specified)	ns	ns	880	260–2000	Lovegren et al. 1979
Split peas (country of origin not specified)	ns	ns	530	ns	Lovegren et al. 1979
Lentils (country of origin not specified)	ns	ns	230	ns	Lovegren et al. 1979
Soybean	ns	ns	ns	4–1600	Maarse and Visscher 1989

Potato chips from USA	ns	ns	110 (fresh) 255 (stale)	ns	Mookherjee et al. 1965
Tomatoes from Indiana, USA	ns	3 varieties	810	640–1030	Nelson and Hoff 1969
Tomatoes	ns	ns	ns	600–16 000	van Straten and Maarse 1983

Abbreviations: Max, maximum; ns, not stated

Table A3-4: Concentrations of acetone detected in foods in Canada and elsewhere, cereal products

Item sampled	Sampling period	No. of samples	Mean concentration (µg/kg)	Concentration range (µg/kg)	Reference
Bread	ns	ns	ns	680–10 100	Maarse and Visscher 1989
Rice	ns	ns	ns	400	van Straten and Maarse 1983

Abbreviations: Max, maximum; ns, not stated

Table A3-5: Concentrations of acetone detected in foods in Canada and elsewhere, beverages

Item sampled	Sampling period	No. of samples	Mean concentration (µg/kg)	Concentration range (µg/kg)	Reference
Beer	ns	ns	ns	20–1700	van Straten and Maarse 1983
Beer from USA	ns	ns	ns	600–1400	Rosculet and Rickard 1968
Cider apple juice from Britain	1971–1974	4 cultivars	109.5 µg/L	6–200 µg/L	Williams et al. 1980
Brandy	ns	ns	ns	4000	Maarse and Visscher 1989

Abbreviations: Max, maximum; ns, not stated

Table A4: Concentration of acetone in soil outside Canada

Location	Sampling period	No. of samples	Detection limit (ng/g)	Mean concentration (ng/g)	Reference
Vega Alta Public Supply well sites, Puerto Rico	ns	ns	ns	9500	ATSDR 1988
Summit National Site, Ohio, USA (toxic waste site)	ns	ns	ns	9484	US EPA 1988

Abbreviation: ns, not stated

Appendix B: Upper-bounding Estimates of Daily Intake of Acetone by the General Population of Canada

Table B1: Upper-bounding estimates of daily intake of acetone by the general population of Canada, birth to 4 years of age

Route of exposure	0–6 months[a,b,c] Breast fed	0–6 months[a,b,c] Formula fed	0–6 months[a,b,c] Not formula fed	0.5–4 years[d]	5–11 years[a]	12–19 years[b]	20–59 years[c]	60+ years[d]
Air[e]	133.3	133.3	133.3	285.5	222.6	126.6	108.7	94.5
Drinking water[f]	Not applicable	5.1	1.3	0.6	0.6	0.3	0.3	0.3
Food and beverages[g]	Not applicable	5.1	396.2	363.8	276.5	173.8	148.4	126.0
Soil[h]	0.04	0.04	0.04	0.06	0.02	4.8×10^{-3}	4.0×10^{-3}	4.0×10^{-3}
Total intake	133.3	138.4	530.7	650.0	499.7	300.7	257.4	220.8

Abbreviation: n.a., not applicable

[a] Assumed to weigh 31.0 kg, to breathe 14.5 m^3 of air per day, to drink 0.4 L of water per day and to ingest 65 mg of soil per day (Health Canada 1998).

[b] Assumed to weigh 59.4 kg, to breathe 15.8 m^3 of air per day, to drink 0.4 L of water per day and to ingest 30 mg of soil per day (Health Canada 1998).

[c] Assumed to weigh 70.9 kg, to breathe 16.2 m^3 of air per day, to drink 0.4 L of water per day and to ingest 30 mg of soil per day (Health Canada 1998).

[d] Assumed to weigh 72.0 kg, to breathe 14.3 m^3 of air per day, to drink 0.4 L of water per day and to ingest 30 mg of soil per day (Health Canada 1998).

[e] The 95th percentile concentration of acetone from personal air sampling (475.9 µg/m^3) was used to calculate the upper-bounding limit of exposure estimate based on 206 personal air samples collected from 45–48 homes from the Windsor Indoor Air Quality Study (Health Canada 2010a). This represents a full 24-hour period for time spent indoors and outdoors.

[f] The 95th percentile value for the concentration of acetone in 71 samples of tap water from homes in Ottawa, Ontario (48 µg/L), was used to calculate the intake from drinking water (2003 personal communication from J. Zhu, Health Canada Chemistry Research Division to Existing Substances Risk Assessment Bureau, unreferenced).

[g] Only limited Canadian data for concentrations of acetone in food were identified; therefore,reported maximum concentrations of acetone in food from other countries were used as surrogate data. Estimates of intake from food are based upon concentrations in foods that are selected to represent the 12 food groups addressed in calculating intake (Health Canada 1998):

Dairy products: 42 µg/kg milk; maximum concentration of acetone in commercial milk from Las Vegas, NV, USA (Hiatt and Pia 2004); this concentration was considered most representative of milk consumed by Canadians
Fats: 20 000 µg/kg; based on maximum value reported in *Fenaroli's Handbook of Flavor Ingredients* (Burdock 2010)
Fruits: 3000 µg/kg; maximum value measured in strawberries (van Straten and Maarse 1983)
Vegetables: 16 000 µg/kg; maximum value measured in tomatoes (van Straten and Maarse 1983)
Cereal products: 10 100 µg/kg; based on maximum value reported in bread (Maarse and Visscher 1989)
Meat and poultry: No data identified

Fish: No data identified
Eggs: No data identified
Foods primarily sugar: 5400 µg/kg; based on maximum value reported in *Fenaroli's Handbook of Flavor Ingredients* (Burdock 2010)
Mixed dishes and soups: No data identified
Nuts and seeds: No data identified
Soft drinks, alcohol, coffee, tea: 1700 µg/kg; maximum value measured in beer (van Straten and Maarse 1983)

Amounts of foods consumed on a daily basis by each age group are described by Health Canada (1998). Daily food intakes were obtained from the 1970–1972 Nutrition Canada Survey.

[h] No Canadian studies or data for concentrations of acetone in soil were identified. As a surrogate, the maximum concentration of acetone of 9500 ng/g found in soil samples collected near the Summit National waste disposal site in Ohio, USA, and from the Vega Alta public supply well sites in Puerto Rico was used to calculate the upper-bounding limit of exposure estimate (ATSDR 1994).

Appendix C: Estimates of Intake to Acetone from the Use of Cosmetic Products and Household Products

Table C1: Concentrations of acetone in air and inhalation intake estimates to acetone via the use of household products

Product	Acetone concentration (%)	Peak event Time (min)	Peak event Concentration (mg/m^3)	Mean event Time (min)	Mean event Concentration (mg/m^3)	4 h TWA[a] Concentration (mg/m^3)	Estimated intake for adult Canadian[b] (mg/kg-bw per event)
Spray paint	60	15	4415	20	2788	232	9
Concrete sealant	25	60	3830[c]	60	2105	526	20
Cleaner/ degreaser	100	10	1500	10	762	32	1.2

[a] Four-hour TWA values were calculated to allow for comparison with hazard endpoint. It is assumed that after the event, the individual leaves the area and is exposed to ambient air with a concentration of 0.4759 mg/m^3 (95th percentile personal air concentration from Windsor study; Health Canada 2010a). 4 h TWA = [(mean concentration during event × time of event) + (ambient air concentration × (4 h – time of event))] ÷ 4 h.

[b] Adult Canadian assumed to weigh 70.9 kg and to breathe 16.2 m^3 of air per day (Health Canada 1998). Intake = (4 h TWA concentration × breathing rate × exposure duration) ÷ bw.

[c] This is the peak concentration to which the individual was exposed during the 60-minute exposure time. The peak concentration in the room was estimated to be 5931 mg/m^3 and occurred at the 120-minute time point.

Table C2: Estimated intake of acetone for an adult Canadian via the use of acetone as a cleaner

Product	Acetone concentration (%)	Dermal (mg/kg-bw per event)	Inhalation (mg/kg-bw per event)	Total (mg/kg-bw per event)
Cleaner/ degreaser	100	0.4	1.2	1.6

Table C3: Concentrations of acetone in air from the use of cosmetic products

Product	Acetone concentration (%)	Peak event Time (min)	Peak event Concentration (mg/m^3)	Mean event Time (min)	Mean event Concentration (mg/m^3)	4 h TWA[a] Concentration (mg/m^3)

Nail remover	100	30	123	30	64	8.4
Hairspray	30	0.25	209	25	141	15
Face mask	100	0.33	117	25	79	8.7

[a] Four-hour TWA values were calculated to allow for comparison with hazard endpoint. It was assumed that after the event, the individual leaves the area and is exposed to ambient air with a concentration of 0.4759 mg/m^3 (95th percentile personal air concentration from Windsor Indoor Air study; Health Canada 2010a). 4 h TWA = [(mean event concentration × time of event) + (ambient air concentration × (4 h – time of event))] ÷ 4 h.

Table C4: Estimated intake of acetone for an adult Canadian via the use of cosmetic products

Product	Acetone concentration (%)	Dermal[a] 12–19 years (mg/kg-bw per event)	Dermal[a] 20–59 years (mg/kg-bw per event)	Inhalation[b] 12–19 years (mg/kg-bw per event)	Inhalation[b] 20–59 years (mg/kg-bw per event)	Total 12–19 years (mg/kg-bw per event)	Total 20–59 years (mg/kg-bw per event)
Nail remover	100	0.58	0.56	0.37	0.32	0.95	0.88
Hairspray	30	N/A	N/A	0.67	0.58	0.67	0.58
Face mask	100	N/A	0.04	N/A	0.33	N/A	0.37
Face cleanser	10	0.03	0.06	N/A	N/A	0.03	0.06
Face Moisturizer	0.3	0.11	0.09	N/A	N/A	0.11	0.09

Abbreviation: N/A, not applicable

[a] The nail remover and face mask products are reported to contain up to 100% acetone; therefore, the physical-chemical properties of pure acetone were considered appropriate for modelling diffusion and evaporation of acetone from the use of these products. Estimates of exposure from the use of these products were generated using the AIHA SkinPerm model (AIHA 2010). The face cleanser and lotion products were primarily creams, and the behaviour of acetone in this matrix was unknown and not likely representative of the pure substance; therefore, all of the acetone remaining on the skin was considered absorbed.

[b] Adolescents 12–19 years of age are assumed to weigh 59.4 kg and to breathe 15.8 m^3 of air per day; adults 20–59 years of age are assumed to weigh 70.9 kg and to breathe 16.2 m^3 of air per day (Health Canada 1998). Intake = (4 h TWA concentration × breathing rate × exposure duration) ÷ bw.

Table C5: Detailed algorithms for intake estimates[a]

Product type	Assumptions	Estimated concentrations and daily intakes
Spray paint	Concentration of acetone in spray paint: 60%, maximum concentration of acetone found in spray paint (HPD 1993–) Applied amount: 300 g, entire can (Bremmer and van Engelen 2007) Room volume: 34 m^3 (Bremmer and van Engelen 2007), similar to small garages in Canada (reported sizes range from 26 m^3 in northern Canada to 102 m^3 in southern Canada) (contractor report prepared for Existing Substances Risk Assessment Bureau, 2011, unreferenced) Ventilation rate: 1.5/h, well ventilated (Bremmer and van Engelen 2007) Emission rate = (300 g/15 min) × 0.6 fraction acetone = 12 g/min Room supply air exchange rate (AER) = (1.5/h × 34 m^3)/60 min = 0.85 m^3/min **Estimated TWA concentration in air using IHMod “Well-mixed Room Model with a Constant Emission Rate” (AIHA 2009a):** • contaminant mass emission rate: 12 000 mg/min • room supply AER: 0.85 m^3/min • room volume: 34 m^3 • release duration: 15 min (Bremmer and van Engelen 2007) • exposure duration: 20 min (Bremmer and van Engelen 2007) • percentage losses through sorption or chemical	Model output: Peak concentration, 15 min = 4415 mg/m^3 Mean event concentration, 20 min = 2788 mg/m^3

	degradation: 0 • initial concentration of acetone in air: 0 mg/m^3 • concentration of acetone in inflow air: 0 mg/m^3	
Concrete sealant	Concentration of acetone in concrete sealant: 25% weight/weight basis, maximum value found (Deco-Crete Supply 2010a) Applied amount: 3.8 L, based on product application directions (400 ft^2/gallon; Deco-Crete Supply 2010b) Density of paint: 0.92 g/mL (Deco-Crete Supply 2010a) Application duration: 60 min (professional judgment) Ventilation rate: 0.6/h (standard room; Bremmer and van Engelen 2007) Mass acetone applied = 3.8 L × 0.92 g/mL × 0.25 wt. fraction = 874 g Emission rate = mass applied ÷ drying time = 874 g/120 min = 7300 mg/min Room supply AER = (0.6/h × 86 m^3)/60 min = 0.86 m^3/min **Estimated TWA concentration in air using IHMod "Well-mixed Room Model with a Constant Emission Rate" (AIHA 2009a):** • contaminant mass emission rate: 7300 mg/min • room supply AER: 0.86 m^3/min • room volume: 86 m^3 (37.5 m^2 × 2.3 m high) (professional judgment) • release duration (time to dry): 120 min (product application directions) • exposure duration: 60 min (professional judgment)	Model output: Peak event concentration, 60 min = 3830 mg/m^3 Mean event concentration, 60 min = 2105 mg/m^3 Peak concentration, 120 min = 5931 mg/m^3

	• percentage losses through sorption or chemical degradation: 0 • initial concentration of acetone in air: 0 mg/m^3 • concentration of acetone in inflow air: 0 mg/m^3	
Cleaner/ degreaser	Concentration of acetone: 100%, maximum value (HPD 1993–) Exposure duration: 10 min (Bremmer and van Engelen 2007) Density of acetone: 0.790 g/mL (West and Lide 1989) Air exchange rate: 0.2 m^3/min (derived from 0.6/h ventilation rate for an unspecified room in Bremmer et al. 2006) Amount used: 40 mL (professional judgment) Room volume: 20 m^3 (volume of unspecified room in Bremmer et al. 2006) Maximum dermal absorption rate (flux): 0.687 $mg/(cm^2 \cdot h)$ (AIHA 2009c) One-half surface area of one hand, 20–59 years: 228 cm^2 (Health Canada 1995) Body weight, 20–59 years: 70.9 kg (Health Canada 1998) $Absorbed_{(Dermal)}$ = Absorption rate × Surface area × Duration = 0.687 $mg/(cm^2 \cdot h)$ × 228 cm^2 × 1/6 h = 26 mg $Intake_{(Dermal)}$ = $Absorbed_{(Dermal)}$ ÷ Body weight = 26 mg ÷ 70.9 kg = 0.4 mg/kg-bw Emission rate = (Amount used – Amount absorbed dermally) ÷ Time of use × Density = [(40 mL × 0.790	Calculated intake from dermal exposure on day of event = 0.4 mg/kg-bw Model output: Peak concentration, 10 min = 1500 mg/m^3 Mean event concentration, 10 min = 762 mg/m^3

	g/mL × 1000 mg/g) – 26 mg] ÷ 10 min = 3150 mg/min Room supply AER = (0.6/h × 20 m^3)/60 min = 0.2 m^3/min **Estimated TWA concentration in air using IHMod "Well-mixed Room Model with a Constant Emission Rate" (AIHA 2009a):** • contaminant mass emission rate: 3150 mg/min • room supply AER: 0.2 m^3/min • room volume: 20 m^3 • release duration: 10 min • exposure duration: 10 min • percentage losses through sorption or chemical degradation: 0 • initial concentration of acetone in air: 0 mg/m^3 • concentration of acetone in inflow air: 0 mg/m^3	
Artificial nail remover	Concentration of acetone: 100% 2011 emails from the Consumer Product Safety Directorate, Health Canada, to the Existing Substances Risk Assessment Bureau, Health Canada; unreferenced) Exposure duration: 30 min (Bremmer and van Engelen 2007) Air exchange rate: 0.2 m^3/min (derived from 0.6/h ventilation rate for an unspecified room in Bremmer et al. 2006). Room volume: 20 m^3 (volume of unspecified room in Bremmer et al. 2006) Maximum dermal absorption rate: 0.687 mg/(cm^2·h) (AIHA 2009c) Body weight, 12–19 years: 59.4 kg (Health Canada 1998) Body weight, 20–59 years: 70.9 kg (Health Canada	Calculated: 12–19 years internal dermal dose, 30 min = 0.58 mg/kg-bw per day 20–59 years internal dermal dose, 30 min

	1998) Surface area fingertips, 1/8th surface area of hands, 12–19 years: 100 cm^2 (Health Canada 1995) Surface area fingertips, 1/8th surface area of hands, 20–59 years: 115 cm^2 (Health Canada 1995) 12–19 years: $Absorbed_{(Dermal)}$ = Absorption rate × Surface area × Duration ÷ Body weight = 0.687 mg/(cm^2·h) × 100 cm^2 × 0.5 h ÷ 59.4 kg = 0.58 mg/kg-bw per day 20–59 years: $Absorbed_{(Dermal)}$ = Absorption rate × Surface area × Duration ÷ Body weight = 0.687 mg/(cm^2·h) × 115 cm^2 × 0.5 h ÷ 70.9 kg = 0.56 mg/kg-bw per day Room supply AER = (0.6/h × 20 m^3)/60 min = 0.2 m^3/min **Estimated evaporation rate using IHMod "Estimating Contaminant Generation Rate from Small Spills" model (AIHA 2009a):** • system pressure: 1 atm • velocity of air: 2 cm/s (2009 email from Toxicology Excellence for Risk Assessment to Existing Substances Risk Assessment Bureau, Health Canada; unreferenced) • surface temperature of pool: 25°C • surface area of pool: 9 cm^2 (assuming approximately 20 g of substance and a depth of liquid of 2 cm to ensure full coverage of the nail bed) • length of pool: 3 cm	= 0.56 mg/kg-bw per day Model output: Peak concentration, 30 min = 123 mg/m^3 Mean event concentration, 30 min = 64 mg/m^3

	Mass emission rate of acetone from pool: 95.1 mg/min **Estimated TWA concentration in air using IHMod "Well-mixed Room Model with a Constant Emission Rate" (AIHA 2009a):** • contaminant mass emission rate: 95.1 mg/min • room supply air exchange rate: 0.2 m^3/min (derived from 0.6/h) • room volume: 20 m^3 • release duration: 1 min • exposure duration: 30 min • percentage losses through sorption or chemical degradation: 0 • initial concentration of acetone in air: 0 mg/m^3 • concentration of acetone in inflow air: 0 mg/m^3	
Face mask	Concentration of acetone: 100% (2011 emails from the Consumer Product Safety Directorate, Health Canada, to the Existing Substances Risk Assessment Bureau, Health Canada; unreferenced). Amount used: 1.2 g (Loretz et al. 2005) Air exchange rate: 0.333 m^3/min (derived from 2/h ventilation rate for bathroom in Bremmer et al. 2006) Room volume: 10 m^3 (volume of unspecified room in Bremmer et al. 2006) Surface area one-half head, 20–59 years: 638 cm^2 (Health Canada 1995) Bathroom supply AER = (2/h × 10 m^3)/60 min = 0.333 m^3/min **IH SkinPerm model**	Calculated: Internal dermal dose = 0.04 mg/kg-bw Model output: Peak concentration, 0.33 min = 117

	Input parameters: • instantaneous deposition: 1200 mg • surface area: 638 cm^2 • chemical: default acetone data • start deposition: 0 h • end observation time: 1 h • calculation intervals/h: 10 000 • report intervals/h: 1000 Output: • Fraction absorbed: 0.2% • Amount absorbed: 2.7 mg Dermal estimated daily intake: Daily intake = Event dose × Use frequency ÷ Body weight = 2.7 mg × 1 time/day ÷ 70.9 kg = 0.04 mg/kg-bw per day Emission rate to air = (Amount used – Amount absorbed dermally) ÷ Time to evaporate × = (1200 mg – 2.7 mg) ÷ 1/3 min = 3530 mg/min **Estimated TWA concentration in air using IHMod “Well-mixed Room Model with a Constant Emission Rate” (AIHA 2009a):** • contaminant mass emission rate: 3530 mg/min • room supply air exchange rate: 0.333 m^3/min (derived from 2/h) • room volume: 10 m^3 • release duration: 1/3 min • exposure duration: 25 min (50th percentile for time spent in bathroom, for adult 18–64 years; US EPA 2011)	mg/m^3 Mean event concentrati on, 25 min = 79 mg/m^3

	• percentage losses through sorption or chemical degradation: 0 • initial concentration of acetone in air: 0 mg/m^3 • concentration of acetone in inflow air: 0 mg/m^3	
Hairspray	Concentration of acetone: 30% (2011 emails from the Consumer Product Safety Directorate, Health Canada, to the Existing Substances Risk Assessment Bureau, Health Canada; unreferenced). Spray duration: 0.24 min (Bremmer et al. 2006) Emission rate: 28 000 mg/min (Bremmer et al. 2006) Air exchange rate: 0.333 m^3/min (derived from 2/h ventilation rate for bathroom in Bremmer et al. 2006) Room volume: 10 m^3 (Bremmer et al. 2006) Exposure duration: 25 min (US EPA 2011) Bathroom supply AER = (2/h × 10 m^3)/60 min = 0.333 m^3/min **Estimated TWA concentration in air using IHMod "Well-mixed Room Model with a Constant Emission Rate" (AIHA 2009a):** • contaminant mass emission rate: 8400 mg/min (based on emission rate of 28 000 mg/min, 30% acetone concentration and spray duration of 0.24 min) • room supply air exchange rate: 0.333 m^3/min (derived from 2/h) • room volume: 10 m^3 • release duration: 0.24 min • exposure duration: 25 min (50th percentile for time spent in bathroom, for adult 18–64 years; US EPA 2011) • percentage losses through sorption or chemical degradation: 0 • initial concentration of acetone in air: 0 mg/m^3	Model output: Peak concentration, 0.25 min = 209 mg/m^3 Mean event concentration, 25 min = 141 mg/m^3

	• concentration of acetone in inflow air: 0 mg/m^3	
Face moisturizer	Concentration of acetone: 0.3% (2011 emails from the Consumer Product Safety Directorate, Health Canada, to the Existing Substances Risk Assessment Bureau, Health Canada; unreferenced). Amount used: 1.2 g (Loretz et al. 2005) Frequency: 1.8/day (Loretz et al. 2005) Body weight, 12–19 years: 59.4 kg (Health Canada 1998) Body weight, 20–59 years: 70.9 kg (Health Canada 1998) Retention factor: 1 (Health Canada 2012b) Absorbed fraction: 1 Dermal event dose = Concentration × Product amount = 0.3% × 1200 mg = 3.6 mg acetone applied per event Daily intake = Event dose × Use frequency ÷ Body weight 12–19 years: Daily intake = 3.6 mg × 1.8 times/day ÷ 59.4 kg = 0.11 mg/kg-bw per day 20–59 years: Daily intake = 3.6 mg × 1.8 times/day ÷ 70.9 kg = 0.09 mg/kg-bw per day	Calculated: Internal daily dermal dose, 12–19 years = 0.11 mg/kg-bw per day Internal daily dermal dose, 20–59 years = 0.09 mg/kg-bw per day

Face cleanser	Concentration of acetone: 10% (2011 emails from the Consumer Product Safety Directorate, Health Canada, to the Existing Substances Risk Assessment Bureau, Health Canada; unreferenced). Amount used: 2.6 g (Loretz et al. 2008) Frequency of use, 12–19 years: 0.7/day (Health Canada 2012b) Frequency of use, 20–59 years: 1.7/day (Loretz et al. 2008) Body weight, 12–19 years: 59.4 kg (Health Canada 1998) Body weight, 20–59 years: 70.9 kg (Health Canada 1998) Retention factor: 0.01 (Health Canada 2012b) Absorbed fraction: 1 Dermal event dose = Concentration × Retention factor × Product amount = 10% × 0.01 × 2600 mg = 2.6 mg acetone applied per event Dermal daily intake = Event dose × Use frequency ÷ Body weight 12–19 years: Daily intake = 2.6 mg × 0.7 times/day ÷ 59.4 kg = 0.03 mg/kg-bw per day	Calculated: Internal daily dermal dose, 12–19 years = 0.03 mg/kg-bw per day Internal daily dermal dose, 20–59 years = 0.06 mg/kg-bw per day

	20–59 years: Daily intake = 2.6 mg × 1.7 times/day ÷ 70.9 kg = 0.06 mg/kg-bw per day	

[a] Estimates of the concentrations of acetone in air using the “Well-mixed Room Model with a Constant Emission Rate” in IHMod (AIHA 2009a) were similar to those obtained using the ConsExpo (2006) exposure to vapour with a constant rate of release.

Appendix D: Summary of Animal Effects Data for Acetone

Table D1-1: Summary of data on acute effects of acetone

Route of Entry / Reference	**Species**	**Protocol**	**Results**
Inhalation / Safronov et al. 1993	Male rats, (number per group not specified)	Exposure to varying (unspecified) concentrations for 15, 30, 60, 120 or 240 min	15 min LC_{50} = 724 000 mg/m^3 4 h LC_{50} = 71 000 mg/m^3 Other LC_{50} values not available in the secondary source
Inhalation / Safronov et al. 1993	Male mice (no other details available from secondary source)	Exposure to varying (unspecified) concentrations for 15, 30, 60, 120 or 240 min	15 min LC_{50} = 604 000 mg/m^3 4 h LC_{50} = 44 000 mg/m^3 Other LC_{50} values not available in the secondary source
Oral / Kimura et al. 1971	Sprague-Dawley rats, newborn, 14 days old, younger adult and older adult (6 males each in young and older adult groups, 6–12 of both sexes in newborn and 14-day-old groups)	Single exposure via gavage to 2.2–9.1 mL/kg (1700- mg/kg-bw)	LD_{50} = 1700 mg/kg-bw (newborn) LD_{50} = 4400 mg/kg-bw (14-day-old) LD_{50} = 7100 mg/kg-bw (younger adult) LD_{50} = 6700 mg/kg-bw (older adult)
Oral / Freeman and Hayes 1985	Rats (strain and number not reported)	Exposure to varying (unspecified) doses	LD_{50} = 5800 mg/kg-bw
Oral / Tanii et al. 1986	Male ddY mice (4 animals per dose group)	Exposure to four (unspecified) doses; animals pretreated with intraperitoneal injection of olive oil 24 h prior to acetone administration	LD_{50} = 5200 mg/kg-bw

Route of Entry / Reference	**Species**	**Protocol**	**Results**
Oral / Krasavage et al. 1982	Rabbits	Detailed information not available	LD_{50} = 5300 mg/kg-bw
Dermal / Roudabush et al. 1965	Male and female White rabbits (4 animals per dose group)	Exposure to a minimum of 3 doses up to 9.4 mL/kg (7400 mg/kg-bw); other doses not specified	LD_{50} > 7400 mg/kg-bw
Dermal / Roudabush et al. 1965	Male Hartley guinea pigs, (4 animals per dose group)	Exposure to a minimum of 3 doses up to 9.4 mL/kg (7400 mg/kg-bw); other doses not specified	LD_{50} > 7400 mg/kg-bw
Dermal / Smyth et al. 1962	Rabbits	Exposure to doses up to 20 mL/kg (15 800 mg/kg-bw)	LD_{50} > 15 800 mg/kg-bw

Abbreviations: bw, body weight; ALT, alanine aminotransferase; bw, body weight; CNS, central nervous system; DNA, deoxyribonucleic acid; EC_{50}, median effective concentration; LC_{50}, median lethal concentration; LD_{50}, median lethal dose; LOAEC, lowest-observed-adverse-effect concentration; LOAEL, lowest-observed-adverse-effect level; NOAEC, no-observed-adverse-effect concentration; NOAEL, no-observed-adverse-effect level; RD_{50}, concentration estimated to result in a 50% decrease in respiratory rate; SRBC, sheep red blood cells; wt., weight

Table D1-2: Summary of data on irritation and sensitization effects of acetone

Route of Entry / Reference	**Species**	**Protocol**	**Results**
Inhalation / Kane et al. 1980	Male Swiss Webster mice (4 per group)	Exposure to unspecified concentrations for 10 min	RD_{50} = 184 136 mg/m^3 (sensory irritation)
Inhalation / De Ceaurriz et al. 1984	Male Swiss OF1 mice	Exposure to unspecified concentrations for 15 min	RD_{50} = 55 776 mg/m^3 (sensory irritation)
Inhalation / Schaper and Brost 1991	Male Swiss Webster mice (4 per group)	Exposure for 30 min once or on 5 consecutive days to 6000 ppm (14 253 mg/m^3)	No change in respiratory cycle (time of inspiration/expiration, time of pause between breaths) or thoracic volume displacement (tidal volume)
Dermal and ocular / Smyth et al.	Albino rabbits (5 per group)	Uncovered application of 0.01 mL of acetone to clipped skin	No irritation to the skin

Route of Entry / Reference	**Species**	**Protocol**	**Results**
1962			
Dermal and ocular / Carpenter and Smyth 1946; Smyth et al. 1962	Rabbits (no other details provided)	Instillation of various volumes and concentrations of acetone to the cornea	Severe burn to the cornea from 0.005 mL of acetone (grade 5 on a scale of 10 for grading degree of corneal necrosis)
Dermal and ocular / Iversen et al. 1988	CD-1 mice (no other details in secondary sources)	0.2 mL of acetone to shaved skin	Increased DNA synthesis and moderate hyperplasia after 24 h; considered signs of slight irritation
Dermal and ocular / Descotes 1988	Male and female mice, various strains	Topical application of acetone 100% on both sides of ear on days 0 and 2, and scapular subcutaneous injection of 0.05 mL acetone 100% on day 2	Mouse ear sensitization assay; no change in ear thickness
Dermal and ocular / Nakamura et al. 1994	Female albino guinea pigs, Hartley strain (2–10 per group)	Initial intradermal injection and topical application of acetone 100%, followed by intradermal injection of 0.01 mL acetone 21 days later	Guinea pig maximization test; no erythema or edema formation was observed
Dermal and ocular / Montelius et al. 1996	Mice, unspecified strain (4 per group)	Daily topical application of 25 µg of acetone or of a mix of acetone and olive oil in various proportions according to local lymph node assay protocol	Acetone induced a non-significant increase in cell proliferation; proliferative response increased only as the proportion of olive oil increased

Abbreviations: bw, body weight; ALT, alanine aminotransferase; bw, body weight; CNS, central nervous system; DNA, deoxyribonucleic acid; EC_{50}, median effective concentration; LC_{50}, median lethal concentration; LD_{50}, median lethal dose; LOAEC, lowest-observed-adverse-effect concentration; LOAEL, lowest-observed-adverse-effect level; NOAEC, no-observed-adverse-effect concentration; NOAEL, no-observed-adverse-effect level; RD_{50}, concentration estimated to result in a 50% decrease in respiratory rate; SRBC, sheep red blood cells; wt., weight

Table D1-3: Summary of data on short-term effects of acetone

Route of Entry / Reference	**Species**	**Protocol**	**Results**

Route of Entry / Reference	**Species**	**Protocol**	**Results**
Oral / NTP 1991	Male and female F344 rats (5 per sex per group)	Exposed to 0, 5000, 10 000, 20 000, 50 000, 100 000 ppm (intakes reported by authors: males: 0, 714, 1616, 2559, 4312, 6942 mg/kg-bw per day; females: 0, 751, 1485, 2328, 4350, 8560 mg/kg-bw per day) of acetone in drinking water for 14 days	No deaths occurred ≥ 2559/2328 mg/kg-bw per day: ↑ liver wt. (♂/♀), ↑ kidney wt. (♀) (non-adverse) ≥ 4312/4350 mg/kg-bw per day: ↓ bw, ↑ kidney wt. (♂/♀),↑ relative testis wt in ♂ ≥ 6942/8560 mg/kg-bw per day: bone marrow hypoplasia (♂), ↓ bw (♀) **LOAEL = 4312 mg/kg-bw per day, based on 13% decreased body weights in males relative to controls**
Oral / NTP 1991	Male and female B6C3F1mice (5 per sex per group)	Exposed to 0, 5000, 10 000, 20 000, 50 000, 100 000 ppm (intakes reported by authors: males: 0, 965, 1579, 3896, 6348, 10 314 mg/kg-bw per day; females: 0, 1569, 3023, 5481, 8804, 12 725 mg/kg-bw per day) of acetone in drinking water for 14 days	≥ 965/1569 mg/kg-bw per day: ↑ liver wt. (♂) ≥ 3896/5481 mg/kg-bw per day: ↑ centrilobular hepatocellular hypertrophy (♂), ↑ liver wt. (♀) ≥ 6348/8804 mg/kg-bw per day: ↑ kidney wt. (♂), ↑ centrilobular hepatocellular hypertrophy, ↑ kidney wt. (♀) **LOAEL = 3896 mg/kg-bw per day, based on liver hypertrophy in males**

Abbreviations: bw, body weight; ALT, alanine aminotransferase; bw, body weight; CNS, central nervous system; DNA, deoxyribonucleic acid; EC_{50}, median effective concentration; LC_{50}, median lethal concentration; LD_{50}, median lethal dose; LOAEC, lowest-observed-adverse-effect concentration; LOAEL, lowest-observed-adverse-effect level;

NOAEC, no-observed-adverse-effect concentration; NOAEL, no-observed-adverse-effect level; RD_{50}, concentration estimated to result in a 50% decrease in respiratory rate; SRBC, sheep red blood cells; wt., weight

Table D1-4: Summary of data on subchronic effects of acetone

Route of Entry / Reference	**Species**	**Protocol**	**Results**
Inhalation / Bruckner and Peterson 1981b	Male ARS/Sprague-Dawley rats (5 per group)	Exposure to 0 or 45 100 mg/m^3 (0, 19 000 ppm) for 3 h/day, 5 days/week, for 8 weeks, with additional group sacrificed after 2, 4 and 8 weeks of exposure and after 2-week recovery	No treatment-related effects on blood chemistry, enzymatic activity or histology of the heart, lung, brain and liver. Body weight gain was slightly lower throughout the experiment, but the difference was not statistically significant. Decrease in absolute brain weight at 4 and 8 weeks at 45 100 mg/m^3. Decrease in absolute kidney weight at 4 weeks at 45 100 mg/m^3, but not at 8 weeks. No statistically significant change in organ weights compared with controls after 2-week recovery.Relative organ weights were consistently higher in exposed rats (data not provided).
Inhalation / Buron et al. 2009	Female OF-1 mice (10–20 per group)	Exposure to fresh air or 4 mL for 5 h/day, 5 days/week, for 4 weeks (concentration reported by authors to rise during first 1.5 h to a constant level of 8000	Behavioural effects: Olfactory sensitivity (assessed by how the mice avoided acetone in a maze) increased (less time spent in the acetone compartment of maze) during exposure (weeks 2 and 4) through the end of the post-exposure period (weeks 6 and 8)

Route of Entry / Reference	**Species**	**Protocol**	**Results**
		ppm [19 000 mg/m^3] for the remaining 3.5 h)	Histological examination: (a) Significant decrease in number of olfactory epithelial cells at week 2, an increase at week 4 that remained at week 6 and a recovery by week 8. (b) Thickness of olfactory epithelium remained stable at weeks 0 and 2, decreased at week 4, increased at week 6 and recovered by week 8. Immunochemistry: (a) No change in olfactory marker protein (b) The number of cells positive for proliferating cell nuclear antigen decreased in the basal layer during week 2, but increased afterwards, recovering to near-baseline level by 4 weeks post-exposure. (Other subchronic inhalation study :Christoph et al. 2003; listed under neurotoxicity).
Oral / Woolhiser et al. 2003	Male CD-1 mice (8 per group)	Exposure to 0, 121, 621, 1144 mg/kg-bw per day (concentrations reported by authors: 0, 600, 3000, 6000 ppm acetone in	No deaths occurred, and no clinical signs of toxicity No changes in body weight

Route of Entry / Reference	**Species**	**Protocol**	**Results**
		drinking water) for 28 days	No treatment-related effects on hematological parameters (total and differential white blood cells, red blood cells, hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, platelets) No effects on spleen or thymus weight or on total or differential white blood cell counts No effects on SRBC antibody response **NOAEL = 1144 mg/kg-bw per day (highest dose tested)**
Oral / American Biogenics Corporation 1986	Male and female Sprague-Dawley rats (30 per sex per group) (10 for interim sacrifice and 20 evaluated at completion of the study)	Exposure to 0, 100, 500, 2500 mg/kg-bw per day by gavage in water for 90 days	No effects on survival or food consumption ≥ 500 mg/kg-bw per day: ↑ kidney wt., ↑ liver wt. (♀), ↓ body wt. (♀), accentuation of renal proximal tubule generation and intracytoplasmic hyaline droplet accumulation (♂) ≥ 2500 mg/kg-bw per day: ↑ kidney wt., ↑ liver wt., ↓ brain wt., ↑ ALT, ↑ mean corpuscular hemoglobin, mean corpuscular volume, ↓ platelets, glucose, potassium (♂); ↑

Route of Entry / Reference	**Species**	**Protocol**	**Results**
			relative heart wt. (♀), ↑ hemoglobin, hematocrit (♂/♀), accentuation of renal proximal tubule generation and intracytoplasmic hyaline droplet accumulation (♂), accentuation of renal proximal tubular degeneration (♀) **LOAEL = 2500 mg/kg-bw per day, based on significant increase in absolute kidney weights supported by histopathological findings**
Oral / NTP 1991	Male and female F344/N rats (10 per sex per group)	Exposure to 0, 2500, 5000, 10 000, 20 000, 50 000 ppm (intakes reported by authors: males: 0, 200, 400, 900, 1700, 3400 mg/kg-bw per day; females: 0, 300, 600, 1200, 1600, 3100 mg/kg-bw per day) of acetone in drinking water for 13 weeks	No effects on survival, and no clinical signs of toxicity or ophthalmic irregularities ≥ 200/300 mg/kg-bw per day: ↑ mean corpuscular hemoglobin, mean cell volume (♂) ≥ 400/600 mg/kg-bw per day: ↓ hematocrit, hemoglobin, erythrocytes, reticulocytes (♀) ≥ 900/1200 mg/kg-bw per day: ↑↓ mean corpuscular hemoglobin, mean cell volume, reticulocytes (♀) ≥ 1700/1600 mg/kg-bw per day: ↓ water consumption, ↑ severity of nephropathy, ↑↓ lymphocytes, leukocytes, hematocrit, hemoglobin,

Route of Entry / Reference	**Species**	**Protocol**	**Results**
			mean corpuscular hemoglobin, mean cell volume, erythrocytes, reticulocytes (♀), ↓ platelets (♂/♀), ↑ spleen pigmentation (♂), ↑ kidney wt. (♀), ↑ liver wt. (♂/♀) ≥ 3400/3100 mg/kg-bw per day: ↑ kidney wt., ↑ liver wt. (♂/♀), ↑ testes wt. (♂), ↑ abnormal sperm, ↓ sperm motility, epididymal wt., ↓ bw (♂), ↑↓ lymphocytes, leukocytes, mean corpuscular hemoglobin, mean cell volume, platelets (♂/♀), ↓ hemoglobin, erythrocytes, reticulocytes **LOAEL = 1700 mg/kg-bw per day, based on hematological effects in female and renal effects in male rats**
Oral / NTP 1991	B6C3F1 mice (10 per sex per group)	Exposure to 0, 1250, 2500, 5000, 10 000, 20 000 ppm (males) (intakes reported by authors: 0, 380, 611, 1353, 2258, 4858 mg/kg-bw per day) and 0, 2500, 5000, 10 000, 20 000, 50 000 ppm (females) (intakes reported by authors: 0, 892, 2007, 4156, 5945, 11 298 mg/kg-bw per	Males: No effects on survival, and no clinical signs of toxicity No significant changes in body weight or water consumption No significant changes in organ weights

Route of Entry / Reference	**Species**	**Protocol**	**Results**
		day) of acetone in drinking water for 13 weeks	≥ 892 mg/kg-bw per day: ↓ water consumption (♀) ≥ 1353 mg/kg-bw per day: ↑ hemoglobin (♂) 4858 mg/kg-bw per day: ↑ mean corpuscular hemoglobin (♂) ≥ 5945 mg/kg-bw per day: ↑ hemoglobin (♀) 11 298 mg/kg-bw per day: ↑ liver wt., ↓ spleen wt., centrilobular hepatocellular hypertrophy, ↑ hematocrit (♀) **LOAEL = 11 298 mg/kg-bw per day, based on increased absolute liver weight coupled with liver histopathology in female mice**
Oral / Ladefoged et al. 1989	Male Wistar rats (11 per group)	Exposure to 0%, 0.5% in drinking water for 6 weeks (0, 700 mg/kg-bw per day)	No effect on nerve conduction velocity at weeks 3, 4, 5 No effect on balance time on rotorod
Oral / Spencer et al. 1978	Sprague-Dawley rats (3 per group; sex not reported)	Exposure to 0%, 0.5% in drinking water (for 8 weeks; 700	No evidence of peripheral neuropathy

Route of Entry / Reference	**Species**	**Protocol**	**Results**
		mg/kg-bw per day) or 1% in drinking water (for 4 weeks; 1400 mg/kg-bw per day)	No clinical signs of toxicity
Oral / Sollman 1921	Rats (3 in total)	Exposed to 2.5% (3500 mg/kg-bw per day) acetone in drinking water for 18 weeks	Decrease in food and water consumption and body weights Histopathology was not conducted
Dermal / Rengstorff et al. 1972	Guinea pigs (8 per group)	Dermal exposure to 0 or 0.5 mL acetone 5 days/week for 8 weeks	Cataracts in 2/8 treated animals and 0/8 controls
Dermal / Rengstorff et al. 1976	New Zealand White rabbits (8 per group)	1 mL acetone on clipped back, 3 times/week, for 3 weeks; saline was used in the control group	No lens abnormalities were observed at end of exposure or after 6 months of follow-up
Dermal / Taylor et al. 1993	Albino guinea pigs, Hartley hairless (20 animals)	Topical exposure to 0.5 mL acetone for 5 days/week for 6 months	No cataracts observed

Abbreviations: bw, body weight; ALT, alanine aminotransferase; bw, body weight; CNS, central nervous system; DNA, deoxyribonucleic acid; EC_{50}, median effective concentration; LC_{50}, median lethal concentration; LD_{50}, median lethal dose; LOAEC, lowest-observed-adverse-effect concentration; LOAEL, lowest-observed-adverse-effect level; NOAEC, no-observed-adverse-effect concentration; NOAEL, no-observed-adverse-effect level; RD_{50}, concentration estimated to result in a 50% decrease in respiratory rate; SRBC, sheep red blood cells; wt., weight

Table D1-5: Summary of data on carcinogenicity and chronic effects of acetone

Route of Entry / Reference	**Species**	**Protocol**	**Results**
Inhalation	Not available	Not available	Not available
Oral	Not available	Not available	Not available

Route of Entry / Reference	**Species**	**Protocol**	**Results**
Dermal / Barr-Nea and Wolman 1972	ICR mice (sex and number per group not specified)	Dermal exposure to unspecified amounts of acetone for 5 or 7 months; untreated group included	0/9 and 2/18 animals diagnosed with amyloid deposition after 5 and 7 months of exposure, respectively, but none in unspecified number of untreated animals Significant increase in amyloid deposition in the heart, liver, kidney, skin, pancreas and adrenals in 12/23 acetone-treated animals compared with 1/18 untreated animals
Dermal / DePass et al. 1989	Male C3H/HeJ mice (40 exposed)	Dermal exposure to approximately 670 mg/kg-bw (amount reported by authors: 25 µL of a 100% solution), 3 times/week for "their complete lifespan; average daily dose of 290 mg/kg-bw per day"; no untreated group included	No skin tumours noted Subcutaneous mesenchymal neoplasms (a fibrosarcoma and a lymphosarcoma) in two animals, ulcerative dermatitis in two animals, epidermal hyperplasia and hyperkeratosis in 2/40, 2/40, 1/40 and 1/40 animals, respectively
Dermal / Ward et al. 1986	Female SENCAR mice (30 per group)	Dermal exposure to 5300 mg/kg-bw (amount reported by authors: 0.2 mL) of acetone, 2 times/week for 92 weeks; average daily dose of 1520 mg/kg-bw per	Authors reported that neoplastic and non-neoplastic lesions occurred with similar incidence, and survival was similar; therefore, results were combined for statistical analysis Only 50% survived past 96 weeks of age; causes of death included non-neoplastic and neoplastic lesions

Route of Entry / Reference	Species	Protocol	Results
		day; another group dermally exposed to 0.2 mL of formalin once, followed 4 weeks later by dermal exposure to similar dose of acetone (1520 mg/kg-bw per day) for 88 weeks; no untreated group included	Glomerulonephritis and histiocytic sarcoma reported as the two major contributing causes of death Other effects not regarded as contributors to death: neoplastic lesions—lung tumours (adenomas and adenocarcinomas) and mammary gland tumours (primarily adenocarcinomas); non-neoplastic lesions—lymphoid and epithelial hyperplasia of the thymus, myeloid metaplasia and lymphoid hyperplasia of the spleen, lymphoid hyperplasia of the lymph nodes, cytomegaly and chronic cholangitis of the liver, amyloidosis of the nasal turbinates, cystic endometrial hyperplasia

Abbreviations: bw, body weight; ALT, alanine aminotransferase; bw, body weight; CNS, central nervous system; DNA, deoxyribonucleic acid; EC_{50}, median effective concentration; LC_{50}, median lethal concentration; LD_{50}, median lethal dose; LOAEC, lowest-observed-adverse-effect concentration; LOAEL, lowest-observed-adverse-effect level; NOAEC, no-observed-adverse-effect concentration; NOAEL, no-observed-adverse-effect level; RD_{50}, concentration estimated to result in a 50% decrease in respiratory rate; SRBC, sheep red blood cells; wt., weight

Table D1-6: Summary of data on reproductive and developmental effects of acetone

Route of Entry / Reference	Species	Protocol	Results
Inhalation / Mast et al. 1988	Sprague-Dawley rats (pregnant) (26–29 per group)	Exposure to 0, 1045, 5200, 26 100 mg/m^3 acetone vapour (concentrations reported by authors: 0, 440, 2200, 11 000 ppm) for 6	No clinical signs of maternal toxicity Statistically significant decrease in extragestational weight gain, uterine weight in the 26 100 mg/m^3 group

Route of Entry / Reference	**Species**	**Protocol**	**Results**
		h/day, 7 days/week, for 14 days (days 6–19 of gestation)	Fetal weights were statistically decreased at 26 100 mg/m^3 At 26 100 mg/m^3, the percentage of litters with resorptions (77% vs. 50%) and percentage of litters with at least one malformation (11.5% vs. 3.8%) were higher than control NTP concluded that acetone had not caused a teratogenic effect in rats **LOAEC (maternal toxicity) = 26 100 mg/m^3, based on significant decreases in body weight gain and uterine weight** **LOAEC (developmental toxicity) = 26 100 mg/m^3, based on significant decrease in fetal weights, increased number of resorptions and increased malformations**
Inhalation / Mast et al. 1988	CD-1 mice (pregnant) (28–31 per group)	Exposure to 0, 1045, 5200, 15 670 mg/m^3 acetone vapour (concentrations reported by authors: 0, 440, 2200, 6600 ppm) for 6 h/day, 7 days/week, for 12 days (days 6–17 of	No clinical signs of maternal toxicity, and no significant effect on maternal body weights, absolute and relative kidney weights, or uterine weights Significant increase in absolute and relative liver weights in pregnant mice at 15 670 mg/m^3

Route of Entry / Reference	**Species**	**Protocol**	**Results**
		gestation); high exposure was initially 11 000 ppm (26 100 mg/m^3), but reduced after 1st day due to severe narcosis	Statistically significant decrease in fetal weights, increased incidence of litters with reduced sternebrae ossification, and a slight but statistically significant increase in the percentage incidence of late resorptions at 15 670 mg/m^3 **LOAEC (maternal toxicity) = 15 670 mg/m^3 based on increase in absolute and relative liver weights in pregnant mice** **LOAEC (developmental toxicity) = 15 670 mg/m^3 based on decrease in fetal weights and increase in the percentage incidence of late resorptions and retarded ossification**
Oral / Larsen et al. 1991	Male Møllegărd/ Wistar rats (10 per group)	Exposure to 0 or 800 mg/kg-bw (0% or 0.5% in drinking water) for 6 weeks, and then mated with untreated females; other groups were exposed for 6 weeks, held for 10 weeks exposure-free, and then mated to untreated females	No changes were observed in reproductive parameters or testicular measurements (number of matings, pregnancies, fetuses, testicular weight and testicular histopathology)
Oral / Dalgaard et al. 2000	Male Wistar rats (10 per group)	0 or 700 mg/kg-bw per day (0% or 0.5% acetone in drinking water) for 9 weeks; or 0 or	No effect on body weight, male fertility, reproductive organ weights or testes histopathology

Route of Entry / Reference	Species	Protocol	Results
		1400 mg/kg-bw per day (0% or 1% acetone in drinking water) for 4 weeks; and then mated with untreated females	Acetone-exposed rats had reduced forelimb and hindlimb grip strength and blood glucose levels (Other reproductive toxicity studies: American Biogenics Corporation 1986, NTP 1991; listed under short-term and subchronic toxicity studies)

Abbreviations: bw, body weight; ALT, alanine aminotransferase; bw, body weight; CNS, central nervous system; DNA, deoxyribonucleic acid; EC_{50}, median effective concentration; LC_{50}, median lethal concentration; LD_{50}, median lethal dose; LOAEC, lowest-observed-adverse-effect concentration; LOAEL, lowest-observed-adverse-effect level; NOAEC, no-observed-adverse-effect concentration; NOAEL, no-observed-adverse-effect level; RD_{50}, concentration estimated to result in a 50% decrease in respiratory rate; SRBC, sheep red blood cells; wt., weight

Table D1-7: Summary of data on immunological effects of acetone

Route of Entry / Referenc e	**Species**	**Protocol**	**Results**
Oral	See subchronic section	See subchronic section	See subchronic section
Dermal / Singh et al. 1996	Female SSIN mice (6 per group)	Dermal exposure to 0; 187 or 380; 375 or 750; 750 or 1500; 1125 or 2250 mg/kg-bw per day—reflecting dosing once or twice a week (concentrations reported by authors: 0, 50, 100, 200 or 300 µL) acetone once or twice weekly for 2 or 4 weeks	No changes in relative percentages of B cells, T cells or ratio of CD4+ to CD8+ T cells Statistically significant suppression of SRBC antibody response at 2250 mg/kg-bw per day; responses at other doses were reported

Route of Entry / Reference	**Species**	**Protocol**	**Results**
			to be schedule dependent Changes in plaque numbers in SRBC assay not accompanied by changes in splenic cellularity No effect on the mixed lymphocyte response

Abbreviations: bw, body weight; ALT, alanine aminotransferase; bw, body weight; CNS, central nervous system; DNA, deoxyribonucleic acid; EC_{50}, median effective concentration; LC_{50}, median lethal concentration; LD_{50}, median lethal dose; LOAEC, lowest-observed-adverse-effect concentration; LOAEL, lowest-observed-adverse-effect level; NOAEC, no-observed-adverse-effect concentration; NOAEL, no-observed-adverse-effect level; RD_{50}, concentration estimated to result in a 50% decrease in respiratory rate; SRBC, sheep red blood cells; wt., weight

Table D1-8: Summary of data on neurological effects of acetone

Route of Entry / Reference	**Species**	**Protocol**	**Results**
Inhalation / Goldberg et al. 1964	Female CFE rats (8–10 per group)	Exposure to 0, 3000, 6000, 12 000 or 16 000 ppm (calculated for this report to be 0, 7120, 14 240, 28 480 and 37 975 mg/m^3) for 4 h/day, 5 days/week, for 10 total exposures	No effect on growth rate Concentration-dependent increase in inhibition of avoidance response: 0%, 38%, 50% and 62% at 7120, 14 240, 28 480 and 37 975 mg/m^3, respectively, after single exposure; this incidence decreased with repeated exposure Ataxia at exposure to 28 480 or 37 975 mg/m^3 after single

Route of Entry / Reference	**Species**	**Protocol**	**Results**
			exposure **LOAEC = 14 240 mg/m^3, based on increase in inhibition of avoidance response**
Inhalation / Christoph et al. 2003	Male Crl:CD BR rats (10 per group)	Exposure to 0, 1000, 2000 or 4000 ppm acetone (0, 2400, 4800 or 9500 mg/m^3) for 6 h/day, 5 days/week, for 13 weeks; exposures preceded by 9 weeks of operant training	No clinical signs at end of exposure or effect on response to auditory alerting stimulus, fixed ratio response rate, fixed interval response rate or fixed interval index of curvature **NOAEC = 9500 mg/m^3 (highest concentration tested)**
Inhalation / De Ceaurriz et al. 1984	Male Swiss OF1 mice (10 per group)	Exposure to 4827, 6129, 6789, 7176 mg/m^3 (concentrations reported by authors: 2032, 2580, 2858 or 3021 ppm) for 4 h	Statistically significant decreases in mobility time at 6129 mg/m^3 and above, but not at 4827 mg/m^3, in the behavioural despair swimming test **ID_{50} (concentration estimated to cause a 50% decrease in the duration of immobility) = 6650 mg/m^3** **LOAEC = 6129 mg/m^3 for 4 h**
Inhalation / Bruckner and Peterson 1981a	Male ARS/Sprague-Dawley rats (5 per group)	Exposure to 29 900, 45 100, 60 100, 120 200 mg/m^3 (concentrations reported by authors: 0, 12 500, 19 000,	Concentration-related increase in depth of CNS depression and increase in rate of depression, based on five tests of unconditioned performance and reflexes (wire manoeuvre, visual

Route of Entry / Reference	**Species**	**Protocol**	**Results**
		25 300 or 50 600 ppm) for up to 3 h; the methods section noted control groups, but no data on the controls were reported	placing, grip strength, tail pinch, righting reflex) 120 200 mg/m^3 was lethal within 2 h **LOAEC = 45 100 mg/m^3 for 1 h**
Inhalation / Glowa and Dews 1987	Mice (strain and number not available in secondary sources)	Exposure to six nominal concentrations ranging from 240 to 133 000 mg/m^3 (concentrations reported by secondary sources: 100–56 000 ppm) for 1 day	No effect on the correct response rate at acetone concentrations < 2380 mg/m^3; the highest concentration tested (133 000 mg/m^3) completely eliminated the response **EC_{50} = 25 000 mg/m^3 for acetone-induced changes in schedule-controlled operant behavior (Morgott 2001)** **NOAEC = 2380 mg/m^3, with a LOAEC of 7130 mg/m^3, based on a 10% decreased response to food presentation in a fixed interval operant behavioural test (ATSDR 1994)**
Inhalation / Geller et al. 1979a	Male juvenile baboon (*n* = 4)	Exposed continuously to 500 ppm (1206 mg/m^3) for 7 days	Neurobehavioural effect (increased response time on match-to-sample operant behavioural test) in all four animals, and possible increased alerting response in two of four animals

Route of Entry / Reference	**Species**	**Protocol**	**Results**
Inhalation / Mashbitz et al. 1936	White mice (sex and number per exposure group not reported)	Exposure to 40 000, 60 000, 80 000, 100 000, 120 000, 133 000 or 200 000 mg/m^3 acetone for durations up to 4 h	Time to narcosis at 40 000, 60 000, 80 000, 100 000, 120 000, 133 000 and 200 000 mg/m^3 was 158, 92, 59, 38, 33, 38 and 34 min, respectively At ≥ 100 000 mg/m^3, drowsiness preceded period of excitement, with impaired coordination at 25–28 min, followed by deep narcosis at 33–38 min. Effects were accompanied by frequent rhythmical clonic movement of the hind legs and abdominal muscles. A similar pattern of effects was seen at lower concentrations, with a longer time to effect. Mice remained in deep narcosis for 38–100 min post-exposure.
Inhalation / Haggard et al. 1944	Rats (no strain or sex reported)	Exposure to 5000, 10 000, 25 000, 50 000, 100 000, 200 000 or 300 000 mg/m^3 acetone for 45 min to 8 h	No intoxication (slight incoordination) ≤ 10 000 mg/m^3 for durations up to 8 h, but intoxication observed at 25 000, 50 000, 100 000, 200 000 and 300 000 mg/m^3 at durations of 100–250, 40–80, 15–35, 10–15 and 5–7 min of exposure, respectively No loss of righting reflex at ≤ 10 000 mg/m^3 for up to 8 h or at 25 000 mg/m^3 for up to 6 h, but loss observed at 50 000, 100 000, 200 000 and 300 000

Route of Entry / Reference	**Species**	**Protocol**	**Results**
			mg/m^3 at durations of 130–160, 50–57, 22–25 and 10–15 min of exposure, respectively No loss of corneal reflex at ≤ 10 000 mg/m^3 for up to 8 h or at 25 000 and 50 000 mg/m^3 for up to 6 h, but was observed at 100 000, 200 000 and 300 000 mg/m^3 at durations of 105–155, 45–50 and 22–25 min of exposure, respectively Slight incoordination at blood concentrations of approximately 1000–2000 mg/L, loss of righting reflex at about 3000 mg/L, loss of corneal reflex at 5000 mg/L and respiratory failure at 9100–9300 mg/L
Oral / Ladefoged et al. 1989	Male Wistar rats (11 per group)	Exposure to 0%, 0.5% acetone (0, 700 mg/kg-bw per day) in drinking water for 6 weeks	No effect on nerve conduction velocity at weeks 3, 4, 5 No effect on balance time on rotarod

Abbreviations: bw, body weight; ALT, alanine aminotransferase; bw, body weight; CNS, central nervous system; DNA, deoxyribonucleic acid; EC_{50}, median effective concentration; LC_{50}, median lethal concentration; LD_{50}, median lethal dose; LOAEC, lowest-observed-adverse-effect concentration; LOAEL, lowest-observed-adverse-effect level; NOAEC, no-observed-adverse-effect concentration; NOAEL, no-observed-adverse-effect level; RD_{50}, concentration estimated to result in a 50% decrease in respiratory rate; SRBC, sheep red blood cells; wt., weight

Table D2-1: *in vitro* genotoxicity studies with acetone for Prokaryotic organisms

Assay	Indicator system	Highest concentration tested	Metabolic activation	Results (with/ without S9)	Reference

Assay	Indicator system	Highest concentration tested	Metabolic activation	Results (with/ without S9)	Reference
Reverse mutation (Ames assay)	*S. typhimurium* TA98, TA100, TA1535 & TA1537	10 mg/plate	Rat & hamster liver S9	−/−	Zeiger et al. 1992
Reverse mutation (Ames assay)	*S. typhimurium* TA98, TA100, TA1535, TA1537 & TA1538	73 mg/plate	None	NA/−	De Flora et al. 1984
Reverse mutation (Ames assay)	*S. typhimurium* TA92, TA94, TA98, TA100, TA1535 & TA1537	10 mg/plate	Rat liver S9	−/NA	Ishidate et al. 1984
Lambda prophage WP2s(λ) induction (Microscreen assay)	*Escherichia coli* TH-008	10% (v/v)	Rat liver S9	−/−	DeMarini et al. 1991
Lambda prophage WP2s(λ) induction (Microscreen assay)	*E. coli* SR714	10% (v/v)	Rat liver S9	−/−	Rossman et al. 1991
β-Galactosidase activation (SOS chromotest)	*E. coli* PQ37	100 mM	Rat liver S9	−/−	Von der Hude et al. 1988
Colitis phage DNA transfection assay	*E. coli* CR63	0.1 mL	Rat liver S9	−/NA	Vasavada and Padayatty 1981
DNA binding assay	*E. coli* Q13	0.05% (v/v)	Rat liver S9	−/−	Kubinski et al. 1981
Recombination assay	*Bacillus subtilis* H-17 & M-45	10 mg/well	Rat liver S9	−/−	McCarroll et al. 1981
β-Galactosidase activation (SOS chromotest)	*S. typhimurium* TA1535/pSK1002	33 mg/mL	Rat liver S9	−/−	Nakamura et al. 1987

Abbreviations: +, positive, −, negative; ±, equivocal; DNA, deoxyribonucleic acid; NA, not applicable; S9/10, 9000/10 000 × *g* supernatant from rodent liver homogenate; SCE, sister chromatid exchange; v/v, volume per volume
Source: Adapted from Morgott (2001)

Table D2-2: *in vitro* genotoxicity studies with acetone for Eukaryotic organisms

Assay	Indicator system	Highest concentration tested	Metabolic activation	Results (with/without S9)	Reference
Chromosomal malsegregation	*Saccharomyces cerevisiae* D61.M	7.8% (v/v)	None	NA/+	Zimmermann et al. 1985
Point mutation and mitotic recombination	*S. cerevisiae* D61.M	7.8% (v/v)	None	NA/−	Zimmermann et al. 1985
Chromosomal malsegregation	*S. cerevisiae* D61.M	50 mg/mL	None	NA/±	Whittaker et al. 1989
Chromosomal malsegregation	*S. cerevisiae* D61.M	8% (v/v)	None	NA/±	Albertini 1991
Reverse mutation	*S. cerevisiae* D7	10% (v/v)	None	NA/±	Yadav et al. 1982
Forward mutation	*Schizosaccharomyces pombe* P1	3.7% (v/v)	Mouse liver S10	−/NA	Abbondandolo et al. 1980
Forward mutation	*S. cerevisiae* D4	5% (v/v)	Rat liver S9	−/NA	Barale et al. 1983
Cell transformation assay	Syrian hamster embryo cells	135 µg/m^3	None	NA/−	Hatch et al. 1983
Cell transformation assay	Syrian hamster embryo cells	8% (v/v)	None	NA/−	Pienta 1980
Cell transformation assay	Rat embryo cells	100 µg/mL	None	NA/−	Freeman et al. 1973
Cell transformation assay	Rat embryo cells	0.1% (v/v)	Rat liver S9	−/−	Mishra et al. 1978
Transformation assay	Asynchronous mouse embryo fibroblasts	0.5% (v/v)	None	NA/−	Peterson et al. 1981
Cell transformation assay	Mouse embryo fibroblasts	0.5% (v/v)	None	NA/−	Lillehaug and Djurhuus 1982
Cell transformation assay	Mouse prostate fibroblasts	0.5% (v/v)	None	NA/−	Gehly and Heidelbe

Assay	Indicator system	Highest concentration tested	Metabolic activation	Results (with/without S9)	Reference
					rger 1982
SCE	Chinese hamster lung fibroblasts	100 mM	Rat liver S9	−/−	von der Hude et al. 1987
Chromosomal aberration	Chinese hamster fibroblasts	5% (v/v)	None	NA/+	Ishidate et al. 1984
SCE	Chinese hamster lung fibroblasts	8.6 mM	None	NA/−	Latt et al. 1981
Chromosomal aberration & SCE	Chinese hamster ovary cells	1 mg/mL	Rat liver S9	−/−	Tates and Kriek 1981
Chromosomal aberration & SCE	Chinese hamster ovary cells	5 mg/mL	Rat liver S9	−/−	Loveday et al. 1990
Chromosomal aberration & SCE	Human lymphocytes[b]	20.9 mM	None	NA/−	Norppa et al. 1981
Mouse lymphoma mutation assay	L5178Y mouse lymphoma cells	470 mM	None	NA/−	Amacher et al. 1980
Mouse lymphoma mutation assay	L5178Y mouse lymphoma cells	1% (v/v)	Rat liver S9	−/NA	McGregor et al. 1988
Mouse lymphoma mutation assay	S49 mouse lymphoma cells	140 mM	Rat lvi	−/NA	Friedrich and Nass 1983
Reverse mutation ouabain resistance	Chinese hamster lung fibroblasts	0.2% (v/v)	None	NA/−	Lankas 1979
Forward mutation thioguanine resistance	Chinese hamster lung fibroblasts	0.5% (v/v)	Rat liver S9	−/NA[a]	Cheng et al. 1981
Micronucleus test	Human lymphocytes[b]	5 mM	Rat liver S9	−	Zarani et al. 1999
Unscheduled DNA synthesis	Bovine lymphocytes	0.4 mg/mL	None	−	Targowski and

Assay	Indicator system	Highest concentration tested	Metabolic activation	Results (with/without S9)	Reference
					Klucinski 1983
Unscheduled DNA synthesis	Human skin cells[b]	10% (v/v)	None	−	Lake et al. 1978
Metabolic cooperation assay	Chinese hamster lung fibroblasts	5% (v/v)	None	+	Chen et al. 1984
Alkaline elution assay	Rat hepatocytes	1% (v/v)	None	−	Sina et al. 1983
Two-stage cell transformation assay	Mouse 3T3 cells	0.5% (v/v)	None	−	Sakai and Sato 1989

Abbreviations: +, positive, −, negative; ±, equivocal; DNA, deoxyribonucleic acid; NA, not applicable; S9/10, 9000/10 000 × *g* supernatant from rodent liver homogenate; SCE, sister chromatid exchange; v/v, volume per volume
[a] The secondary source reported the results as NA/−, but this is not consistent with the inclusion of rat liver S9 and so presumably was a typographical error.
[b] Included in Table E2 for consistency, even though not an animal test system.
Source: Adapted from Morgott (2001)

Table D2-3: *in vivo* genotoxicity studies with acetone for Eukaryotic organisms

Assay	Indicator system	Highest concentration tested	Metabolic activation	Results (with/without S9)	Reference
Micronucleus test	Chinese hamster bone marrow cells	865 mg/kg-bw	NA	−	Basler 1986
Micronucleus test	Mouse bone marrow	5000–20 000 ppm in drinking water (1000–4000 mg/kg-bw per day)[a] for 13 weeks	NA	−	Unpublished study cited in NTP 1991
Host-mediated assay	Hamster fetal cells	2300 mg/kg-bw	NA	−	Quarles et al. 1979

Abbreviations: +, positive, −, negative; NA, not applicable; S9/10, 9000/10 000 × *g* supernatant from rodent liver homogenate
[a] Intakes were calculated according to reference values in Health Canada (1994).
Source: Adapted from Morgott (2001)

Appendix E: Summary of Human Effects Data for Acetone

Table E1-1: Summary of volunteer exposure

Subjects	Protocol	Results	Reference
31 acetone-exposed workers from a cellulose acetate production facility employed for 1.5–33 years and age- and sex-matched controls unexposed to acetone except for infrequent nail polish remover use	Volunteers were presented with pairs of bottles with a blank solution or various dilutions of acetone, inserted the nose-piece in each nostril, sniffed and tried to identify the bottle containing acetone	Olfactory threshold was 855 ppm (2031 mg/m^3) in exposed workers and 41 ppm (97 mg/m^3) in unexposed controls Lateralization threshold (to indicate sensory irritation) was 36 669 ppm (87 106 mg/m^3) in exposed workers and 15 758 ppm (37 433 mg/m^3) in unexposed controls	Wysocki et al. 1997
8 subjects (4 anosmics, 4 normosmics)	Volunteers were presented with pairs of bottles with a pop-up spout and squeezed the bottle to sniff varying dilutions of acetone or a blank into one nostril	Odour threshold in normosmics was approximately 10 000 ppm (23 755 mg/m^3). Nasal pungency threshold was 100 000 ppm (237 500 mg/m^3) in anosmics.	Cometto-Muñiz and Cain 1993
25 males	Exposed to acetone vapour 240, 590, 1190 and 2400 mg/m^3 (concentrations reported by authors: 100, 250, 500 and 1000 ppm) for 3 h in morning and 3 h in afternoon for 1 day or exposed to 590 or 1190 mg/m^3 (250 or 500 ppm) for 6 h/day (with 45 min break) for 6 days	≥ 240 mg/m^3: very mild nose, eye and throat irritation after 1 day of exposure; effects were inconsistent among exposed subjects ≥ 1190 mg/m^3: irritating to nose, eyes, throat and trachea; very slight irritation at lower concentrations; statistically significant increase in white blood cell counts and decrease in	Matsushita et al. 1969a, b

Subjects	Protocol	Results	Reference
		phagocytic activity of neutrophils at 1190 mg/m^3 after single day exposure of 6 h (2×3h in same day) or repeated 6 h exposure for 6 days, possibly reflecting inflammatory response 1190 mg/m^3 was considered the most appropriate LOEC	
Average of 10 people per group of both sexes	Exposed to acetone vapour 475, 713 and 1190 mg/m^3 (concentrations reported by authors: 200, 300 or 500 ppm) for 3–5 min	Symptoms of eye and throat irritation were reported by the volunteers at concentrations ≥ 713 mg/m^3	Nelson et al. 1943
10 males	Exposed to acetone vapour 551 mg/m^3 (concentration reported by authors: 231 ppm) for 2 h	No subjective symptoms of eye, nose, throat or airway irritation and no subjective CNS effects, based on ratings on an analogue scale; acetone smell was detected	Ernstgård et al. 1999
9 males	Exposed to acetone vapour 240 and 1190 mg/m^3 (concentrations reported by authors: 100 and 500 ppm) for 2 or 4 h	No effect on clinical chemistry or hematology; no subjective symptoms	DiVincenzo et al. 1973
Males or females (2–4 per group)	Exposure to 0, 475, 2370 and 2970 mg/m^3 (concentrations reported by authors: 0, 200, 1000 and 1250 ppm) for 3 or 7.5	No significant neurological abnormalities Visual evoked response changes at 2970 mg/m^3 following repeated	Stewart et al. 1975

Subjects	Protocol	Results	Reference
	h/day for up to 4 days	exposures Premature menstruation in 3 of 4 women at 2370 mg/m^3 for 7.5 h/day for 4 days (early by 1 week or more), but not at same concentration for 3 h/day for 4 days Pulmonary function testing showed no abnormalities at any concentration No effect on complete blood count or clinical chemistry Eye and throat irritation was present at all concentrations, but complaints were inconsistent from one week to the other; however, throat irritation at an incidence greater than controls was reported in subjects exposed to 2370 mg/m^3 for 3 or 7.5 h	
32 subjects, sex not specified	Exposure to 2375 mg/m^3 (concentration reported by author: 1000 ppm) for 4 or 8 h	Throat irritation at both durations No increased reporting of subjective symptoms of tiredness, tension, complaints or annoyance	Seeber et al. 1992

Subjects	Protocol	Results	Reference
11 male and 11 female volunteers	Exposure to 600 mg/m^3 (concentration reported by authors: 250 ppm) for 4 h	Increase in response time and percentage of incorrect responses in dual auditory tone discrimination compensatory tracking test Profile of Mood States test showed increase in anger-hostility score in males	Dick et al. 1989

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CI, confidence interval; CNS, central nervous system; ECG, electrocardiogram; LOEC, lowest-observed-effect concentration; NOEC, no-observed-effect concentration; TWA, time-weighted average

Table E1-2. Epidemiological studies

Subjects	Protocol	Results	Reference
776 female university employees in laboratory work	Exposure was evaluated through a questionnaire on type of work and substances handled, but was not quantified. Pregnancies and outcome of pregnancies were investigated through questionnaire, and information was verified in medical records.	Overall miscarriage rate was 11.1%. When divided by main occupation during pregnancy, miscarriage rates were 9.9%, 7.7% and 7.2% for laboratory work, laboratory study and work at home, respectively. Outcome of pregnancy related to solvent exposure in the first trimester indicates that miscarriage was higher among women not engaged in laboratory work (11.5%) compared with those working with solvent (10.6%). No dose–response trend was observed when comparing frequency of work with solvent with	Axelsson et al. 1984

Subjects	Protocol	Results	Reference
		frequency of miscarriage. No effects of solvent exposure were apparent on incidence of malformation. Birth weight was not correlated with exposure to solvent. Miscarriage rate was 12.5% among women exposed to acetone during the first trimester.	
Retrospective case–referent study of female laboratory workers Spontaneous abortion study included 535 women (206 cases and 329 referents) Malformation study included 141 women (36 cases and 105 referents)	Solvent use was self- reported, with frequency of use per week specified on an individual chemical basis. An exposure index was calculated for each individual.	Odds ratio of spontaneous abortion for acetone was 1.2 (95% CI 0.7–1.8) in women exposed 1–2 days/week and 1.3 (95% CI 0.7–2.4) in women exposed 3–5 days/week. Odd ratios for congenital malformations were not increased for any type of chemical exposure. Acetone was not assessed individually. Birth weight was negatively associated with mothers employed in a laboratory (133 g decrease). Acetone was not assessed individually.	Taskinen et al. 1994

Subjects	Protocol	Results	Reference
Birth weight analysis included 500 referent women			
25 males working in reinforced plastic production plant matched to male patients from a fertility clinic	Average breathing zone acetone concentrations in workers were 224, 385 and 164 mg/m^3 for 10, 15 and 28 weeks, respectively, before semen collection. Semen was collected within 3 weeks of closure of the plant. Workers were also exposed to high concentrations (294–552 mg/m^3) of styrene.	No effects on serum concentration of follicle stimulating and luteinizing hormones or on sperm concentration. Increased live sperm (80% vs. 68% in controls). Decreased percentage of immobile sperm (30% vs. 40% in controls). Decreased percentage of normal sperm morphology (47% vs. 60% in controls).	Jelnes 1988
Cross-sectional study 110 exposed males (ages 18.7–56.8 years, mean 37.6 years) 67 unexposed males (ages 20.7 –57.5 years, mean 41.9 years)	Exposure to concentrations ranging from 5 to 1212 ppm (12–2888 mg/m^3); mean TWA exposure over the course of the workday was 361 ppm (858 mg/m^3)	Exposure-related increase in 1) eye irritation, tearing and acetone odour at the end of the workshift and 2) heavy, vague or faint feeling in the head, nausea and loss of weight. No changes in hematological parameters, serum biochemistry or phagocytic activity of peripheral neutrophils. No changes in Manifest	Satoh et al. 1996

Subjects	Protocol	Results	Reference
		Anxiety Scale scores, Self-rating Depression Scale scores or R-R interval variation on ECG	
Retrospective mortality study of 948 subjects; additional evaluation on 341 subjects: 188 men, 153 women	TWA acetone concentration was 1000 ppm (2400 mg/m^3) 13.9% of the employees employed for less than 1 year and 55.1% employed for more than 5 years in a cellulose fibre plant; acetone used as only solvent	Mortality study found no significant excess risk of death from any cause compared with the general population in the USA All hematological and clinical blood chemistry parameters were within normal limits Study did not include control group. Study conducted to use the acetone-exposed group as reference group to examine the hematopoietic effect of methylene chloride during co-exposure of methylene chloride, acetone and methanol.	Ott et al. 1983a, b, c
120 volunteers (30 per exposed group, 60 controls)	Exposure to TWA acetone concentrations ranging from 948 to 1048 ppm in high-exposure group and from 549 to 653 ppm in low-exposure group (2300–2500 mg/m^3 and 1300–1600 mg/m^3, respectively). Exposed volunteers employed for at least 5 years at an	Reported average urinary acetone levels were 93 mg/L and 62 mg/L for high- and low-exposure groups, respectively. No statistically significant differences in hematological and clinical parameters noted, after adjusting for confounding factors such as smoking, alcohol consumption, age and past medical histories (liver and	Grampella et al. (1987)

Subjects	Protocol	Results	Reference
	acetate fibre manufacturing plant. Controls were never exposed to acetone.	kidney damage).	
157 (71 occupationally exposed workers, 86 matched controls)	Exposure to TWA acetone concentrations of 988–2114 mg/m^3 over an 8 h shift. Workers employed for an average length of 14 years.	Compared with controls, increased prevalence of neurotoxic syndrome (mood disorders, irritability, memory difficulties, sleep disturbances, headache, and numbness in hands and feet) and irritation syndrome (upper respiratory tract irritation), and significant differences in motor nerve conduction velocity in median, ulna and peroneal nerves Questions have been raised about the study methods (Graham 2000)	Mitran et al. 1997
800 workers	Exposure to acetone concentrations ranging from 1425 to 5100 mg/m^3. Length of exposure not reported.	Sensory irritation and systemic toxicity (hematology and urinalysis) evaluated No systemic toxicity or adverse health effects noted NOEC for human sensory irritation was 3560 mg/m^3	Oglesby et al. 1949
410 volunteers (150 occupationally exposed employees, 260 non-exposed	Exposure to an average 8 h TWA concentration of 900 ppm (2140 mg/m^3). Length of exposure not	ALT, AST, total bilirubin and hematocrit were not significantly different between exposed and control groups	Soden 1993

Subjects	Protocol	Results	Reference
controls)	reported.	No difference in response rates for symptoms such as loss of memory, headache or dizziness between the exposed and control groups	
9 workers	Exposure for the 1st and 2nd years of study to short-term (about 2–3 h) acetone concentrations of 2300 ppm (5500 mg/m^3) and 300 ppm (710 mg/m^3) in the breathing zone at two different work stations. Acetone concentration in the general air was 110 ppm (260 mg/m^3).	Exposure caused transient and intermittent eye, throat and nasal irritation, headaches and lightheadedness in individuals only when concentration exceeded 1000 ppm (2400 mg/m^3) CNS effects attributable to acetone exposure not observed	Raleigh and McGee 1972

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CI, confidence interval; CNS, central nervous system; ECG, electrocardiogram; LOEC, lowest-observed-effect concentration; NOEC, no-observed-effect concentration; TWA, time-weighted average