Screening Assessment for the Challenge

Methane, nitro- (Nitromethane)

Chemical Abstracts Service Registry Number 75-52-5

Environment Canada
Health 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 on methane, nitro- (nitromethane), Chemical Abstracts Service Registry Number 75-52-5. This substance was identified in the categorization of the *Domestic Substances List* as a high priority for action under the Challenge. Nitromethane was identified as a high priority because it was considered to pose intermediate potential for exposure of individuals in Canada and had been classified on the basis of carcinogenicity. Although nitromethane met the ecological categorization criteria for persistence, it did not meet the criteria for bioaccumulation potential or inherent toxicity to aquatic organisms. Therefore, the focus of this assessment of nitromethane relates primarily to human health risks.

In response to a notice issued under section 71 of the *Canadian Environmental Protection Act, 1999* (CEPA 1999), nitromethane was not reported to be manufactured at a quantity above the reporting threshold of 100 kg in 2006. Importation activities (whether alone, in a mixture, in a product or in manufactured items) were reported to be in the range of 100–1000 kg in 2006. Nitromethane's principal uses that have been identified as potentially ongoing in Canada as of the 2006 reporting year were use as a non-traditional fuel additive for drag racing cars and model engines, laboratory and industrial solvent, chemical intermediate in the synthesis of biocides, chemicals, agricultural products and other intermediates, stabilizer in degreaser, carrier solvent for opaquing porcelain for dental manufacturing applications, adhesive remover, dry cleaning solvent stabilizer, and formulant in flux remover, magnetic tape head cleaner and multi-purpose lubricant.

Population exposure to nitromethane through environmental media is expected to be low, based on the data identified and negligible environmental releases of nitromethane in Canada during the 2006 calendar year as reported in responses to a notice issued under section 71 of CEPA 1999. Emissions of nitromethane in the ambient environment are expected to be primarily from anthropogenic sources. Inhalation constitutes the principal route of environmental exposure. Although there are only very limited consumer products available containing nitromethane, subpopulation exposure is anticipated through off-gassing from some products (i.e., instant adhesive remover, false nail remover and eyelash adhesive remover). Potential exposure was estimated for false nail remover using available data and represents an upper-bound exposure potential from consumer products.

As nitromethane was classified on the basis of carcinogenicity by other national and international agencies, carcinogenicity was a key focus for this screening assessment. Following exposure to nitromethane via inhalation, tumours were observed at multiple organ sites in mice and at one site in female rats. Nitromethane is not genotoxic in *in vitro* or *in vivo* assays. Although the mode of action for carcinogenicity has not been elucidated, the tumours observed are not considered to have resulted from direct interaction with genetic material. Therefore, a threshold approach is used to characterize risk to human health. Other adverse health effects observed in experimental animals

include reproductive toxicity, hyaline droplet formation in the respiratory epithelium and neurotoxicity.

The margins between a conservative upper-bounding estimate of exposure to nitromethane from air and the levels associated with effects in experimental animals are considered to be adequately protective. The margins between a conservative upper-bounding estimate of exposure from false nail remover and levels associated with effects in experimental animals and humans are considered to be adequately protective.

On the basis of the adequacy of the margins between exposure to nitromethane in ambient air or consumer products and critical effect levels in experimental animals and humans, it is concluded that nitromethane 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.

Nitromethane does not meet the criteria for persistence or bioaccumulation as set out in the *Persistence and Bioaccumulation Regulations*. Furthermore, it is expected to have a low potential for toxicity to aquatic organisms. Based on this information and the expected low environmental concentrations, it is concluded that nitromethane 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.

Based on the information available, it is concluded that nitromethane does not meet the criteria set out in section 64 of CEPA 1999.

This substance will be considered for inclusion in the *Domestic Substances List* inventory update initiative. In addition and where relevant, research and monitoring will support verification of assumptions used during the screening assessment.

Introduction

The *Canadian Environmental Protection Act, 1999* (CEPA 1999) (Canada 1999) requires the Minister of the Environment and the Minister of Health to conduct screening assessments of substances that have met the categorization criteria set out in the Act to determine whether these substances present or may present a risk to the environment or to human health.

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

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

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

The substance methane, nitro- (nitromethane) was identified as a high priority for assessment of human health risk because it was considered to present IPE and had been classified by other agencies on the basis of carcinogenicity. The Challenge for this substance was published in the *Canada Gazette* on January 31, 2009 (Canada 2009). A substance profile was released at the same time. The substance profile presented the technical information available prior to December 2005 that formed the basis for categorization of this substance. As a result of the Challenge, submissions of information pertaining to the substance were received.

Although nitromethane met the ecological categorization criteria for persistence, it did not meet the criteria for bioaccumulation potential or inherent toxicity to aquatic organisms. Therefore, this assessment focuses principally on information relevant to the evaluation of risks to human health.

Screening assessments focus on information critical to determining whether a substance meets the criteria 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, hazards, uses and exposure, including the additional information submitted under the Challenge. Data relevant to the screening assessment of this substance were identified in original literature, review documents, stakeholder research reports and from literature searches up to August 2009 for human health components and May 2010 for ecological components. Key studies were critically evaluated; modelling results may have been used to reach conclusions. Evaluation of risk to human health involves consideration of data relevant to estimation of exposure (non-occupational) of the general population, as well as information on health hazards (based principally on the weight of evidence assessments of other agencies that were used for prioritization of the substance). Decisions for human health are based on the nature of the critical effect and/or margins between conservative effect levels and estimates of exposure, taking into account confidence in the completeness of the identified databases on both exposure and effects, within a screening context. The screening assessment does not represent an exhaustive or critical review of all available data. Rather, it presents a summary of the critical information upon which the conclusion is based.

This screening assessment was prepared by staff in the Existing Substances Programs at Health Canada and Environment Canada and incorporates input from other programs within these departments. Both the human health and ecological portions of this assessment have undergone external written peer review/consultation. Comments on the technical portions relevant to human health were received from Dr. Mike Dourson (Toxicology Excellence for Risk Assessment), Dr. Michael Jayjock (The LifeLine Group) and Dr. Bob Benson (US Environmental Protection Agency). Additionally, the draft of this screening assessment was subject to a 60-day public comment period. While external comments were taken into consideration, the final content and outcome of the screening risk assessment remain the responsibility of Health Canada and Environment Canada. Approaches used in the screening assessments under the Challenge have been reviewed by an independent Challenge Advisory Panel.

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

[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 on the substances in the Chemicals Management Plan (CMP) Challenge Batches 1-12 is not relevant to, nor does it preclude, an assessment against the hazard criteria specified in the Controlled Products Regulations, which is part of regulatory framework for the Workplace Hazardous Materials Information System [WHMIS] for products intended for workplace us

Substance Identity

For the purposes of this document, this substance will be referred to as nitromethane, a common name for this substance. Information on the identity of nitromethane is summarized in Table 1.

Table 1. Substance identity

CAS RN	75-52-5
DSL name	Methane, nitro-
NCI names	Methane, nitro- (AICS, ASIA-PAC, DSL, PICCS, SWISS, TSCA) Nitromethane (English, French) (DSL, ECL, EINECS, ENCS, PICCS) Nitromethane, inhibited (PICCS)
Other names	Nitrocarbol NSC 428 UN 1261 UN 1261 (DOT)
Chemical group (DSL stream)	Discrete organics
Major chemical class or use	Low molecular weight hydrocarbons
Major chemical subclass	Nitro compounds
Chemical formula	CH_3NO_2
Chemical structure	
SMILES	N(=O)(=O)C
Molecular mass	61.04 g/mol

Abbreviations: AICS, Australian Inventory of Chemical Substances; ASIA-PAC, Asia-Pacific Substances Lists; CAS RN, Chemical Abstracts Service Registry Number; DSL, Domestic Substances List;ECL , Korean Existing Substances; EINECS, European Inventory of Existing Commercial Chemical Substances; NCI, National Chemical Inventories; PICCS, Philippine Inventory of Chemicals and 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)

Physical and Chemical Properties

Table 2 contains experimental and modelled physical and chemical properties of nitromethane that are relevant to its environmental fate.

Table 2. Physical and chemical properties for neutral form of nitromethane

Property	Type	Value[1]	Descriptors	Reference
Melting point (°C)	Experimental	−28.50		PhysProp 2009
Boiling point (°C)	Experimental	101.10		PhysProp 2009
Density (kg/m^3 at 20°C)	Unspecified	1138 kg/m^3 (1.138 g/cm^3)		Markofsky 2005
Vapour pressure (Pa at 25°C)	Experimental	4778.26* (35.84 mmHg)	High	Daubert and Danner 1989
Henry's Law constant (Pa·m^3/mol at 25°C)	Experimental	2.9* (2.86×10^{-5} atm·m^3/mol)	Moderate	Gaffney et al. 1987
Log K_{ow} (dimensionless)	Experimental	−0.35*	Negligible	Hansch and Leo 1995
Water solubility (mg/L)	Experimental (at 15–25°C)	111 000*	Very high	Riddick et al. 1986
Log K_{oc} (dimensionless)	Modelled	0.913	Negligible	PCKOCWIN 2000
pK_a (dimensionless)	Modelled	10.2		ACD/pK_aDB 2005

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

[1] Values and units in parentheses represent those originally reported by the authors or estimated by the models. Values marked with an asterisk (*) are values selected for modelling purposes.

Models based on quantitative structure–activity relationships (QSARs) were used to generate data for some of the physical and chemical properties of nitromethane. These models are mainly based on fragment addition methods (i.e., they rely on the structure of a chemical). Since these models accept only the neutral form of a chemical as input (in SMILES form), the modelled values shown in Table 2 are for the neutral form of nitromethane.

Sources

Nitromethane is an anthropogenic substance that has not been identified to occur naturally except perhaps as a metabolite of a fungus that grows on particleboard and as a synthesis product of a photolytic reaction of nitrogen dioxide and ethylene (NTP 1997; IARC 2000; Claeson et al. 2002). Production of nitromethane involves the high-temperature vapour-phase nitration of propane (Bollmeier 1996). Nitromethane may also occur as a combustion product of cigarettes and fuels (Seizinger and Dimitriades 1972; Smith et al. 2003) and as a degradation product of nitromethane-derived soil fumigants, such as chloropicrin (Dungan and Yates 2003).

In response to a notice issued under section 71 of CEPA 1999, nitromethane was not reported to be manufactured at a quantity above the reporting threshold of 100 kg in 2006 (Environment Canada 2009a). Importation activities (whether alone, in a mixture, in a

product or in manufactured items) were reported to be in the range of 100–1000 kg in 2006 (Environment Canada 2009a).

The quantity reported to be manufactured in, imported into, or in commerce in Canada during the 1986 calendar year was between 100 000 and 1 000 000 kg (Environment Canada 1986). The number of notifiers for the 1984–1986 calendar years was fewer than five. It is uncertain why the quantity imported since 1986 appears to have dropped significantly.

Uses

In response to a notice issued under section 71 of CEPA 1999, total use of nitromethane in Canada in the 2006 calendar year was reported to be in the range of 100–1000 kg (Environment Canada 2009a).

According to recent submissions made under section 71 of CEPA 1999 and information derived from other sources, including the scientific and technical literature, nitromethane may currently be used in Canada as a stabilizer in halogenated solvents used for vapour degreasing of workpieces, as a laboratory and industrial solvent, as a solvent for removal or debonding of α-cyanoacrylate instant adhesives, as a carrier solvent for opaquing porcelain for dental applications, as a fuel mixture with methanol in drag racing cars and miniature internal combustion engines (model cars, boats, planes, etc.), as a formulant in flux remover, magnetic tape head cleaner and multi-purpose lubricant, and as a dry cleaning solvent stabilizer (Lundberg 1989; Dow 2004; MSDS 2005, 2007, 2008; NTP 2005; DENTSPLY TRUBYTE 2006; TDS 2006; Environment Canada 2009a; Sigma-Aldrich 2009; 2007 email from Department of National Defence to DSL Survey Coordinator, Environment Canada; unreferenced).

Nitromethane has been reported as an ingredient in two current professional use cosmetic products in Canada that are listed in the Cosmetic Notification System database (CNS 2009). However, nitromethane does not appear on the cosmetic ingredient hotlist, Health Canada's administrative list of ingredients that are intended to be prohibited or restricted for use in cosmetics in Canada (Health Canada 2007). The two cosmetic products in Canada containing nitromethane are a gel eyelash adhesive remover and a false nail remover (CNS 2009). Nitromethane was historically present in some aerosol hairspray products in Canada; however, this use has been discontinued (CNS 2009; 2009 email from Cosmetics Division, Consumer Product Safety Bureau, Health Canada, to Risk Assessment Bureau, Health Canada; unreferenced). There is one registered pesticide that contains nitromethane as a List 2 formulant in Canada at a concentration of 0.2% by weight; however, sale of this pesticide has been discontinued in Canada, and the registration will expire on August 1, 2011 (PMRA 2007). Nitromethane is used as a chemical intermediate in the manufacture of bronopol, technical β-bromo-β-nitrostyrene and technical chloropicrin, but monitoring for residuals of nitromethane in these pesticides has not been performed (2009 email from Pest Management Regulatory Agency, Health Canada, to Risk Management Bureau, Health Canada; unreferenced).

Nitromethane is not listed as an approved food additive under the Index of Food Additives contained within the *Food and Drug Regulations* (Canada 1978). Nitromethane has not been identified to be present in formulations for food packaging materials (2009 email from Food Directorate, Health Canada, to Risk Management Bureau, Health Canada; unreferenced). The *Controlled Products Regulations* under the *Hazardous Products Act* provide a minimum reporting limit for nitromethane concentration of 1% by weight on Material Safety Data Sheets accompanying workplace chemicals as specified on the Ingredient Disclosure List (Canada 1988).

Nitromethane is not listed in the Drug Products Database, the Natural Health Products Ingredients Database or the Licensed Natural Health Products Database as a medicinal or non-medicinal ingredient present in final pharmaceutical products, natural health products or veterinary drugs manufactured in Canada (2009 emails from Therapeutic Products Directorate, Natural Health Products Directorate and Veterinary Drugs Directorate, Health Canada, to Risk Management Bureau, Health Canada; unreferenced). However, as nitromethane is used as a chemical intermediate in the synthesis of some pharmaceutical products, it may be present in trace amounts in certain pharmaceutical products (2009 email from Therapeutic Products Directorate, Health Canada, to Risk Management Bureau, Health Canada; unreferenced). For example, nitromethane is used as a methylating agent in the synthesis of Atorvastatin, a 3-hydroxy-3-methyl-glutaryl- (HMG) coenzyme A reductase inhibitor (Radl 2003). Nitromethane is listed as a Class 2 residual solvent (solvent to be limited) in pharmaceutical products, natural health products and veterinary medicinal products with a concentration limit of 50 ppm (where the maximum daily dose of the product does not exceed 10 g) or a permitted daily exposure of 0.5 mg/day (Health Canada 1999). The manufacture of dental crowns and bridges uses carrier solvent for opaquing porcelain containing nitromethane at a concentration of 74% by weight (MSDS 2005; 2009 email from Medical Devices Bureau, Health Canada, to Risk Management Bureau, Health Canada; unreferenced). The liquid opaquer is applied to the metal framework of dental crowns and bridges to mask the underlying structure and to provide some colour.

The following uses of nitromethane were identified as global or historical in nature; however, they were not determined to be ongoing uses in Canada. As an industrial solvent, nitromethane is used to dissolve cellulose esters, polymers, waxes and artificial resins, such as acrylic coatings (Lundberg 1989; IARC 2000). Nitromethane is a component of cleaners applied to semiconductors, lenses and electronic circuit boards (IARC 2000; Markofsky 2005). Rocket fuel contains nitromethane as a fuel additive (Lundberg 1989). Nitromethane was formerly used as a component in binary explosive formulations and in shaped charges (Bollmeier 1996). It can be used as an aprotic solvent in electrodeposition of polymers (US Patent 1992). Nitromethane can also be used as a corrosion inhibitor for the interior lining of tin-plated steel cans containing water-based aerosol formulations (Markofsky 2005). It is used as a chemical intermediate in the manufacture of several derivatives, including industrial antimicrobials and pharmaceuticals, such as the anti-ulcer drug ranitidine (Bollmeier 1996). Nitromethane is used in the production of a nitro alcohol intended as a buffering agent in several pharmaceutical applications (Bollmeier 1996). There is no information on nitromethane

with respect to the Biocidal Products Directive (Directive 98/8EC) in the European Chemicals Bureau's European Chemical Substances Information System (ESIS) database (ESIS 2009); however, there is information that nitromethane is currently used in agricultural fumigants (ECB 2005).

Releases to the Environment

In response to a notice issued under section 71 of CEPA 1999, no releases of nitromethane to environmental media were reported in the 2006 calendar year (Environment Canada 2009a). Section 71 data indicate that transfers of under 100 kg of nitromethane to hazardous waste facilities occurred in the 2006 calendar year (Environment Canada 2009a). Nitromethane is not reportable to the National Pollutant Release Inventory (NPRI 2007) or to the US Toxics Release Inventory Program (TRI 2006); therefore, no release information was available from these sources.

Environmental Fate

Based on its physical and chemical properties (Table 2), the results of Level III fugacity modelling (Table 3) indicate that nitromethane is expected to reside predominantly in air, water or soil, depending on the compartment of release. Given the volatility of nitromethane, most releases would probably be to air, although this is not certain.

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

Substance released to:	Percentage of substance partitioning to each compartment			
	Air	Water	Soil	Sediment
Air (100%)	68.60	25.90	5.48	0.05
Water (100%)	0.12	99.70	0.01	0.20
Soil (100%)	0.24	36.90	62.7	0.07

The relatively high acid dissociation constant (pK_a) of 10.2 for the acidic functional group indicates that half of the chemical will be partly dissociated at pH 10.2. In water bodies at environmentally relevant pH (6–9), 100% will be undissociated, which indicates that biotic exposure will be to the neutral form of nitromethane. The relatively low proportion of dissociated chemical also indicates that predicting partitioning behaviour using the log K_{ow} and log K_{oc} is appropriate.

Persistence and Bioaccumulation Potential

Environmental Persistence

Table 4a presents the photodegradation information for nitromethane, expressed as the half-life in air estimated from an empirical degradation rate constant (Atkinson 1989). The half-life in air from indirect photolysis with hydroxyl radicals is quite long – 82 days.

However, nitromethane absorbs ultraviolet radiation > 290 nm and undergoes photodissociation with a measured half-life of 4.3 hr (Ryon 1984). Therefore, nitromethane is not likely to persist in that environmental compartment.

Table 4a. Empirical data for degradation of nitromethane

Medium	Fate process	Degradation value	Degradation endpoint (units)	Reference
Air	Photodegradation (indirect)	82	Half-life (days)	Atkinson 1989
Air	Photolysis	4.3	Half-life (hours)	Ryon 1984
Water	Biodegradation (aerobic)	10	% BOD at 28 days	Freitag et al. 1988
Water	Biodegradation (aerobic)	36.2	% BOD at 5 days	Freitag et al. 1988
Soil	Biodegradation (aerobic)	5.1	% BOD at 35 days	Freitag et al. 1988
Soil	Biodegradation (anaerobic)	2.2	% BOD at 35 days	Freitag et al. 1988

BOD, biochemical oxygen demand

Table 4a presents empirical biodegradation data for nitromethane. One study (Freitag et al. 1988) shows 10% BOD over 28 days in a ready biodegradation test for nitromethane using the OECD 301 Guideline. However, another study (also Freitag et al. 1988) shows a much faster rate of degradation: 36.2 % BOD over 5 days. Half-lives, in water, ranging from 7.7 - 184 days can be calculated with the first-order kinetics rate equation using the experimental biodegradation rates of 36.2% in 5 days and 10% in 28 days. Robust Study Summaries have found both studies to be acceptable but there is concern about volatilization in the test which indicated low biodegradation.

Table 4a also presents empirical data for degradation in soil that seem to indicate that nitromethane is persistent in that medium, although there is some evidence that nitromethane is a bacterial inhibitor (Okamura et al. 1974). It is noted that a significant amount of volatilization of nitromethane occurred during the tests (22 and 32%, respectively).

Since few experimental data for the degradation of nitromethane are available, a QSAR-based weight of evidence approach (Environment Canada 2007) was also applied using the degradation models shown in Table 4b. Given the ecological importance of the water compartment, the fact that most of the available models apply to water and the fact that nitromethane is expected to be released to this compartment; primarily biodegradation in water was examined. Nitromethane does not contain functional groups expected to undergo

hydrolysis. Table 4b summarizes the results of available QSAR models for degradation in various environmental media.

Table 4b. Modelled data for degradation of nitromethane

Fate process	Model and model basis	Model result and prediction	Extrapolated half-life (days)
Water			
Hydrolysis	HYDROWIN 2000	na	n/a
Biodegradation (aerobic)	BIOWIN 2000 Submodel 3: Expert Survey (ultimate biodegradation)	3.06[2] "biodegrades fast" (weeks)	<182
Biodegradation (aerobic)	BIOWIN 2000 Submodel 4: Expert Survey (primary biodegradation)	3.76[2] "biodegrades fast" (days)	<182
Biodegradation (aerobic)	BIOWIN 2000 Submodel 5: MITI linear probability	0.53[3] "biodegrades fast"	<182
Biodegradation (aerobic)	BIOWIN 2000 Submodel 6: MITI non-linear probability	0.69[3] "biodegrades fast"	<182
Biodegradation (aerobic)	TOPKAT 2004 Probability	1[3] "biodegrades fast"	<182
Biodegradation (aerobic)	CPOPs 2008 % BOD	% BOD = 0 "biodegrades slowly"	>182

BOD, biochemical oxygen demand; MITI, Ministry of International Trade & Industry, Japan; n/a, not applicable; $t_{½}$, half-life.

[1] Model does not provide an estimate for this type of structure.

[2] Output is a numerical score from 0 to 5.

[3] Output is a probability score.

Four of the five ultimate biodegradation models, including TOPKAT (2004), indicate that biodegradation is likely to be fast and that the half-life in water would be <182 days. There is uncertainty surrounding some of the modelled results. Catabol (CPOPs) assigns a 0% probability of transformation for the nitro reduction step, the only possibility it identifies for the parent molecule. TOPKAT does not have many nitro substances in the training set and the substances in the training set, which have results closest to nitromethane, do not have nitro groups. BIOWIN does not have compounds with aliphatic nitro groups in the training set.

Nitromethane does not meet the persistence criterion for air (half-life ≥2 days) as set out in the *Persistence and Bioaccumulation Regulations* (Canada 2000). Although the experimental data for persistence in water and soil are not in full agreement, the weight of evidence supports the conclusion that nitromethane does not meet the criteria for persistence in water and soil (half-lives in soil and water ≥ 182 days) and in sediment (half-life in sediment ≥ 365 days) as set out in the *Persistence and Bioaccumulation Regulations* (Canada 2000).

Potential for Bioaccumulation

The experimental log K_{ow} for nitromethane (see Table 2 above) indicates that this chemical has low potential to bioaccumulate in biota.

Table 5a presents the empirical bioconcentration factor (BCF) values in fish and algae. Although the results indicate a low bioaccumulation potential, it is probably very difficult to perform a test or measure the bioaccumulation potential accurately, because nitromethane is highly volatile.

Table 5a. Empirical data for bioaccumulation of nitromethane

Test organism	Endpoint	Value (L/kg wet weight)	Reference
Fish	BCF	1.4	Freitag et al. 1988
Alga	BCF	960	Freitag et al. 1988

Since few experimental BCF data and no experimental bioaccumulation factor (BAF) data for nitromethane were found, a predictive approach was applied using available BAF and BCF models, as shown in Table 5b. Metabolism information for this substance was not available, nor was it considered in the BAF or BCF models.

Table 5b. Modelled data for bioaccumulation of nitromethane

Test organism	Endpoint	Value (L/kg wet weight)	Reference
Fish	BAF	1	Arnot and Gobas 2003 (Gobas BAF middle trophic level)
Fish	BCF	1	Arnot and Gobas 2003 (Gobas BCF lower trophic level)
Fish	BCF	3.12	CPOPs 2008
Fish	BCF	3	BCFWIN 2000

The modified Gobas BAF middle trophic level model for fish predicted a BAF of 1 L/kg, indicating that nitromethane does not have the potential to bioconcentrate in fish and to biomagnify in food webs, which is consistent with what would be expected based on its structure and other physical and chemical properties. The results of BCF model calculations provide additional evidence supporting the low bioconcentration potential of this substance.

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

Potential to Cause Ecological Harm

Ecological Effects Assessment

The experimental data for the effects of nitromethane on aquatic organisms is summarized in Tables 6a. Test conditions in both cases were static, not flow-through, so loss of nitromethane to air during testing could have occurred. Some caution, therefore, should be exercised in interpreting the results, although they appear to support the conclusion that nitromethane has low toxicity to aquatic organisms.

Table 6a. Empirical data for aquatic toxicity of nitromethane in aquatic organisms

Test organism	Test type	Endpoint	Value (mg/L)	Reference
Fathead minnow	Acute (96 h)	LC_{50}	< 278	Curtis et al. 1981
Zebrafish (*Brachydanio rerio*)	Acute (48 h)	LC_{50}	ca. 460	ECB 2000

Abbreviation: LC_{50}, the concentration of a substance that is estimated to be lethal to 50% of the test organisms.

The modelled data for the effects of nitromethane on aquatic organisms are summarized in Table 6b.

Table 6b. Modelled data for aquatic toxicity of nitromethane in aquatic organisms

Test organism	Type of test	Endpoint	Value (mg/L)	Reference
Fish	Acute (96 h)	LC_{50}	2916	ECOSAR 2004
			3048	CPOPs
			127	AIES 2003–2005
	Acute (14 days)	LC_{50}	2853	ECOSAR 2004
Fathead minnow	Acute (48 h)	LC_{50}	127	AIES 2003–2005
	Acute (96 h)	LC_{50}	6347	ASTER 1999
Daphnid	Acute (48 h)	EC_{50}	1217	ECOSAR 2004
			399	TOPKAT 2004
Alga	Acute (96 h)	EC_{50}	238	ECOSAR 2004

Abbreviations: EC_{50}, the concentration of a substance that is estimated to cause some toxic sublethal effect on 50% of the test organisms; LC_{50}, the concentration of a substance that is estimated to be lethal to 50% of the test organisms.

A study on the acute aquatic toxicity of nitromethane to fathead minnow (*Pimephales promelas*) resulted in an LC_{50} of 278 mg/L (Table 6a). This value is considered to reflect low acute toxicity. Hence, nitromethane is not expected to cause harm to aquatic organisms at relatively low concentrations. Although there is uncertainty associated with the empirical result given the potential for loss of nitromethane from the test system by volatilization, this conclusion is supported by the modelled data (Table 6b).

Industrial Release

As nitromethane is used industrially and could be released to water, a worst-case industrial release scenario was used to estimate the aquatic concentration of the substance with the help of Environment Canada's (2008) Industrial Generic Exposure Tool – Aquatic (IGETA). The scenario is made conservative by assuming that the total quantity

of the substance used by Canadian industry is used by a single industrial facility at a small, hypothetical site and that the loss to sewers is high, at 5% of the total quantity, resulting from the cleaning of chemical containers and process equipment. The scenario also assumes that the release occurs 250 days/year, typical for small and medium-sized facilities, and is sent to a local sewage treatment plant (STP). The STP removal rate was estimated using the STP modelling program (STP 2001). In Canada, the receiving water at such a small site normally has a 10-fold dilution capacity for the STP effluent, which was assumed to be 3456 m^3/day. Based on the above assumptions, industrial use of the substance at a total quantity of between 100 and 1000 kg/year yields an aquatic concentration of 0.0026 mg/L (Environment Canada 2009b).

Characterization of Ecological Risk

The approach taken in this ecological screening assessment was to examine various supporting information and develop conclusions based on a weight of evidence approach and using precaution, as required under CEPA 1999. Lines of evidence considered include results from a conservative risk quotient calculation, as well as information on persistence, bioaccumulation, toxicity, sources and fate of the substance.

Nitromethane is not expected to be persistent in air, water, soil or sediment. It is expected to have a low bioaccumulation potential. The importation volumes of nitromethane into Canada, along with information on its uses, indicate potential for some releases into the Canadian environment. Once released into the environment, nitromethane could be found in air, water or soil, depending on the medium of release. Based on experimental and modelled results, nitromethane is expected to have low potential for toxicity to aquatic organisms.

A risk quotient analysis, integrating conservative estimates of exposure with toxicity information, was performed for the aquatic medium to determine whether there is potential for ecological harm in Canada. The hypothetical industrial scenario presented above yielded a predicted environmental concentration (PEC) of 0.0026 mg/L (Environment Canada 2009b). A predicted no-effect concentration (PNEC) was derived from the acute toxicity value of 278 mg/L for the fathead minnow by dividing this value by an assessment factor of 100 (to account for interspecies and intraspecies variability in sensitivity and to estimate a long-term no-effects concentration from a short-term LC_{50}), to give a value of 2.78 mg/L. The resulting risk quotient (PEC/PNEC) equals 0.0009. Therefore, harm to aquatic organisms is unlikely.

Based on the information available, nitromethane is unlikely to be causing ecological harm in Canada.

Uncertainties in Evaluation of Ecological Risk

There is uncertainty associated with the experimental data for persistence in water because the results are not in full agreement and it is unclear whether nitromethane's high volatility was taken into account during the studies.

There is uncertainty associated with the use of QSAR models to estimate persistence, bioaccumulation and aquatic toxicity. There are a limited number of nitro compounds in the training sets for these QSARs.

Uncertainty exists because of the very limited information on environmental concentrations (e.g., monitoring data) of nitromethane in Canada or elsewhere. There is also uncertainty associated with the fraction of nitromethane in commerce that is released and with the fraction that is removed in STPs. A predicted environmental concentration was therefore estimated using an exposure model based on conservative assumptions.

Potential to Cause Harm to Human Health

Exposure Assessment

Environmental Exposure

There were no empirical data identified regarding measured concentrations of nitromethane in environmental media or food in Canada. However, empirical data in other locations were identified for concentrations of nitromethane in ambient air and in a limited number of beverages and are used as surrogates for Canadian-specific data in order to estimate exposure, as described below. No monitoring data were identified for nitromethane in indoor air, surface water, drinking water, soil or sediment, regardless of location. Residual levels of nitromethane in food are not currently monitored by the Canadian Food Inspection Agency (2009 email from Canadian Food Inspection Agency to Risk Assessment Bureau, Health Canada; unreferenced).

Nitromethane is a gas-phase pollutant resulting from vehicle exhaust that was detected in at least 1 (July 24, 1996) of 44 ambient air samples collected in downtown Porto Alegre, Brazil, during the period from March 20, 1996, to April 16, 1997, at a level of 10.0 $\mu g/m^3$ (Grosjean et al. 1998). This concentration was used in deriving the ambient air intake estimate (see Appendix 1). Another study (Seizinger and Dimitriades 1972) found nitromethane in ambient air from automobile exhaust at levels of <2–12.5 mg/m^3 (<0.8–5 ppm); however, the River Road emission testing facility in Ottawa suggested that 2.5–5 $\mu g/m^3$ (1–2 ppb) may be more likely, because it takes into account newer emission regulations and weighs in a dilution factor (2009 email from River Road emission testing facility to Risk Assessment Bureau, Health Canada; unreferenced). The ambient air concentration in Porto Alegre, Brazil, is considered representative of exposure to nitromethane resulting from vehicle exhaust at the point of exposure (human receptor). This ambient air concentration is used to represent indoor air as well, since no indoor air data were available.

In the United States and Canada, vehicle exhaust may represent an increasing source of nitromethane emissions to ambient air in the future, as large diesel engines manufactured from January 1, 2010, onwards must be fitted with a selective catalytic reduction (SCR) process to meet new federal diesel emission standards aimed at reducing nitrogen oxide concentrations (Financial 2009; Miller 2009). Europe has also been phasing in this SCR technology since 2006, with an expected 3.7 million heavy-duty vehicles and 5 million distribution vehicles being fitted by 2012 (Peckham 2003). This SCR technology uses a liquid additive containing organic nitrogen, and nitromethane has been identified as a by-product of the process (Miller 2009).

Nitromethane was measured in air at a concentration range of 0.21–2 μg/m^3 at three sites along the boundary of a munitions plant in Tennessee in 1984. However, these ambient air data were not considered in assessing exposure of the general population in Canada, as use of nitromethane in the manufacture of Royal Demolition Explosive and High Melting Explosive was a former application in the United States and not identified to have occurred in Canada (Ryon et al. 1984; NTP 2005). Also, the concentration used to estimate ambient air intake (see above) is higher than the values reported in this study.

Nitromethane is present in mainstream cigarette smoke, generated at levels in the range 0.3–0.6 μg per unfiltered cigarette (Rodgman 2003). Therefore, cigarette smoke is a potential source of exposure to nitromethane, especially in indoor air.

In terms of drinking water, a 1975 US Environmental Protection Agency (US EPA) survey detected nitromethane in the drinking water of 4 of 10 American cities, although the concentrations were not specified (US EPA 1975). Nitromethane was also qualitatively detected in surface water (NTP 2005).

A recent paper describing a method for quantifying nitromethane in blood also reported detection of nitromethane in a limited number of beverages, ranging in concentration from 0.13 to 1.4 μg/L in nine samples of fruit juice, 1% cow milk, and soy milk (Alwis et al. 2008). Due to limited study details, it is not known if other foods were tested, nor is the mean concentration or distribution of concentrations among the food items known. Also this study would not be considered comprehensive for the purposes of determining nitromethane concentrations in a typical market basket of foods and beverages representative of Canadian consumption. While Alwis et al. (2008) did not specifically identify the source of the nitromethane, they speculated, based on information presented in a previous study (Castro et al. 1983), that nitromethane may be present in vegetables and food products due to bacterial dehalogenation of trichloronitromethane by *Pseudomonas* sp. Trichloronitromethane, also known as chloropicrin, is a formulant of a soil sterilant and post-harvest grain and cereals fumigant registered in Canada that is widely used with methyl bromide in pesticide applications (Alwis et al. 2008; 2009 email from Pest Management Regulatory Agency, Health Canada, to Risk Management Bureau, Health Canada; unreferenced).

As no other quantitative food data were identified for nitromethane, the maximum concentration of 1.4 μg/L determined in nine samples of fruit juice, 1% cow milk and soy

milk was assumed to be the concentration of nitromethane for 3 of 12 food categories: dairy products, fruits and fruit products, and vegetables including legumes (Appendix 1). As these food categories encompass many products not measured in the Alwis et al. (2008) study, the use of the Alwis et al. (2008) data is considered to result in a conservative estimate of exposure. The conservative nature of the exposure estimate is also increased by the use of a maximum concentration, the lack of detail of concentration distributions among the beverages, and the lack of representation of a typical market basket of foodstuffs that Canadians consume.

While no monitoring studies have been identified regarding nitromethane levels in soil or sediment, the levels in soil and sediment relative to those in air and water are anticipated to have a minimal impact on the exposure estimate due to the negligible log K_{oc} and the environmental releases being primarily to air and water based upon expected use patterns. However, as chloropicrin may degrade to nitromethane, some soil levels of nitromethane may be anticipated in agricultural regions (Dungan and Yates 2003).

Although adding to the knowledge base for nitromethane, additional data identified were not used to quantify exposure. Nitromethane was qualitatively identified in indoor air, resulting from microbial growth on particleboard in Sweden (Claeson et al. 2002). It was detected in three experimental samples of stored food exudates at unspecified concentrations (Wilkins and Larsen 1995). In two studies in the United States, 1 of 12 samples of breast milk was found to contain nitromethane, although the detection limit was unspecified (Erickson et al. 1980; Pellizzari et al. 1982). In addition, a biomarker study quantified the blood nitromethane concentration as ranging from 0.28 to 3.79 µg/L (median 0.66 µg/L) in 632 individuals with no known exposure to nitromethane or halonitromethanes. The study also used *in vitro* methods to demonstrate the possibility that dehalogenation of halonitromethanes and peroxynitrite-mediated reactions with other molecules in blood could be endogenous sources of nitromethane in the human body (Alwis et al. 2008). Thus, the blood nitromethane in these individuals may have derived from direct exposure to nitromethane, but it may have been in part or entirely due to exposure to halonitromethanes or a result of endogenous biochemical reactions involving peroxynitrite.

The maximum daily intake of nitromethane was estimated as 6.1 µg/kg body weight (kg-bw) per day for toddlers between the ages of 0.5 and 4 years. Intake of nitromethane from air was the predominant source of environmental exposure at a maximum nitromethane concentration of 10.0 µg/m^3 (Grosjean et al. 1998). Nonetheless, since nitromethane was qualitatively detected at unspecified concentrations in breast milk and drinking water, these media cannot be ruled out as potential contributors to total exposure. Appendix 1 displays the estimated total multimedia intakes for different age groups.

Consumer/Commercial Product Exposure

In considering exposure to nitromethane present in products in Canada, uses reported for the calendar year of 2006 in response to a notice issued under section 71 of CEPA 1999, along with literature searches and contact with industry, were used to identify uses that

are ongoing in Canada. Nitromethane is currently present as an intentional ingredient in fuel applications (drag racing and model engines), limited personal care products used in a professional setting (one type of gel eyelash adhesive remover and one type of false nail remover), a dry cleaning solvent, and solvents for removing instant adhesives and flux, as described below.

Inhalation exposure is the principal route of exposure to nitromethane from products, as nitroalkanes are not readily absorbed through the skin (Markofsky 2005). In addition, an *in vivo* study in monkeys did not demonstrate potential for dermal absorption of nitromethane, likely due to the rapid evaporation of nitromethane (Norman 1990).

In terms of fuel applications, hobbyists may be exposed to nitromethane vapours during refuelling of model engines. However, refuelling is an outdoor activity and exposure potential considered low to negligible due to large atmospheric volume and minimal quantities of fuel used per model engine tank (125 mL). While spills of nitromethane may occur to the hand when refuelling model engines, dermal absorption is not expected. Since some amount of nitromethane may be released as an uncombusted product in the exhaust of nitrofuel engines, spectators at drag racing events may be exposed. Because an estimate of the efficiency of combustion in these engines has not been identified, the concentration of nitromethane (10.0 µg/m^3) in ambient air in downtown Porto Alegre, Brazil, is considered representative of exposure of spectators at drag racing events, as it was attributed to automobile exhaust (Grosjean et al. 1998).

In addition, nitromethane is present in industrial solvents for removing flux at a maximum concentration of 2% by weight (MSDS 2002). Flux is applied during soldering of electrical equipment to remove metal oxides from the two surfaces to provide a clean contact for bonding of the metal alloy (GBPPR [date unknown]). Exposure was not characterized for this use as it is considered to occur primarily in an occupational setting and to not be applicable to exposure of the general population.

Nitromethane has been reported as an ingredient in two personal care product formulations notified to Health Canada. It is present at a maximum concentration of 100% by weight in one eyelash adhesive remover and 25% by weight in one false nail remover (CNS 2009). These products are anticipated to be applied primarily in professional settings, such as salons, where exposure of the general population (customers) may occur (2009 email from Cosmetics Division, Health Canada, to Risk Assessment Bureau, Health Canada; unreferenced). As the service life of liquid nails is approximately 3–6 weeks, a reasonable upper-bound frequency of application of false nail remover is 17 events per year (2009 email from Cosmetics Division, Health Canada, to Risk Assessment Bureau, Health Canada; unreferenced). As this frequency does not constitute a chronic source of exposure, an inhalation time-weighted average event concentration of 13 mg/m^3 was determined for false nail remover. The assumptions underlying the scenario are presented in Appendix 2. This scenario assumed a one-box model (well-mixed room) rather than a two-box model (near-field box was breathing zone of individual using false nail remover and the far-field box was the remainder of the room), as the air exchange rate between the two compartments of the room was unknown

(AIHA 2009). There is some uncertainty in the scenario. The use of the Estimating Contaminant Generation Rate from Small Spills model to determine the mass generation rate is considered by the model to produce only an order of magnitude estimate. The model (AIHA 2009) functions best for substances with a ratio of vapour pressure to atmospheric pressure of greater than 5% (while nitromethane was 4.7%) and for air velocities of 50–500 cm/s (while the room air velocity in the false nail scenario was 2 cm/s). In addition, the density of nitromethane (relative density of 2.1) is greater than that of air, so this adds to the uncertainty regarding the ability of the substance to evaporate and distribute from a container being used. Also, there are alternate nail removal procedures that may employ different product volumes and variable duration of product use.

Regarding eyelash adhesive remover, an exposure scenario was not conducted, as the exposure estimate would be below that of false nail remover due to lower exposure duration (5 min) and product amount used (0.5 g).

In terms of removing agents, nitromethane may be present at a maximum concentration of 100% by weight in removers for acrylate instant adhesives (MSDS 2007). Consumer use of instant adhesive remover is assumed to be limited to small applications, such as removing excess instant adhesive during the reattachment of a broken mug handle. Exposure was not characterized as the exposure estimate would be below that of false nail remover due to lower product amount used (0.5 g) over the same estimated exposure duration (0.5 hour).

Nitromethane may also be present at a concentration of 74% by weight as a carrier solvent for opaquing porcelain applied to the metal framework of dental crowns and bridges in a laboratory setting for masking the underlying structure and providing some colour (MSDS 2005). Exposure to nitromethane in this application would not occur, as the applied liquid is not bioavailable (2009 email from Medical Devices Bureau, Health Canada, to Risk Assessment Bureau, Health Canada; unreferenced). Nitromethane is used as a stabilizer in a dry cleaning solvent (<0.6% by weight; MSDS 2008) and, as such, may be present as a residue on clothing. However, dermal absorption of nitroalkanes does not occur (Norman 1990; Markofsky 2005). Possible uses as magnetic tape head cleaner and multi-purpose lubricant would not constitute a concern to the general population, as they have not been identified in Canada outside of a military setting (2007 email from Department of National Defence to DSL Survey Coordinator, Environment Canada; unreferenced).

An additional study related to product exposure from use of products containing nitromethane was not used as it took place in an occupational setting. This study quantified exposure of workers to nitromethane in a factory producing vehicle headlights; exposure occurred when workers sprayed nitromethane from spray bottles onto the headlights to clean off excess glue (Page et al. 2001). As part of a US Occupational Safety and Health Administration investigation, nitromethane concentrations in personal breathing zones were sampled for four workers at a maximum 8-hour time-weighted average concentration of 50 mg/m^3 (20 ppm), with a mean of 31.81 mg/m^3 (12.75 ppm).

The average volume of pure nitromethane used by each table of four workers per half-hour was approximately 35 mL (totalling 560 mL in an 8-hour shift) (Page et al. 2001).

Confidence in the assessment of environmental exposure is low. Although there were minimal literature data identified for media concentrations, environmental releases reported under section 71 of CEPA 1999 would be expected to produce negligible exposure of the general population. However, the detection without quantification of nitromethane in some studies indicates a data gap in quantifying environmental exposure. Confidence in the assessment of product exposure is moderate, as several uses were comprehensively identified in responses to the notice issued under section 71 of CEPA 1999, in addition to literature searches and industry follow-up.

Health Effects Assessment

A summary of the health effects of nitromethane in laboratory animals and humans is presented in Appendix 3.

Nitromethane has been classified by the International Agency for Research on Cancer (IARC, 2000) as a Group 2B carcinogen (possibly carcinogenic to humans, based on sufficient evidence in experimental animals) and by the US National Toxicology Program (NTP, 1997, 2005) as reasonably anticipated to be a human carcinogen (based on clear evidence of carcinogenic activity in B6C3F1 mice and in female F344/N rats). The database for the carcinogenicity of nitromethane due to chronic inhalation exposure includes significantly increased incidences of benign and malignant tumours at multiple sites in both sexes of mice and in the mammary glands of female rats.

Female F344/N rats chronically exposed to nitromethane at 470 and 938 mg/m^3 via inhalation exhibited significantly increased incidences of mammary gland fibroadenomas that were higher than the highest historical control incidence. Female rats exposed to nitromethane at 938 mg/m^3 also exhibited a significantly increased incidence of mammary gland carcinoma. No carcinogenic effect was observed in male Fischer 344/N rats in the same study (NTP, 1997). In another chronic inhalation study, Griffin et al. (1996) did not find significant carcinogenicity in BLU:(LE)BR rats exposed to nitromethane at 250 or 500 mg/m^3.

Female B6C3F1 mice chronically exposed to nitromethane at 470 and 1875 mg/m^3 via inhalation exhibited significantly increased incidences of hepatocellular adenomas that were higher than the highest historical control incidence (NTP, 1997). However, the number of tumours observed at 938 mg/m^3 was not statistically significant. Alveolar/bronchiolar carcinoma was also significantly increased in female mice exposed to nitromethane at 938 mg/m^3 and in male mice exposed to 1875 mg/m^3. The incidence of Harderian gland adenoma was significantly increased in both sexes exposed to nitromethane at 938 and 1875 mg/m^3.

Nitromethane is not genotoxic in *in vitro* or *in vivo* assays. Nitromethane was negative in multiple assays for mutagenicity in bacteria and *Drosophila* (Brusick 1975; Chiu et al.

1978; Domoradzki 1980; Gocke et al. 1981; Lofroth et al. 1986; Mortelmans et al. 1986; Dayal et al. 1989; Dellarco and Prival 1989) and did not cause sister chromatid exchanges or chromosomal aberrations in mammalian cells (NTP 1997). Nitromethane did not induce micronuclei formation *in vitro* or in mice (Gocke et al. 1981; Gibson et al. 1997; NTP 1997; Witt et al. 2000). However, at the two highest concentrations tested and without S9 activation, nitromethane caused morphological transformation of Syrian hamster embryo cells (Kerckaert et al. 1996).

Although the mechanism of nitromethane carcinogenicity is unknown, given that nitromethane is not genotoxic in *in vitro* or *in vivo* assays, other modes of action have been proposed. It has previously been hypothesized that reactive radicals may be involved in nitromethane carcinogenicity (NTP 1997) because nitromethane metabolism yields intermediate superoxide radicals, hydrogen peroxide, nitrite, formaldehyde and/or acetone, depending on the metabolizing enzyme (Porter et al. 1972; Kido and Soda 1978; Sakurai et al. 1980; Dahl and Hadley 1983; Kido et al. 1984; Dayal et al. 1991). Given that nitromethane was positive in a cell transformation assay without S9 activation (Kerckaert et al. 1996), it is also possible that the parent molecule promotes tumour growth through a direct effect on the cell. Nitromethane is readily absorbed from the respiratory and gastrointestinal tracts (Scott 1943), but the predominant pathway of metabolism in mammals is unknown.

In terms of non-cancer effects, slight nasal congestion (one of four animals) and transient weight loss (three of four animals) were observed in male rats after acute inhalation exposure to nitromethane at 2495 mg/m^3 for 4 hours (acute lowest-observed-effect concentration [LOEC]: 2495 mg/m^3) . At 9980 mg/m^3, rats exhibited under-responsiveness; at 14 970 and 19 960 mg/m^3, one of four and three of four died, respectively (Haskell Laboratory 1961). Liver effects were observed in laboratory animals following short-term inhalation or oral exposure to nitromethane. The LOEC was 235 mg/m^3, a concentration at which increased absolute and relative liver weights were observed in mice exposed for 16 days. At higher concentrations, there was minimal degeneration of the olfactory epithelium in mice and rats and moderate, dose-dependent degeneration of the sciatic nerve in rats (lowest-observed-adverse-effect concentration [LOAEC]: 938 mg/m^3) (NTP 1997). As characterized by the study authors, liver impairment occurred in both rats and rabbits exposed for 2 months via drinking water (lowest-observed-adverse-effect level [LOAEL]: 23.5 mg/kg-bw per day) (Subbotin 1967).

The LOEC for subchronic inhalation exposure was 235 mg/m^3 based on hyaline droplet formation in the respiratory epithelium (females) and increased absolute and relative kidney weights (males) of mice exposed for 13 weeks. At higher concentrations, rats exhibited degeneration of the sciatic nerve and lumbar spinal cord (LOAEC: 938 mg/m^3) (NTP 1997). A transient increase in serum transaminase activity at 2-3 months was also observed in rats and rabbits exposed for 6 months via drinking water (lowest-observed-effect level/no-observed-adverse-effect level [LOEL/NOAEL]: 0.5 mg/kg-bw per day; no-observed-effect level [NOEL]: 0.05 mg/kg-bw per day) (Subbotin 1967).

Nitromethane exposure resulted in changes in reproductive parameters in laboratory animals. There was a dose-related significant decrease in sperm motility in rats exposed to nitromethane at 1875 and 3750 mg/m^3 and in mice exposed to nitromethane at 938, 1875 and 3750 mg/m^3 via inhalation for 13 weeks. Female mice exhibited a dose-dependent increase in estrous cycle length at 938, 1875 and 3750 mg/m^3 (NTP 1997). However, mice exposed to 235 and 470 mg/m^3 in the NTP (1997) study were not examined for reproductive effects, thus lowering the confidence in 938 mg/m^3 as the lowest effect level for changes in reproductive parameters (LOAEC for reproductive effects: $\leq$ 938 mg/m^3).

There are a limited number of case reports of occupational exposure to nitromethane by the inhalation route. Two headlight subassembly plant workers exposed to nitromethane at 31.81 mg/m^3 daily for 4 to 6 weeks developed peripheral neuropathy manifesting as diminished reflexes and leg weakness. One individual experienced pain and swelling in both legs and feet (Page et al. 2001). Another case report identified a worker chronically exposed to vapours from a solvent containing 0.25% nitromethane; this individual developed parkinsonism and depression (Sandyk and Gillman 1984). The nervous system effects seen in humans are similar to effects seen in laboratory animals exposed to nitromethane; however, these results must be interpreted with caution, because in both cases, the workers were also exposed to other potentially hazardous compounds and to at least one with known neurological toxicity. Severe toxic effects in humans resulted from inhalation exposure to nitromethane at 1996 mg/m^3 for 1 hour. Symptoms of illness resulted from exposure to 1248 mg/m^3 "for more than a short time" (Strafford et al. 1956). Further details were not available from the primary source.

The confidence in the health effects data set for nitromethane is moderate to high, as data were identified in a limited number of well-conducted studies for carcinogenicity, neurotoxicity, reproductive parameters and other endpoints. However, there is limited information on non-lethal acute toxicity.

Characterization of Risk to Human Health

Based principally on a weight of evidence assessment by IARC (2000), a critical effect for the characterization of risk to human health is carcinogenicity, based on observation of tumours at multiple organ sites in mice and at one site in rats (NTP, 1997). Nitromethane is not genotoxic in *in vitro* or *in vivo* assays. Although the mode of action for carcinogenicity has not been elucidated, the tumours observed are not considered to have resulted from direct interaction with genetic material. Therefore, a threshold approach is used to characterize risk to human health. Other adverse health effects observed in laboratory animals include reproductive toxicity and neurotoxicity. Acute effects are limited to reduced body weight, nasal congestion or lethality at high exposure levels.

With respect to air as the principal source of environmental exposure, a comparison between the maximum air concentration of nitromethane (10.0 µg/m^3) and the lowest conservative chronic or subchronic LOEC (235 mg/m^3) for hyaline droplet formation and

increased absolute and relative kidney weights in mice, and subchronic LOAEC for more adverse effects, including neurotoxicity, in rats (938 mg/m^3), resulted in margins of exposure of 23 500 and 93 800, respectively. Margins of exposure were not calculated for other routes of exposure (i.e., for environmental media or foods), as air is the principal route of exposure. This margin is considered adequate in light of the uncertainties in the database (Appendix 4).

The principal source of exposure to nitromethane in consumer products is through use of false nail remover. Only one such product is reported to be in the marketplace; therefore, potential exposure to this product would be limited to a small subpopulation. A comparison of the air concentrations anticipated from off-gassing of nitromethane from this product (13 mg/m^3) with acute inhalation rat and human effect levels (2495 and 1248 mg/m^3, respectively) result in margins of exposure ranging from approximately 100 to 200 (Appendix 4). As the effects in laboratory animals at this exposure level are considered minimal in nature, the margin calculated using the human toxicity values does not require extrapolation across species, and the fact that exposure in the hazard studies was for a longer duration than the potential exposure period, these margins are considered adequately protective of human health in light of the uncertainties in the database (Appendix 4). In addition, if lifetime average daily exposure from this use is considered, exposure would be low and the corresponding cancer risk very low.

Uncertainties in Evaluation of Risk to Human Health

The detection of nitromethane in drinking water and one sample of breast milk without quantification indicates that it is possible for these media to contribute to exposure. However, these data are very old, the potential source of the nitromethane is not documented in the studies and their relevance to the current Canadian situation is unknown. Also, while this screening assessment addresses in concept the possibility that nitromethane could be present in some foods because of the agricultural use of chloropicrin, no data were identified that quantify the amount of nitromethane that might be present in cereal- or grain-based food products. Intake of nitromethane from these foods, if there is any, was not included in the exposure estimate. Although there is some uncertainty regarding the modelling of air concentrations of nitromethane during the use of consumer products, based on the physical and chemical properties of the substance as well as likely higher ventilation rates in salons, the resulting estimates are likely to be conservative in nature.

The scope of this screening assessment does not take into account possible differences in species sensitivity to nitromethane or inter-individual variability in sensitivity in the human population.

Conclusion

Based on the information presented in this screening assessment, it is concluded that nitromethane 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. Nitromethane does not meet the criteria for persistence or bioaccumulation potential as set out in the *Persistence and Bioaccumulation Regulations* (Canada 2000).

On the basis of the adequacy of the margins between exposure to nitromethane and critical effect levels in laboratory animals and humans, it is concluded that nitromethane be considered as a substance that 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.

It is therefore concluded that nitromethane does not meet any of the criteria in section 64 of CEPA 1999.

This substance will be considered for inclusion in the *Domestic Substances List* inventory update initiative. In addition and where relevant, research and monitoring will support verification of assumptions used during the screening assessment.

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Appendix 1. Upper-bounding estimates of daily intakes of nitromethane for various age groups

Route of exposure	Estimated intake (µg/kg-bw per day) of nitromethane by various age groups							
	0–0.5 years[1,2,3]			0.5–4 years[4]	5–11 years[5]	12–19 years[6]	20–59 years[7]	60+ years[8]
	Breast milk fed	Formula fed	Not formula fed					
Air[9]	2.8	2.8	2.8	6.0	4.7	2.7	2.3	2.0
Drinking water[10]	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Food and beverages[11]	0.000	0.000	0.156	0.090	0.051	0.026	0.018	0.015
Soil[12]	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Total intake	2.8	2.8	3.0	6.1	4.7	2.7	2.3	2.0
Maximum total intake from all routes of exposure: 6.090 µg/kg-bw per day								

N/A, not available

[1] No quantitative data were identified for concentrations of nitromethane in breast milk.

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

[3] For exclusively formula-fed infants, intake from water is synonymous with intake from food. No quantitative data on concentrations of nitromethane in drinking water or formula were identified for Canada. Nitromethane was detected in 4 of 10 American cities in a 1975 survey by the US EPA; however, it was not quantified. For non-formula-fed infants, approximately 50% are introduced to solid foods by 4 months of age and 90% by 6 months of age (NHW 1990).

[4] Assumed to weigh 15.5 kg, to breathe 9.3 m^3 of air per day, to drink 0.7 L of water per day and to ingest 100 mg of soil per day (Health Canada 1998).

[5] Assumed to weigh 31.0 kg, to breathe 14.5 m^3 of air per day, to drink 1.1 L of water per day and to ingest 65 mg of soil per day (Health Canada 1998).

[6] Assumed to weigh 59.4 kg, to breathe 15.8 m^3 of air per day, to drink 1.2 L of water per day and to ingest 30 mg of soil per day (Health Canada 1998).

[7] Assumed to weigh 70.9 kg, to breathe 16.2 m^3 of air per day, to drink 1.5 L of water per day and to ingest 30 mg of soil per day (Health Canada 1998).

[8] Assumed to weigh 72.0 kg, to breathe 14.3 m^3 of air per day, to drink 1.6 L of water per day and to ingest 30 mg of soil per day (Health Canada 1998).

[9] No quantitative data were identified for concentrations of nitromethane in indoor air. One of 44 ambient air samples collected in downtown Porto Alegre, Brazil, during the period from March 20, 1996, to April 16, 1997, revealed a nitromethane concentration of 10.0 µg/m^3 (Grosjean et al. 1998). This ambient air concentration is used to represent indoor air also (therefore, exposure occurs 24 h/day).

[10] No quantitative data were identified for concentrations of nitromethane in drinking water. Nitromethane was detected in 4 of 10 American cities in a 1975 survey by the US EPA; however, it was not quantified.

[11] Estimates of intake from food are based upon the highest concentrations of nitromethane in foods from the only identified study to have reported the concentration of nitromethane in foods. A study by Alwis et al. (2008) "detected nitromethane levels ranging from 0.13–1.4 µg/L in fruit juices, 1% cow milk and soy milk (n = 9)." Since Alwis et al. (2008) reported the range of concentrations as applying to fruit juices, 1% cow milk and soy milk, without specifying which concentration applies to which food type, the concentration of 1.4 µg/L was conservatively assumed to be present in all dairy products, all fruits and fruit products, and all vegetables (including legumes). These are 3 of the 12 food categories that are addressed in calculating intake; the others, for which no data were identified, are fats, cereal products, meat and poultry, fish, eggs, foods primarily sugar, mixed dishes, nuts and seeds, and beverages (Health Canada 1998). The beverages measured in the Alwis et al. 2008 study were considered to apply more to those three food categories than the "beverages" category of the Health Canada 1998 document (e.g. alcohol, coffee, tea, powdered drinks, soft drinks, etc.).

[12] No quantitative data were identified for concentrations of nitromethane in soil.

Appendix 2: Upper-bounding inhalation exposure estimate for nitromethane volatilization from false nail remover

Consumer product	Assumptions	Exposure estimates
False nail remover	Maximum weight fraction: 0.25 (CNS 2009) Models available in the Exposure Assessment Strategies Committee Industrial Hygiene Model (1) Estimated evaporation rate using the Estimating Contaminant Generation Rate from Small Spills model: - overall system pressure of 1 atm - velocity of air of 2 cm/s (2009 email from reviewer from Toxicology Excellence for Risk Assessment to Risk Assessment Bureau, Health Canada; unreferenced) - surface temperature of pool of 25°C - surface area of pool of 9 cm^2 (assuming 20 g of substance and a depth of liquid of 2 cm to ensure full coverage of the nail bed) - length of pool of 3 cm ($\sqrt{9}$ cm^2) (2) Estimated time-weighted average concentration in air using the Well-Mixed Room Model with a Constant Emission Rate: - contaminant mass emission rate of 19.3 mg/min - room supply air exchange rate of 0.2 m^3/min (derived from 0.6/h ventilation rate for an unspecified room in RIVM 2006) - room volume of 20 m^3 (volume of unspecified room in RIVM 2006) - exposure duration of 30 min - percentage losses through sorption or chemical degradation of zero - initial concentration of nitromethane in air of 0 mg/m^3 - concentration of nitromethane in inflow air of 0 mg/m^3	Inhalation time-weighted average concentration: 13 mg/m^3

Appendix 3: Summary of health effects information for nitromethane

Endpoint	Lowest effect levels[1]/Results
Experimental animals and cells	
Acute toxicity	**Oral LD_{50}** (mouse) = 950–1440 mg/kg-bw (Weatherby 1955; Subbotin 1967) **Oral LD_{50}** (rat) = 940–1478 mg/kg-bw (Subbotin 1967; IMC 1980) **Oral LD_{50}** (rabbit) = 750 mg/kg-bw ≤ LD_{50} ≤ 1000 mg/kg-bw (Machle et al. 1940) **Oral LD_{50}** (dog) = 125 mg/kg-bw ≤ LD_{50} ≤ 250 mg/kg-bw (Weatherby 1955). Liver effects noted at 125 mg/kg-bw included mild fatty changes of the hepatic parenchyma and a few lymphocytes in the portal areas. **Oral LD_{50}** (human) = 500 mg/kg-bw (Gosselin et al. 1984) **Lowest inhalation LOEC:**2495 mg/m^3 was identified based on slight nasal congestion (1/4 animals) and transient weight loss (3/4 animals) in male albino rats exposed to nitromethane at 2495, 9980, 14 970 or 19 960 mg/m^3 for 4 h (Haskell Laboratory 1961). Weight loss and under-responsiveness were observed at 9980 mg/m^3, and deaths were observed at the two highest concentrations (1/4 and 3/4 animals, respectively). **Inhalation LCL_o** (rat) = 12.75 g/m^3; 1-h exposure (Baldwin 1956) **Inhalation LC_{100}** (rat) = 32.5 g/m^3; 6-h exposure (Dequidt et al. 1973) **Dermal LD_{50}** (rabbit) = >2000 mg/kg-bw (IMC 1980) **Intravenous LD_{50}** (rabbit) = 750 ≤ LD_{50} ≤ 1000 mg/kg-bw (Weatherby 1955) **Intravenous LD_{50}** (dog) = ≤3800 mg/kg-bw (Weatherby 1955)

Endpoint	Lowest effect levels[1]/Results
Short-term repeated-dose toxicity	**Lowest inhalation LOEC:** 235 mg/m^3 (94 ppm) was identified based on significantly increased absolute and relative liver weights of female B6C3F1 mice (5/group) exposed to nitromethane at 0, 235, 470, 938, 1875 or 3750 mg/m^3 (0, 94, 188, 375, 750 or 1500 ppm) for 6 h/day, 5 days/week, for 16 days (NTP, 1997). **Lowest inhalation LOAEC:** 938 mg/m^3 was identified based on minimal to moderate sciatic nerve degeneration, reduced sciatic axon myelination and hindlimb incoordination in male and female F344/N rats (5/group) exposed to nitromethane at 0, 235, 470, 938, 1875 or 3750 mg/m^3 (0, 94, 188, 375, 750 or 1500 ppm) for 6 h/day, 5 days/week, for 16 days. Rats, and male and female B6C3F1 mice (5/group) similarly exposed, also exhibited mild to minimal degeneration of the olfactory epithelium at ≥938 mg/m^3(NTP 1997). NOAEC: 470 mg/m^3. **Other inhalation studies:** Exposure to nitromethane at 245 mg/m^3 (98 ppm) for 7 h/day, 5 days/week, for 1 month resulted in depressed serum thyroxin and statistically significant elevated serum ornithine carbanyl transferase in male New Zealand White rabbits (5/group) and smaller lung weights in male Sprague-Dawley rats (10/group). At the highest concentration (1860 mg/m^3, or 745 ppm), rabbits experienced statistically significant depressed serum thyroxin (Lewis et al. 1979). **Lowest oral LOAEL:** 23.5 mg/kg-bw per day was identified based on liver impairment (decreased plasma prothrombin) in rats and rabbits consuming nitromethane (23.5, 47 or 94 mg/kg-bw per day) in drinking water for 2 months. Other effects included significantly increased activities of serum alanine and aspartate transaminase and significantly increased blood concentrations of α- and γ-globulin and cholinesterase (Subbotin 1967). **[**Other studies administered nitromethane to laboratory animals via the subcutaneous, intraperitoneal, intradermal or intravenous route and are not considered relevant to the evaluation of the health hazard of nitromethane (Lee and Wang 1975; Whitman et al. 1977; Douay and Kamoun 1980; Zitting et al. 1982; Dayal et al. 1989; Dutra-Filho et al. 1989).]

Endpoint	Lowest effect levels[1]/Results
Subchronic toxicity	**Lowest inhalation LOEC:** 235 mg/m^3 (94 ppm) was identified based on hyaline droplet formation in the respiratory epithelium of female B6C3F1 mice (2/10 animals) and significantly increased absolute and relative kidney weights in male mice after exposure to nitromethane at 0, 235, 470, 938, 1875 or 3750 mg/m^3 (0, 94, 188, 375, 750 or 1500 ppm) for 6 h/day, 5 days/week, for 13 weeks (NTP 1997). Female mice exposed to nitromethane at 470 mg/m^3 (188 ppm) exhibited minimal degeneration of the olfactory epithelium (7/10 animals), minimal hyaline droplet formation (9/10 animals) and significantly increased absolute kidney weights (NTP 1997). **Lowest inhalation LOAEC:** 938 mg/m^3 (375 ppm) was identified based on dose-dependent anemia and degeneration of the olfactory epithelium, sciatic nerve and lumbar spinal cord in both sexes of F344/N rats (10/group) exposed to nitromethane at 0, 235, 470, 938, 1875 or 3750 mg/m^3 for 6 h/day, 5 days/week, for 13 weeks. Exposure to ≥1875 mg/m^3 resulted in hindlimb paralysis, and hindlimb grip strength was significantly decreased in females at ≥1875 mg/m^3 and in males at 3750 mg/m^3. NOAEC: 470 mg/m^3 (NTP 1997). **Other inhalation studies:** A dose-dependent increase in absolute and relative thyroid weights occurred in male New Zealand White rabbits (5/group) and Sprague-Dawley rats (10/group) exposed to nitromethane at 0, 245 or 1860 mg/m^3 for 7 h/day, 5 days/week, for 6 months. In rabbits, significant depressed serum thyroxin at both doses was also observed (Lewis et al. 1979). **Lowest oral LOEL:** 0.5 mg/kg-bw per day was identified based on transient increases in the activities of serum alanine and aspartate transaminase [at 2-3 months] in rats and rabbits consuming nitromethane (0.05, 0.5 or 12.5 mg/kg-bw per day) in drinking water for 6 months (Subbotin 1967). **Lowest oral LOAEL:** 130 mg/kg-bw per day was identified based on the deaths of 4 male albino rats after consumption of nitromethane (0, 130 or 286 mg/kg-bw per day; 10/group) in drinking water for 15 weeks (Weatherby 1955). Rats consuming nitromethane lagged in weight gain; in the high dose group, 2 rats exhibited prominent splenic Malpighian corpuscles, and 6 rats exhibited hepatic cells with granular cytoplasm and prominent nuclei and numerous lymphocytes in the periportal areas.
Chronic toxicity/ carcinogenicity	**Inhalation carcinogenicity in rats:** Male and female F344/N rats (50/group) were exposed to nitromethane at 0, 135, 470 or 938 mg/m^3 (0, 94, 188 or 375 ppm) for 6 h/day, 5 days/week, for 103 weeks. Female rats exhibited a dose-related significant increase in the incidence of mammary gland fibroadenomas at 470 and 938 mg/m^3 (respective incidences of 66% and 72% versus 38% in the control group). The incidence of mammary gland carcinomas was significantly increased at 938 mg/m^3 (incidence of 22% versus 4% in the control group). No neoplastic lesions in male rats were attributed to exposure to nitromethane (NTP, 1997).

Endpoint	Lowest effect levels[1]/Results
	Inhalation carcinogenicity in mice: Male and female B6C3F1 mice (50/group) were administered nitromethane at 0, 470, 938 or 1875 mg/m^3 (0, 188, 375 or 750 ppm) for 6 h/day, 5 days/week, for 103 weeks. The incidence of Harderian gland adenoma was dose related and significantly increased in both sexes at 938 and 1875 mg/m^3 (respective incidences were 38% and 64% in males compared with 18% in the control and 32% and 38% in females compared with 10% in the control). The incidence of alveolar/bronchiolar carcinoma was significantly increased in female mice at 938 mg/m^3 (10% compared with 0% in the control) and significantly increased in male mice at 1875 mg/m^3 (22% compared to 4% in the control). The incidence of hepatocellular adenoma was significantly increased in female mice at 470 and 1875 mg/m^3 (respective incidences of 51%[2] and 70% compared with 28% in the control), but was not significantly increased at 938 mg/m^3 (incidence of 35%) (NTP 1997). **Non-neoplastic effects in mice:** In the same study described above, mild to moderate degeneration of the olfactory and respiratory epithelium occurred in both sexes of mice exposed to nitromethane at 938 and 1875 mg/m^3. Male mice also exhibited a significantly greater incidence of nasolacrimal duct inflammation compared with controls when exposed to nitromethane at ≥938 mg/m^3 (NTP 1997). **Inhalation carcinogenicity in rats:** Both sexes of BLU:(LE)BR rats (40/group) were exposed to nitromethane at 0, 250 or 500 mg/m^3 (0, 100 or 200 ppm) for 7 h/day, 5 days/week, for 2 years. No overt toxicity or carcinogenicity was noted[3] (Griffin et al. 1996). No oral or dermal studies were identified.
Reproductive toxicity	**Inhalation reproductive toxicity LOAEC: ≤**938 mg/m^3 was identified in a study with male and female B6C3F1 mice (10/group) exposed to nitromethane at 0, 235, 470, 938, 1875 or 3750 mg/m^3 (0, 94, 188, 375, 750 or 1500 ppm) for 6 h/day, 5 days/week, for 13 weeks. Statistically significant effects at ≥938 mg/m^3 included decreased sperm motility and increased estrous cycle length (NTP 1997). These endpoints were not examined at the lowest two exposure levels. No oral or dermal studies were identified.
Developmental toxicity	No oral, inhalation or dermal studies were identified.
Genotoxicity and related endpoints: *in vitro*	**Mutagenicity:** **Negative:** *Salmonella typhimurium* TA98, TA100, TA102, TA1535, TA1537 and TA1538 in the presence or absence of induced rat liver S9; nitromethane was tested at 0–50 mg/plate and 0–47 465 ppm [0-118.4g/m^3] (Brusick 1975; Chiu et al. 1978; Domoradzki 1980; Gocke et al. 1981; Lofroth et al. 1986; Mortelmans et al. 1986; Dayal et al. 1989; Dellarco and Prival 1989). **Sister chromatid exchange:**

Endpoint	Lowest effect levels[1]/Results
	Negative: Chinese hamster ovary (CHO) cells incubated with nitromethane at 4965 µg/mL in media with and without S9 (NTP 1997). **Micronuclei assay:** **Negative:** Syrian hamster embryos (SHEs) were incubated with nitromethane at 5–6 µg/mL in dimethylsulfoxide or at 3500–5000 µg/mL in Dulbecco's modified Eagle's medium (DMEM), without S9 (Gibson et al. 1997). **Chromosomal aberrations:** **Negative:** CHO cells were incubated with nitromethane at 1077, 2316 or 4980 µg/mL in McCoy's 5A medium with or without S9 (NTP 1997). **Cell transformation assay:** **Positive:** SHEs were incubated with nitromethane at 2000–5000 µg/mL in DMEM-Leboeuf's modification (DMEM-L) without S9. Morphological transformation was noted at the highest concentrations (4000 µg/mL [p = 0.0291] and 5000 µg/mL [p = 0.0027]) (Kerckaert et al. 1996).
Genotoxicity and related endpoints: *in vivo*	**Micronucleus tests:** **Negative:** No increase in micronucleated normochromatic erythrocytes (NCEs) was observed in the peripheral blood of male or female B6C3F1 mice exposed to nitromethane at 0, 235, 470, 938, 1875 or 3750 mg/m^3 (0, 94, 188, 375, 750 or 1500 ppm) for 6 h/day, 5 days/week, for 13 weeks (NTP 1997; Witt et al. 2000). There was a trend to higher frequency of micronucleated NCEs in males at 235 mg/m^3 (p = 0.006) that was not seen at higher concentrations. **Sex-linked recessive lethal mutation assay:** **Negative:** No significant increase in sex-linked recessive lethal mutations was observed in germ cells of male *Drosophila melanogaster* treated with nitromethane at 7625 µg/mL without S9 in feed (Gocke et al. 1981).
Humans	
Acute toxicity	Severe toxic effects in humans result after inhalation exposure to nitromethane at 1996 mg/m^3 for 1 h. Symptoms of illness result from exposure to nitromethane at 1248 mg/m^3 for "more than a short time." An air concentration greater than 499 mg/m^3 may be an unsatisfactory environment (Strafford et al. 1956). Further details were not available from the primary source.
Case report: two workers presenting to hospital reporting weakness and pain in the extremities	Workers exposed to nitromethane daily for 4–6 weeks via inhalation (8-h time-weighted average mean = 12.75 ppm [31.81 mg/m^3]) were diagnosed with severe peripheral neuropathy (Page et al. 2001). Exposures via the dermal route were not quantified. Exposures to ethyl cyanoacrylate (8-h TWA mean = 0.09 ppm [0.47 mg/m^3]) and methyl methacrylate (not quantified) were concurrent with exposure to nitromethane.
Case report: four workers who developed allergic	Workers were exposed to an unknown quantity of adhesive solvent containing nitromethane (Webb and Fowler 2002). Symptoms resolved upon discontinuation of handling the solvent.

Endpoint	Lowest effect levels[1]/Results
contact dermatitis on their hands	
Case report: one worker who presented to hospital with parkinsonism (hand and arm tremors) and severe depression	During a 2-year period, the worker was exposed via inhalation to a cleaning solution containing trichlorofluoroethane (94%), methanol (5.7%) and nitromethane (0.25%) (Sandyk and Gillman 1984). It was suggested that the symptoms were due to exposure to either nitromethane or methylisocyanide (the latter formed by reduction of nitromethane).

[1] LC_{100}, absolute lethal concentration; LCL_o, lowest lethal concentration; LD_{50}, median lethal dose; LOEL, lowest-observed-effect level; LOAEC, lowest-observed-adverse-effect concentration; LOAEL, lowest-observed-adverse-effect level; NOAEC, no-observed-adverse-effect concentration.

[2] Incidence reported as 49% (24/49) in IARC (2000); however, it is reported as 51% (25/49) elsewhere (see pages 9, 188 and 214 in NTP 1997).

[3] Male rats exposed to nitromethane at 250 mg/m^3 had a combined tumour incidence 3 times the rate of the control group (15 versus 5) and developed rare tumours such as bone marrow leukemia (2 cases) and colon lymphosarcoma (1 case). However, a combined tumour incidence of only 8 was noted in male rats exposed to nitromethane at 500 mg/m^3, and therefore a biological gradient for tumour induction was not established. Caveats of the study include the following: an outbred rat species with a high average body weight was used; smaller group sizes were used; only two doses of nitromethane were tested; and the high dose was not a maximum tolerated dose.

Appendix 4: Estimated margins of exposure for nitromethane

Exposure source and duration	Route of exposure	Concentration/ intake	Critical effect levels	Margin of exposure
Air (chronic)	Inhalation	0.010 mg/m^3 (Grosjean et al. 1998)	235 mg/m^3 – hyaline droplet formation and increased absolute and relative kidney weights in mice (subchronic LOEC) (NTP 1997)	23 500
			938 mg/m^3 – sciatic nerve and spinal cord degeneration in rats (subchronic LOAEC) (NTP 1997)	93 800
False nail remover (acute exposure)	Inhalation	13 mg/m^3 (time-weighted average concentration per event)	2495 mg/m^3 – slight nasal congestion in 1/4 rats and transient weight loss in 3/4 rats (acute LOEC) (Haskell Laboratory 1961)	190
			1248 mg/m^3 – "symptoms of illness" in humans if exposure more than a short time (acute LOEC) (Strafford et al., 1956)	100