Screening Assessment for the Challenge

Propane, 2-nitro-
(2-Nitropropane)

Chemical Abstracts Service Registry Number
79-46-9

Environment Canada
Health Canada

July 2010
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 propane, 2-nitro-, also known as 2-nitropropane, Chemical Abstracts Service Registry Number 79-46-9. This substance was identified in the categorization of the Domestic Substances List as a high priority for action under the Challenge. 2-Nitropropane was identified as a high priority as it was determined to present an intermediate potential for exposure of individuals in Canada and had been classified by other agencies on the basis of carcinogenicity. Although 2-nitropropane 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 relates primarily to human health risks.

According to information reported in response to a notice under section 71 of the *Canadian Environmental Protection Act, 1999* (CEPA 1999), no companies in Canada reported manufacturing 2-nitropropane in a quantity greater than or equal to the reporting threshold of 100 kg for the 2006 calendar year. According to information submitted by Canadian companies, the total quantity imported into Canada in 2006 was between 100 and 1000 kg. Potential sources of exposure identified in the publicly available literature include residual concentrations in vegetable oils for human consumption and pharmaceutical products, as well as formulated products including inks, paints, adhesives, varnishes, polymers, and synthetic materials that may contain 2-nitropropane.

The most significant sources of potential exposure to 2-nitropropane are likely to include inhalation of cigarette smoke and possibly the ingestion of vegetable oil that may contain residual concentrations of the substance. However, based on recent discussions that Health Canada has had with its stakeholders, 2-nitropropane is not used in vegetable oil processing in North America and, indeed, its use as a food processing solvent is discouraged internationally.

Other potential sources of exposure include food packaging and therapeutic products that may contain residual concentrations. However, there have been no recent food packaging submissions received by Health Canada’s Food Directorate that include the use of 2-nitropropane. Therefore, it is likely that 2-nitropropane has been replaced by other alternative solvents in food packaging applications.

The information available suggests that use of 2-nitropropane in paints and coatings is limited to a few specific industrial applications, thus no consumer exposure scenarios for use of paints and coatings were generated. The exposure of the general population as a result of the industrial use of 2-nitropropane within Canada is likely to be negligible.

Based principally on weight of evidence-based assessments of international and other national agencies, the critical effect for the characterization of risks to human health from exposure to 2-nitropropane is carcinogenicity. An increased incidence of liver tumours in experimental animals was reported in various studies. 2-Nitropropane induced benign and malignant liver tumours in rats in an oral study as well as multiple hepatocellular...
carcinomas in rats in an inhalation study. Metastases were also observed in the lungs of exposed animals. In addition, 2-nitropropane showed initiating activity in rat liver following intraperitoneal injection or inhalation exposures. 2-Nitropropane has also demonstrated clear evidence of genotoxicity in the liver of rats, the same organ in which tumours were found. Furthermore, studies have shown that the anionic form of 2-nitropropane, propane 2-nitronate, interacts directly with genetic material in the liver of rodents, and the enzymes that activate the metabolism in rodents also exist in human organs. The International Agency for Research on Cancer has also concluded that propane 2-nitronate may act as an intermediate in the mechanism by which 2-nitropropane exerts its genotoxic and carcinogenic effects.

On the basis of the carcinogenic potential of 2-nitropropane, for which there may be a probability of harm at any exposure level, it is concluded that 2-nitropropane is a substance that may be entering the environment in a quantity or concentration under conditions that constitute or may constitute a danger in Canada to human life or health. 2-Nitropropane 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 2-nitropropane is not entering the environment in a quantity or concentration 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 2-nitropropane meets one or more of 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 and, where appropriate, the performance of potential control measures identified during the risk management phase.
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; and/or
- met the categorization criteria for greatest potential for exposure (GPE) or presented an intermediate potential for exposure (IPE) and had been identified as posing a high hazard to human health based on classifications by other national or international agencies for carcinogenicity, genotoxicity, developmental toxicity or reproductive toxicity.

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

The substance 2-nitropropane 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 2-nitropropane 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 were received.

2-Nitropropane was determined to be a high priority for assessment with respect to human health. Although 2-nitropropane met the ecological categorization criteria for persistence, it did not meet the criteria for potential for bioaccumulation or inherent toxicity to aquatic organisms. Therefore, this assessment focuses principally on information relevant to the evaluation of risks to human health.
Screening assessments focus on information critical to determining whether a substance meets the criteria for defining a chemical as “toxic” as set out in section 64 of CEPA 1999. Screening assessments examine scientific information and develop conclusions by incorporating a weight-of-evidence approach and precaution.1

This final 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, reviews, assessment documents and stakeholder research reports, as well as from recent literature searches, up to August 2009 for the human health exposure and effects sections, and May 2010 for the ecological portions of the document. Key studies were critically evaluated; modelling results may have been used to reach conclusions. Evaluation of risk to human health involves consideration of data relevant to estimation of exposure (non-occupational) of the general population, as well as information on health hazards (based principally on the weight of evidence assessments of other agencies that were used for prioritization of the substance). Decisions for human health are based on the nature of the critical effect and/or margins between conservative effect levels and estimates of exposure, taking into account confidence in the completeness of the identified databases on both exposure and effects, within a screening context. The final 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 final 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 ecological and human health portions of this assessment have undergone external written peer review/consultation. Comments on the technical portions relevant to human health were received from scientific experts selected and directed by Toxicology Excellence for Risk Assessment (TERA), including Bernard Gadagbui (TERA), Pam Williams (E Risk Sciences) and Bob Benson (US Environmental Protection Agency [EPA]). 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 final assessment is based are summarized below.

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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 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 use.
Substance Identity

For the purposes of this document, this substance will be referred to as 2-nitropropane, as listed on the Domestic Substances List. Information on the identity of 2-nitropropane is summarized in Table 1.

Table 1. Substance identity

<table>
<thead>
<tr>
<th><strong>CAS RN</strong></th>
<th>79-46-9</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DSL name</strong></td>
<td>Propane, 2-nitro-</td>
</tr>
<tr>
<td><strong>NCI names</strong></td>
<td>Dimethylnitromethane&lt;br&gt;Isonitropropane&lt;br&gt;1-Methylnitroethane&lt;br&gt;2-Nitropropane (English, French) (DSL, ECL, EINECS, ENCS)&lt;br&gt;sec-Nitropropane&lt;br&gt;2-NP&lt;br&gt;NSC 5369&lt;br&gt;Propane, 2-nitro- (AICS, ASIA-PAC, DSL, NZIoC, PICCS, SWISS, TSCA)&lt;br&gt;UN 2608&lt;br&gt;UN 2608 (DOT)</td>
</tr>
<tr>
<td><strong>Other names</strong></td>
<td>Nitroisopropane&lt;br&gt;beta-Nitropropane</td>
</tr>
<tr>
<td><strong>Chemical group</strong></td>
<td>Discrete organics</td>
</tr>
<tr>
<td><strong>Major chemical class</strong></td>
<td>Low molecular weight hydrocarbons</td>
</tr>
<tr>
<td><strong>Chemical formula</strong></td>
<td>C₃H₇NO₂</td>
</tr>
<tr>
<td><strong>Chemical structure</strong></td>
<td><img src="image" alt="Chemical Structure" /></td>
</tr>
<tr>
<td><strong>SMILES</strong></td>
<td>N(=O)(=O)C(C)C</td>
</tr>
<tr>
<td><strong>Molecular mass</strong></td>
<td>89.1 g/mol</td>
</tr>
</tbody>
</table>

Abbreviations: AICS, Australian Inventory of Chemical Substances; ASIA-PAC, Asia-Pacific Substances Lists; CAS RN, Chemical Abstracts Service Registry Number; DSL, Domestic Substances List; ECL, Korean Existing Chemicals List; EINECS, European Inventory of Existing Commercial Chemical Substances; ENCS, Japanese Existing and New Chemical Substances; NCI, National Chemical Inventories; NZIoC, New Zealand Inventory of Chemicals; 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 2009
Physical and Chemical Properties

A summary of key physical and chemical properties of 2-nitropropane that are relevant to its environmental fate is presented in Table 2.

Table 2. Physical and chemical properties of 2-nitropropane

<table>
<thead>
<tr>
<th>Property</th>
<th>Type</th>
<th>Value</th>
<th>Rating</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melting point (°C)</td>
<td>Experimental</td>
<td>−93.0</td>
<td></td>
<td>Howard 1990</td>
</tr>
<tr>
<td>Boiling point (°C)</td>
<td>Experimental</td>
<td>120.2</td>
<td></td>
<td>Lide 2000</td>
</tr>
<tr>
<td>Density (kg/m³ at 25°C)</td>
<td>Experimental</td>
<td>982.1 (0.9821 g/ml)</td>
<td></td>
<td>Budavari 2001</td>
</tr>
<tr>
<td>Vapour pressure (Pa at 25°C)</td>
<td>Experimental</td>
<td>2.29 × 10⁴ (17.2 mmHg)</td>
<td>High</td>
<td>Daubert &amp; Danner 1989</td>
</tr>
<tr>
<td>Henry’s Law constant (Pa·m³/mol)</td>
<td>Estimated</td>
<td>12.1 (1.19 × 10⁻⁴ atm·m³/mol)</td>
<td>Moderate</td>
<td>PhysProp 2006</td>
</tr>
<tr>
<td>Water solubility (mg/L at 25°C)</td>
<td>Experimental</td>
<td>17 000*</td>
<td>Very high</td>
<td>Budavari 2001</td>
</tr>
<tr>
<td>Log K_{ow} (dimensionless)</td>
<td>Experimental</td>
<td>0.93*</td>
<td>Low</td>
<td>CITI 1992</td>
</tr>
<tr>
<td>Log K_{oc} (dimensionless)</td>
<td>Modelled</td>
<td>1.489–1.659</td>
<td>Low</td>
<td>KOCWIN 2008</td>
</tr>
<tr>
<td>Log K_{oa} (dimensionless)</td>
<td>Modelled</td>
<td>3.243</td>
<td></td>
<td>KOAWIN 2004</td>
</tr>
<tr>
<td>pK_{a} (dimensionless)</td>
<td>Modelled</td>
<td>8.44</td>
<td></td>
<td>ACD/pK_{a}DB 2005</td>
</tr>
</tbody>
</table>

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

1 Values in parentheses represent the original values reported by the authors or estimated by the models. Values marked with an asterisk (*) were selected for modelling.

Sources

2-Nitropropane may enter the environment as a result of anthropogenic activities. The role that natural processes might play in the formation of 2-nitropropane is unclear. The substance may be formed during the combustion of nitrogen-rich organic material, as is the case with cigarette smoke (Hoffman and Rathkamp 1968); however, no studies characterizing this potential exposure source were identified.

Vapour-phase production methods for nitroparaffins, including 2-nitropropane, were developed in the 1930s (Bollmeier 2000). In 1992, two North American facilities producing 2-nitropropane were identified in the Environmental Health Criteria monograph published by the World Health Organization (WHO): ANGUS Chemical

According to data submitted in response to a notice published under section 71 of CEPA 1999, no companies in Canada reported manufacturing 2-nitropropane in a quantity greater than or equal to the reporting threshold of 100 kg for the 2006 calendar year. Information received from Canadian companies indicated the importation of 100–1000 kg in 2006 (Environment Canada 2008a). One submitter, a waste management company, indicated the importation of 2-nitropropane in 2006 for consolidation and incineration at a hazardous waste facility.

The information provided by industry indicates no domestic manufacture of this substance and importation of only small quantities (100–1000 kg). However, 2-nitropropane may be entering Canada in formulated products, including inks, paints, adhesives, varnishes, polymers and synthetic materials (NTP 2005), that may not be fully captured under section 71 reports.

Uses

2-Nitropropane is used as a solvent and chemical intermediate (NTP 2005). As a solvent, it may be used in vinyl inks, electrostatic paints, adhesives, varnishes, polymers and synthetic materials (IARC 1999; NTP 2005). 2-Nitropropane may be used to dissolve a large number of resins; these solvent–resin mixtures have reportedly found use as coatings in the lining of beverage cans (IARC 1999).

2-Nitropropane is also reportedly used as a component of explosives and propellants and in fuels for internal combustion engines (NTP 2005). Further reported applications include use in vinyl, epoxy, nitrocellulose and chlorinated rubbers, printing inks and adhesives, highway maintenance (traffic markings) and marine coatings (NIOSH 1980). Additionally, 2-nitropropane may be used in paint and varnish removers, as an intermediate in the synthesis of pharmaceuticals, dyes and insecticides, as a smoke depressant in diesel fuel and as an additive to racing car fuels (HSDB 2006).

It is acknowledged that the information that has been presented in published reviews to characterize the uses of this substance may be somewhat dated and may not reflect the current uses in Canada. In developing exposure scenarios in the following sections, consideration has been given to the corroboration and support provided by information obtained from Canadian companies and other sources in the public literature.

Recent data submitted to the US EPA under the High Production Volume (HPV) Challenge Program by the principal North American manufacturer of 2-nitropropane indicate that less than 16 000 kg annually is diverted for sale to external customers. Approximately 0.9 million kilograms are shipped in bulk to another of the manufacturer’s facilities in Europe for use as a chemical intermediate in other processes. The
manufacturer suggests that 2-nitropropane sold externally to customers is primarily for use as a taggant in C-4 explosives and also for use by laboratories for research and development (Dow 2007).

With respect to use as a solvent in painting and coating products, Bollmeier (2000) suggested that quantities of up to 9100 tonnes of 2-nitropropane per year had been consumed by the coatings industry in the past, but that concerns regarding toxicity and a shift towards coatings with a lower content of volatile organic compounds had resulted in “an almost complete disappearance of this use for 2-nitropropane.” This assertion is supported by the presence of 2-nitropropane on the list of excluded ingredients published by the European Printing Ink Association (EuPIA 2007).

However, sources in the publicly available literature do indicate continued use in certain paint and coating applications including laquers, primers, and heat resistant paints. The products identified as containing 2-nitropropane appear to be for industrial or commercial use.

2-Nitropropane may also be found as a residual in other nitroparaffins and nitroparaffin derivatives. A publicly available material safety data sheet for nitroethane indicated a residual concentration of 2-nitropropane in the range of 0–4% (Anachemia 2007). The technical data sheet for a nitroparaffin-derived product with application in chemical syntheses as a stabilizer, free-radical scavenger and polymerization terminator, indicates that this product contains a residual (>0.02%) concentration of 2-nitropropane (ANGUS Chemical Company 2000).

With respect to food packaging applications, 2-nitropropane has reportedly been used in printing inks and adhesives (WHO 1992; NTP 2005). 2-Nitropropane is approved in the United States for use in food packaging adhesives under Code of Federal Regulations Title 21, Part 175, Section 105 (ECFR 2009). As well, 2-nitropropane may have use in the production of linings for beverage cans (WHO 1992). However, Health Canada’s Food Directorate has indicated that no use of 2-nitropropane in food packaging applications has been reported in Canada for at least 10 years (2009 personal communication from Food Directorate, Health Canada, to Risk Assessment Bureau, Health Canada; unreferenced).

In Canada, 2-nitropropane is permitted for use in the fractionation of vegetable oils intended for human consumption under the Food and Drug Regulations (Part B, Division 16, Table XV) (Canada 1978), with a maximum allowable residual concentration of 0.5 mg/kg. However, recent communications with industry stakeholders indicate that 2-nitropropane is not used in vegetable oil processing in Canada or the United States (2009 personal communication from Food Directorate, Health Canada, to Risk Assessment Bureau, Health Canada; unreferenced).

The Joint Food and Agriculture Organization of the United Nations (FAO)/WHO Expert Committee on Food Additives (JECFA), an international expert body on the safety of food additives, decided at its 35th meeting in 1989 that its previous temporary acceptance
of 2-nitropropane as a fractionating solvent in the production of fats and oils should not be extended (WHO 1990a). In 1992, the Environmental Health Criteria monograph published by WHO concluded that 2-nitropropane should not be used in food processing (WHO 1992).

2-Nitropropane is not currently listed on Health Canada’s Cosmetic Ingredient Hotlist, which would prohibit its use in cosmetic products (Health Canada 2007). However, the European Commission has listed this substance under Annex II of the Cosmetic Ingredients and Substances list, indicating that it must not form part of the composition of a cosmetic product in the European Union (CosIng 2009).

In Canada, 2-nitropropane is not listed in the Drug Product Database, the Natural Health Products Ingredients Database or the Licensed Natural Health Products Database as a medicinal ingredient or non-medicinal ingredient in final pharmaceutical products, natural health products or veterinary drugs (Health Canada 2009a, b, c). However, as 2-nitropropane is marketed as a chemical intermediate for pharmaceutical synthesis under the brand name SYNTHATANE™ NP 200 (Green and Johnson 2000; ANGUS Chemical Company 2009), 2-nitropropane may be present in trace amounts in pharmaceuticals.

The Controlled Products Regulations established under the Hazardous Products Act require that 2-nitropropane be disclosed on a material safety data sheet when it is present at a concentration of 0.1% or greater, as specified on the Ingredient Disclosure List (Canada 1988).

**Releases to the Environment**

2-Nitropropane is not manufactured in reportable quantities in Canada. In 2006, 2-nitropropane was imported by a hazardous waste management company (Environment Canada 2008a). The notifier indicated that the imported material was consolidated with compatible waste and incinerated at an incineration facility operated by the company.

2-Nitropropane is a core substance reportable under the National Pollutant Release Inventory (NPRI) program, meaning that any facility meeting the reporting criteria that has manufactured, processed or otherwise used more than 10 tonnes of material containing greater than 0.1% 2-nitropropane is required to report. No domestic releases were reported to NPRI between 1997 and 2007 (the most recent data available). In 1994, 1995 and 1996, Waltec Plastics of Midland, Ontario, reported total on-site releases of 0.125 tonne/year; the medium of release was not specified (NPRI 2007). Additionally, no releases to the environment were reported for 2006 under section 71 of CEPA 1999 (Environment Canada 2008a).

The Great Lakes Commission, representing the Province of Ontario and the eight Great Lakes states, publishes annual reports on toxic air emissions in the Great Lakes region. Total estimated releases of 2-nitropropane to air in the region in 2001 and 2002 were 71.7 kg and 83.0 kg, respectively. The contribution to these release estimates from Ontario
was approximately 10.4 kg in 2001 and 11.3 kg in 2002 (GLC 2004, 2006). Release estimates in Ontario are based on two sources: a per capita emission factor intended to address releases of solvents from consumer and commercial use of adhesives and sealants, and an emission factor for wastewater treatment. Both emission factors are derived from guidance published by the US EPA (2009 personal communication from Ontario Ministry of the Environment to Risk Assessment Bureau, Health Canada; un referenced).

2-Nitropropane is identified as an HPV chemical in the United States. Quantity information submitted under the Inventory Update Reporting system in the United States indicates that between 4.5 million and 22.7 million kilograms of the chemical was produced or imported in 2002; however, 2-nitropropane does not appear in the non-confidential 2006 Inventory Update Report (US EPA 2009). In the United States, the Toxics Release Inventory (TRI) database indicates on-site releases from eight facilities totalling 11 725 kg in 2007. The manufacturing facility in Sterlington, Louisiana, accounts for more than 96% of the total releases (TRI 2009).

With respect to environmental releases arising from combustion of nitrogen-rich organic material, such as forest fires and wildfires, no data were identified.

**Environmental Fate**

The acid pKa of 8.44 is near the high end of the normal pH range for surface waters (6–9) so 2-nitropropane is expected to occur mainly in the neutral form in the environment.

Based on its physical and chemical properties (Table 2), the results of Level III fugacity modelling (Table 3) indicate that 2-nitropropane will reside predominantly in the medium to which it is released. The main receiving compartment is expected to be air.

**Table 3. Results of the Level III fugacity modelling for the neutral form of 2-nitropropane (EQC 2003)**

<table>
<thead>
<tr>
<th>Substance released to:</th>
<th>Air</th>
<th>Water</th>
<th>Soil</th>
<th>Sediment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Air (100%)</td>
<td>83.4</td>
<td>15.1</td>
<td>1.54</td>
<td>0.03</td>
</tr>
<tr>
<td>Water (100%)</td>
<td>5.77</td>
<td>93.9</td>
<td>0.11</td>
<td>0.20</td>
</tr>
<tr>
<td>Soil (100%)</td>
<td>8.48</td>
<td>24.1</td>
<td>67.4</td>
<td>0.05</td>
</tr>
</tbody>
</table>
Persistence and Bioaccumulation Potential

Environmental Persistence

Table 4a presents the empirical data for the persistence of 2-nitropropane.

<table>
<thead>
<tr>
<th>Medium</th>
<th>Fate process</th>
<th>Degradation value</th>
<th>Degradation endpoint (units)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Air</td>
<td>Photooxidation</td>
<td>41.13</td>
<td>Half-life (days)</td>
<td>Atkinson 1989</td>
</tr>
<tr>
<td>Air</td>
<td>Photolysis</td>
<td>9.8</td>
<td>Half-life (days)</td>
<td>Wallington et al. 1990</td>
</tr>
<tr>
<td>Air</td>
<td>Photolysis</td>
<td>67.8</td>
<td>% degradation after 24 hours</td>
<td>Coulston and Korte 1987</td>
</tr>
<tr>
<td>Water</td>
<td>Biodegradation</td>
<td>0.1</td>
<td>% BOD at 28 days</td>
<td>Freitag et al. 1990</td>
</tr>
<tr>
<td>Water</td>
<td>Biodegradation</td>
<td>8</td>
<td>% BOD at 28 days</td>
<td>NITE 2002</td>
</tr>
<tr>
<td>Water</td>
<td>Biodegradation</td>
<td>14</td>
<td>% BOD at 28 days</td>
<td>NITE 2002</td>
</tr>
<tr>
<td>Soil (aerobic)</td>
<td>Biodegradation (aerobic)</td>
<td>3.0</td>
<td>% conversion to CO₂ at 35 days</td>
<td>Freitag et al. 1988</td>
</tr>
<tr>
<td>Soil (acidic)</td>
<td>Biodegradation (aerobic)</td>
<td>0.66</td>
<td>Half-life (days)</td>
<td>Freitag et al. 1988</td>
</tr>
<tr>
<td>Soil</td>
<td>Biodegradation (aerobic)</td>
<td>3.5</td>
<td>Half-life (days)</td>
<td>Freitag et al. 1988</td>
</tr>
</tbody>
</table>

Abbreviation: BOD, biological oxygen demand.

1 Test concentration = 9.9 mg/L
2 Test concentration = 2.0 mg/L

The empirical photooxidation data (half-life in air of 41 days, Table 4a) indicates that the chemical is relatively stable in air. A study by Wallington et al. (1990) found a half-life in air of 9.8 days but the results appear to be based on rate constants for the reaction with chlorine atoms. Another study shows that 2-nitropropane absorbs ultraviolet radiation and undergoes rapid photodissociation, with 67.8% of the substance being reported to be degraded after 24 hours (Coulston and Korte 1987). Using first-order kinetic rate equation, this result gives a half-life in air of 1.78 days. Therefore, 2-nitropropane is not likely to persist in air.
A number of studies provide data for the biodegradation of 2-nitropropane in water (see Table 4a above). The results, ranging from 0.1 to 14 % BOD in 28 days, seem to indicate that 2-nitropropane does not biodegrade readily in water, However, very few details are available for two of the studies (NITE 2002) and there is a concern about volatilization for all three of the experimental biodegradation results presented in Table 4a.

There are a number of studies that provide data for the biodegradation of 2-nitropropane in soil (see Table 4a above). As with the studies for biodegradation in water, there is a concern about volatilization, which was reported to be almost 30% in the 35 day study. There is additional uncertainty associated with the results because of evidence that 2-nitropropane has adverse effects on bacteria (Kido et al. 1975) although the concentration of 2-nitropropane that was found to inhibit bacteria in that study was relatively high (500 mg/L).

Although there are experimental data for the degradation of 2-nitropropane, a quantitative structure–activity relationship (QSAR)-based weight of evidence approach (Environment Canada 2007) was also applied using the degradation models shown in Table 4b below. 2-Nitropropane 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 2-nitropropane

<table>
<thead>
<tr>
<th>Fate process</th>
<th>Model and model basis</th>
<th>Model result and prediction</th>
<th>Extrapolated half-life (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AIR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atmospheric oxidation</td>
<td>AOPWIN 2000</td>
<td>$t_{1/2} = 63.6$ days (12 hr. days)</td>
<td>n/a (degradation by photolysis is much more rapid.</td>
</tr>
<tr>
<td>Ozone reaction</td>
<td>AOPWIN 2000</td>
<td>n/a¹</td>
<td>n/a</td>
</tr>
<tr>
<td>WATER</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hydrolysis</td>
<td>HYDROWIN 2000</td>
<td>n/a¹</td>
<td>n/a</td>
</tr>
<tr>
<td>Biodegradation (aerobic)</td>
<td>BIOWIN 2000 Submodel 3: Expert Survey (ultimate biodegradation)</td>
<td>3.00² “biodegrades fast”</td>
<td>&lt; 182</td>
</tr>
<tr>
<td>Biodegradation (aerobic)</td>
<td>BIOWIN 2000 Submodel 4: Expert Survey (primary biodegradation)</td>
<td>3.72² “biodegrades fast”</td>
<td>&lt; 182</td>
</tr>
<tr>
<td>Biodegradation (aerobic)</td>
<td>BIOWIN 2000 Submodel 5: MITI linear probability</td>
<td>0.39³ “biodegrades fast”</td>
<td>&lt; 182</td>
</tr>
<tr>
<td>Biodegradation (aerobic)</td>
<td>BIOWIN 2000 Submodel 6: MITI non-linear probability</td>
<td>0.47³ “biodegrades fast”</td>
<td>&lt; 182</td>
</tr>
<tr>
<td>Biodegradation (aerobic)</td>
<td>TOPKAT 2004 Probability</td>
<td>0.95⁴ “biodegrades fast”</td>
<td>&lt; 182</td>
</tr>
<tr>
<td>Biodegradation (aerobic)</td>
<td>CPOPs 2008 % BOD</td>
<td>% BOD = 5.6 “biodegrades slowly”</td>
<td>≥ 182</td>
</tr>
</tbody>
</table>

Abbreviations: BOD, biological oxygen demand; MITI, Ministry of International Trade & Industry, Japan; n/a, not applicable; $t_{1/2}$, half-life.

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

² Output is a numerical score from 0 to 5.
In air, a predicted atmospheric oxidation half-life value of 64 days (see Table 4b above) is consistent with the empirically-based estimate (Table 4a), indicating that this substance is likely to be slowly oxidized. 2-Nitropropane is not expected to react with other photo-oxidative species in the atmosphere, such as ozone. However, based on the expected rapid degradation by photolysis, 2-nitropropane is considered to be "not persistent" in air.

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 2-nitropropane, do not have nitro groups. BIOWIN does not have compounds with aliphatic nitro groups in the training set.

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

**Potential for Bioaccumulation**

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

Table 5a presents the empirical bioconcentration factor (BCF) values for a fish and an alga.

**Table 5a. Empirical data for bioaccumulation of 2-nitropropane**

<table>
<thead>
<tr>
<th>Test organism</th>
<th>Endpoint</th>
<th>Value (L/kg wet weight)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common carp</td>
<td>BCF</td>
<td>&lt;8.4</td>
<td>NITE 2002</td>
</tr>
<tr>
<td>Green algae</td>
<td>BCF</td>
<td>19.95</td>
<td>Freitag <em>et al.</em> 1985</td>
</tr>
</tbody>
</table>

Since no experimental bioaccumulation factor (BAF) data and few BCF data for 2-nitropropane were found, a predictive approach was applied using available BAF and BCF models, as shown in Table 5b.

**Table 5b. Modelled data for bioaccumulation of 2-nitropropane**

<table>
<thead>
<tr>
<th>Test</th>
<th>Endpoint</th>
<th>Value (L/kg wet weight)</th>
<th>Reference</th>
</tr>
</thead>
</table>

3 Output is a probability score.
The modified Gobas BAF middle trophic level model for fish predicted a BAF of 1.47 L/kg, indicating that 2-nitropropane does not have the potential to bioconcentrate in fish and to biomagnify in food webs. 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, 2-nitropropane does not meet the bioaccumulation criteria (BAF or BCF ≥5000) as set out in the *Persistence and Bioaccumulation Regulations* (Canada 2000).

<table>
<thead>
<tr>
<th>organism</th>
<th>BAF</th>
<th>BCF</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fish</td>
<td>1.47</td>
<td>1.38</td>
<td>Arnot and Gobas 2003 (Gobas BAF middle trophic level)</td>
</tr>
<tr>
<td>Fish</td>
<td>4.51</td>
<td>3.16</td>
<td>CPOPs 2008</td>
</tr>
<tr>
<td>Fish</td>
<td></td>
<td></td>
<td>BCFWIN 2000</td>
</tr>
</tbody>
</table>
There is experimental and modelled evidence that 2-nitropropane does not cause acute harm to aquatic organisms at low concentrations (see Tables 6a and 6b).

An OECD Guideline 202 test performed with *Daphnia magna* indicates that the 24-hour EC$_{50}$ value in this species is 290 mg/L (Coulston and Korte 1987). This is considered to indicate low acute toxicity. Other experimental results for less sensitive species (zebrafish and algae) are shown as well in Table 6a. There is however some uncertainty associated with these empirical results because of the potential for loss of 2-nitropropane from the test systems by volatilization.

![Table 6a. Empirical data for aquatic toxicity of 2-nitropropane in aquatic organisms](image)

<table>
<thead>
<tr>
<th>Test organism</th>
<th>Test type</th>
<th>Endpoint</th>
<th>Value (mg/L)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zebrafish</td>
<td>Acute (48 hours)</td>
<td>LC$_{50}$</td>
<td>620</td>
<td>Coulston and Korte 1987</td>
</tr>
<tr>
<td>Daphnids</td>
<td>Acute (24 hours)</td>
<td>EC$_{50}$</td>
<td>290</td>
<td>Coulston and Korte 1987</td>
</tr>
<tr>
<td>Algae</td>
<td>Acute (72-hour)</td>
<td>EC$_{50}$</td>
<td>1088</td>
<td>Coulston and Korte 1987</td>
</tr>
</tbody>
</table>

Abbreviations: EC$_{50}$ (median effective concentration), the concentration of a substance that is estimated to cause some toxic sublethal effect on 50% of the test organisms; LC$_{50}$ (median lethal concentration), the concentration of a substance that is estimated to be lethal to 50% of the test organisms.

A range of aquatic toxicity predictions were obtained from the various QSAR models considered. These results are consistent with the empirical data, indicating that the substance is not highly hazardous to aquatic organisms (acute LC/EC$_{50}$ $>>$ 1.0 mg).

As 2-nitropropane 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 (2008b) 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). 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 3,456 m$^3$/day. Based on the above assumptions, industrial use of the substance at a total quantity of between 100 and 1000 kg/year for industrial use yields an aquatic concentration of 0.0007 mg/L (Environment Canada 2009).

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.

2-Nitropropane is not expected to be persistent in any medium. It is expected to have a low bioaccumulation potential. The importation volumes of 2-nitropropane into Canada, along with information on its uses, indicate potential for low releases into the Canadian environment. Once released into the environment, 2-nitropropane can be found in air, water or soil, depending on the medium of release. Based on experimental and modelled results, 2-nitropropane is expected to have low potential for toxicity to aquatic organisms.

A risk quotient analysis, integrating conservative estimates of exposure with ecotoxicity 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 0.0007 mg/L (Environment Canada 2009). A predicted no-effect concentration (PNEC) was derived by dividing the acute toxicity value of 290 mg/L for daphnids by an assessment factor of 100 (10 to account for interspecies and intraspecies variability in sensitivity and 10 to estimate a long-term no-effects concentration from a short-term EC$_{50}$) to give a value of 2.9 mg/L. The resulting risk quotient (PEC/PNEC) is 0.0002 (0.0007/2.9). Therefore, harm to aquatic organisms from 2-nitropropane is unlikely.

Based on the information available, 2-nitropropane is unlikely to be causing ecological harm in Canada.

**Uncertainties in Evaluation of Ecological Risk**

There is uncertainty associated with the use of QSAR models to estimate persistence, bioaccumulation potential, and aquatic toxicity. For this reason when empirical and model results were in conflict, greater weight was typically assigned to the empirical data.
Uncertainty exists because of the lack of information on environmental concentrations (e.g., monitoring data) of 2-nitropropane in Canada, or elsewhere. There are also uncertainties associated with the fraction of 2-nitropropane 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.

Although no information is available on the quantity of 2-nitropropane that is imported in consumer products, it is anticipated that given the diffuse nature of the releases the concentrations of 2-nitropropane in the various environmental media would not be significantly different.

Potential to Cause Harm to Human Health

Exposure Assessment

Environmental Media and Food

No measurements of 2-nitropropane in the Canadian environment were identified. No domestic releases were reported to NPRI between 1997 and 2007 (the most recent data available) (NPRI 2007). The Ontario Ministry of the Environment estimated releases in Ontario for 2001 and 2002 to be approximately 10 kg/year (GLC 2004, 2006). Based on these very small release estimates, predicted concentrations of 2-nitropropane in air and water would be very low, at approximately 1.95 ng/m$^3$ and 1.22 ng/L, respectively (ChemCAN 2003).

The US National-Scale Air Toxics Assessment (NATA) program has published estimated ambient concentrations for 177 air pollutants, including 2-nitropropane. Although not directly informative to the potential exposure of Canadians, these estimates do provide an indication of the relative magnitude of exposure that would be expected both near and distant from point source emissions. In the most recent publication (US EPA 2006), the vast majority (99.7%) of ambient concentration estimates in the NATA tables were less than 1 ng/m$^3$. The maximum estimated ambient concentration was 75.3 ng/m$^3$.

Given the very small release estimates made by the Ontario Ministry of the Environment, the low ambient concentrations predicted by the US EPA both near and away from point sources and the small import quantities reported by Canadian companies (Environment Canada 2008a), it seems unlikely that Canadians are exposed to appreciable concentrations of 2-nitropropane from ambient air.

The US National Tap Water Quality Database, maintained by the Environmental Working Group, identified one municipality in the United States in which 2-nitropropane was detected in drinking water. The database indicated that in one of three tests conducted by the Upper Southampton Municipal Authority between 1998 and 2002, 2-nitropropane was present at a detectable level (3.43 µg/L). The database also indicated that 2-nitropropane is not frequently tested for, with only 211 of 39 751 suppliers in their database reporting tests for this chemical (EWG 2009). No Canadian data were available;
however, there is no evidence to suggest that drinking water would be a significant source of exposure for this substance.

In Canada, 2-nitropropane is permitted for use as a carrier or extraction solvent for vegetable oils with a maximum residue level of up to 0.5 mg/kg (0.5 ppm) of 2-nitropropane. However, because industry stakeholders have indicated that it is no longer used for this purpose in North America (2009 personal communication from Food Directorate, Health Canada, to Risk Assessment Bureau, Health Canada; unreferenced) exposure estimates were not generated based on the permitted maximum residue specified in the Food and Drug Regulations. Indeed, the use of 2-nitropropane as a food processing solvent is also discouraged internationally. Nonetheless, to account for the possibility that 2-nitropropane may be present in vegetable oils imported into Canada, an assessment of the potential exposure from vegetable fats and oils was conducted. JECFA has previously characterized the potential exposure associated with consumption of vegetable oil processed with 2-nitropropane. At its 35th meeting in 1989, JECFA noted that procedures used at that time for the processing of fats and oils with 2-nitropropane did not lead to detectable levels of this substance in the finished product; thus, their assessment was based on the assumption that all oil may contain 2-nitropropane at the detection limit of 10 µg/kg (WHO 1990a). It was very conservatively assumed that all vegetable fats and oils from all food sources ingested by Canadians may contain this concentration of 2-nitropropane. Based on the consumption data available for vegetable fats and oils from all food sources, the calculated mean daily intake of 2-nitropropane ranged from 0.0023 to 0.0078 µg/kg body weight (kg-bw) per day (Appendix 1). As the use of 2-nitropropane is permitted only as a carrier or extraction solvent for vegetable oils, intake estimates based on consumption of all vegetable fats and oils are likely to overestimate exposure. Note that if estimates of daily intake were based on the maximum residual concentration permitted under Canadian regulation, the estimates would be 50-fold higher.

The WHO Environmental Health Criteria monograph (WHO 1992) describes an additional existing intake estimate made by the US Food and Drug Administration (FDA) in 1983 (Modderman 1983), suggesting that daily intake from residual concentrations in vegetable oil would be 0.030 µg. A detailed description of the basis for this estimate was not provided. WHO (1992), referring to the same 1983 estimate (Modderman 1983), indicated that when 2-nitropropane was used for processing of vegetable oil, residual concentrations of up to 204 µg/kg have been detected. As noted above, industry stakeholders have indicated that 2-nitropropane is no longer used in North America for the processing of vegetable oils; as well, this use is no longer supported by JECFA.

2-Nitropropane has found use in printing inks for flexible food packaging, as a solvent in coatings for beer and beverage cans, and in film laminating adhesives (WHO 1992; NTP 2005). In the 11th Report on Carcinogens, the US National Toxicology Program (NTP 2005) refers to the exposure estimate made by the US FDA in 1983 (Modderman 1983), which suggested a potential daily intake of 0.1 µg of 2-nitropropane per person as a result of its presence in food, food additives and food packaging. The worst-case estimate of the contribution from food packaging was estimated to be 0.036 µg/day, arising from
beverage can coatings, film laminating adhesives and printing inks (NTP 2005). 2-Nitropropane is approved in the United States for use in food packaging adhesives, under Code of Federal Regulations Title 21, Part 175, Section 105 (ECFR 2009). However, there have been no recent food packaging submissions received by Health Canada’s Food Directorate that include the use of 2-nitropropane. Therefore, it is likely that 2-nitropropane has been replaced by other alternative solvents in food packaging applications (2009 personal communication from Food Directorate, Health Canada, to Risk Assessment Bureau, Health Canada; unreferenced). Therefore, no exposure scenario was generated for food packaging applications of 2-nitropropane.

In an investigation of tobacco smoke composition, Hoffman and Rathkamp (1968) reported amounts of 2-nitropropane of 1.1–1.2 µg in the smoke from one 85-mm US-blended unfiltered cigarette. The authors suggested that production of nitroaliphatic substances is a result of interaction between hydrocarbons and nitrogen dioxide in the combustion zone. Based on a review of the available literature (Hoffman and Rathkamp 1968; Hoffman and Hoffman 1997; Hoffman et al. 2001; Rodgman 2003; Gaworski et al. 2008; Patskan et al. 2008), 1.2 µg/cigarette was deemed to be a reasonable worst-case estimate of 2-nitropropane emissions in mainstream smoke, as it was obtained from a study of United States blended, unfiltered cigarettes. Using the mean smoking frequency data collected through the Canadian Tobacco Use Monitoring Survey (CTUMS 2008), the estimated exposure of smoking youths (aged 15–19; 12.2 cigarettes/day), young adults (aged 20–24; 12.2 cigarettes/day) and adults (aged >25; 14.9 cigarettes/day) to 2-nitropropane in Canada is predicted to be 0.25, 0.21 and 0.25 µg/kg-bw per day, respectively (Appendix 2).

2-Nitropropane is marketed for use in the synthesis of pharmaceutical ingredients (ANGUS Chemical Company 2009). Solvent residue limits specific for 2-nitropropane were not available from the Health Canada Therapeutic Products Directorate or Guideline Q3C(R4) of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH 2009). As 2-nitropropane may be used as a chemical intermediate in the synthesis of pharmaceutical ingredients, in the absence of more substantive data, it is assumed that 2-nitropropane may be present in trace/residual amounts in certain pharmaceuticals. No information was obtained on what products, if any, might contain residual concentrations of 2-nitropropane.

**Consumer Products**

A potential source of consumer product exposure considered was the use of 2-nitropropane in paints and coatings. Bollmeier (2000) suggested that use of 2-nitropropane in these applications has largely been eliminated. In a search of the publicly available literature, products identified as containing 2-nitropropane were intended for industrial or commercial applications.

The confidence in the exposure database for 2-nitropropane is considered to be low, as is the confidence in the resulting estimates of exposure. As no environmental monitoring data were identified, environmental concentrations were estimated using a model based
on physicochemical properties and an area sources release estimate available for a single region of Canada (ChemCAN 2003). In the absence of quantitative information on residual concentrations in vegetable oil, a very conservative intake estimate was based on the limit of detection of 2-nitropropane referenced from a previous assessment completed by JECFA. The probability of exposure of Canadians from vegetable oil is an additional uncertainty; as noted above, JECFA no longer endorses the use of 2-nitropropane in the processing of vegetable oils. In Canada, 2-nitropropane is permitted for use in the fractionation of vegetable oils intended for human consumption under the Food and Drug Regulations; however, North American industry stakeholders have indicated that it is no longer used for this purpose.

Health Effects Assessment

A summary of the available health effects information for 2-nitropropane is presented in Appendix 3.

The International Agency for Research on Cancer (IARC 1999) has classified 2-nitropropane as a Group 2B carcinogen (possibly carcinogenic to humans), whereas the European Commission (ESIS 2009) has classified the chemical as a Category 2 carcinogenic substance (which should be regarded as if it is carcinogenic to humans). The US NTP (2005) has concluded that 2-nitropropane is reasonably anticipated to be a human carcinogen. These classifications and conclusions were based principally on observation of increases in tumour incidences in experimental animals.

Liver tumours were observed in rats treated with 2-nitropropane via different routes of administration. In one carcinogenicity study, rats were orally administered 2-nitropropane at 0 or 40 mg/kg-bw per day for 16 weeks. All of the rats treated with 2-nitropropane developed benign and/or malignant liver tumours. Metastases were also observed in the lungs of some of these rats (Fiala et al. 1987). In another study, rats were administered 2-nitropropane via inhalation at 0, 98 or 755 mg/m³ for up to 6 months. All of the rats exposed to 755 mg/m³ for 6 months developed multiple hepatocellular carcinomas. Although there were no tumours seen in the rats exposed to 755 mg/m³ for 3 months, hyperplastic changes in the liver were observed. No tumours were noted in the rats exposed to 98 mg/m³ (Lewis et al. 1979). In addition to these cancer studies, it was reported that inhalation or intraperitoneal exposure to 2-nitropropane had an initiating action in rats also treated with established promoters (Denk et al. 1990; Astorg et al. 1994). No human cancer data were identified.

On the basis of available evidence on mutagenicity, the IARC (1999) working group concluded that 2-nitropropane “is mutagenic in a wide variety of in vitro and in vivo systems by a direct action.” A detailed overview of the available genotoxicity studies is presented in Appendix 3; these data are briefly summarized below.

2-Nitropropane is genotoxic to a wide range of organisms in vitro and in vivo. The chemical tested positive in bacterial mutation assays. It induced gene mutations in Chinese hamster cells and rat hepatoma cells. In cultured human peripheral lymphocytes,
it showed clear evidence of chromosomal aberration and induction of sister chromatid exchanges, although negative results for sister chromatid exchange were found in Chinese hamster ovary cells. 2-Nitropropane induced unscheduled DNA synthesis in human, rat and mouse hepatocytes. It also induced micronuclei in three rat hepatoma cell lines but not in Chinese hamster lung V79 cells.

The genotoxic effects of 2-nitropropane were corroborated in a series of in vivo studies. In mice exposed by intraperitoneal injection, an increased frequency of mutations in the LacI gene and an increased expression of the tumour suppressor gene p53 were observed in the liver. 2-Nitropropane also induced DNA base modifications in the liver of rats treated orally and intraperitoneally. Significant increases in 8-hydroxydeoxyguanosine levels, an indication of oxidative stress-induced DNA damage, were observed in the liver of rats and mice treated with 2-nitropropane orally or intraperitoneally, but no effect was observed on the kidney of rats. Furthermore, DNA strand breaks were reported in the bone marrow of rats and in the stomach, colon and liver of mice after administration of 2-nitropropane by intraperitoneal injection; however, no effects on the kidney, urinary bladder, lung, brain or bone marrow of mice were observed. Unscheduled DNA synthesis occurred in the hepatocytes of orally treated rats. 2-Nitropropane also induced micronuclei in the hepatocytes of rats treated orally, but not in the peripheral blood of mice treated via intraperitoneal injection.

The underlying mechanisms of the genotoxicity and carcinogenicity of 2-nitropropane have also been studied. It was reported that the genotoxicity of 2-nitropropane in rats has been attributed to sulfotransferase-mediated formation of DNA-reactive nitrenium ions that were produced from the anionic form of 2-nitropropane, propane 2-nitronate (Sodum et al. 1993; Sodum et al. 1994; Sodum and Fiala 1998). Kreis et al. (2000) conducted a study to investigate whether human sulfotransferases are capable of activating propane 2-nitronate in various V79-derived cell lines engineered for expression of individual forms of human sulfotransferases. The results of the study showed that the human phenol sulfotransferases P-PST and M-PST are capable of metabolically activating propane 2-nitronate and that the underlying mechanism is apparently identical to that resulting in the activation of propane 2-nitronate in rat liver, where 2-nitropropane causes carcinomas. These results support the notion that 2-nitropropane should be regarded as a potential human carcinogen. IARC (1999) also concluded that propane 2-nitronate may act as an intermediate in the mechanism by which 2-nitropropane exerts its genotoxic and carcinogenic effects.

However, Griffin et al. (1980) suggested a different pathway of carcinogenesis in rats exposed to 2-nitropropane. Their study indicated that the initial liver damage caused by 2-nitropropane may lead to a physiological process of hyperregeneration, which, under the continuing stress of exposure to 2-nitropropane, has the potential to induce neoplasia.

Exposure to 2-nitropropane has also induced non-cancer effects, mainly on the liver, in experimental animals. In rats exposed by gavage for 2 weeks, a significant increase of hepatic lipid peroxidation was observed at 26 mg/kg-bw per day, which is the lowest oral lowest-observed-adverse-effect level (LOAEL). In the higher dose group (47 mg/kg-bw
per day), a significant increase in serum glutamic-oxaloacetic transaminase\(^2\) level, an index of injury to the liver, was observed. There were also increases in oxidative DNA damage, cell proliferation and histopathological changes in the liver observed in a dose-dependent manner (Sai et al. 1998). In an inhalation study, slightly increased focal vacuolization of the cytoplasm of hepatocytes and focal areas of hepatocellular nodules were observed at 91 mg/m\(^3\), the lowest inhalation lowest-observed-adverse-effect concentration (LOAEC), in male rats exposed to 2-nitropropane for 22 months (Griffin et al. 1981). In another short-term oral study, increases in hepatic DNA synthesis, moderate signs of cholestasis and hepatotoxicity were observed in a dose-dependent manner in male rats exposed for 10 days; the LOAEL was 40 mg/kg-bw per day (Cunningham and Matthews 1991). In a short-term inhalation study, increased total glutathione, glutathione S-transferase activity and uridine 5'-diphosphate-glucuronosyltransferase activity were observed in the liver of male rats exposed to 365 mg/m\(^3\) for 4 days (Haas-Jobelius et al. 1992). In addition, in two 4-week oral studies, Griffin and Coulston (1986) reported a slight elevation in liver weights at 17 mg/kg-bw per day in male rats; and Berryman and Wilson (1989) reported reduced body weight gain and adverse liver effects at 200 mg/kg-bw per day in the surviving female rats. Severe adverse liver effects were also observed in rats exposed to 2-nitropropane by inhalation at 130 mg/m\(^3\) for up to 6 months (Griffin et al. 1978; ANGUS Chemical Company 1985). Morton et al. (2002) reported a subchronic oral study in male Eker rats exposed to 2-nitropropane at 38 mg/kg-bw per day for 4 or 6 months. No consistent effect on numbers of preneoplastic or neoplastic renal lesions was observed, and no neoplasms in the liver were found. However, in a subchronic inhalation study, Lewis et al. (1979) reported that liver cellular damage, which is considered to be preneoplastic, was observed at 755 mg/m\(^3\) in rats exposed via inhalation for 3 and 6 months. The lung was also a target for non-cancer effects in rodents exposed to 2-nitropropane. Pulmonary lesions in male rats exposed to 2-nitropropane via inhalation for 1–6 months were observed at 755 mg/m\(^3\). However, no adverse effects were observed in rabbits (Lewis et al. 1979).

No adequate reproductive studies were identified. In the only developmental toxicity study identified, intraperitoneal injection to female rats with 2-nitropropane at 170 mg/kg-bw per day on days 1–15 of pregnancy reduced pre- or post-implantation survival and reduced fetal body weight or length. There was no evidence of maternal toxicity identified in the exposed animals (Hardin et al. 1981).

Several epidemiological studies were identified. A retrospective mortality study was conducted among 1815 workers in a chemical plant in the United States; it was followed by an updated study, which included 1915 workers. Employees were divided into three cohorts covering those with direct, indirect or no exposure to 2-nitropropane. Data were expressed as standardized mortality ratios (SMRs). There were no differences in the causes of death between individuals grouped according to degree of exposure to 2-nitropropane. However, since the cohort was small and the period of latency was short for most of the subjects, the study did not prove that 2-nitropropane was not carcinogenic to humans (Miller and Temple 1979; Bolender 1983). Crawford et al. (1985) reported on an

\(^2\) Now usually referred to as aspartate aminotransferase.
employee health examination including workers exposed to personal time-weighted average levels of 2-nitropropane below 91 mg/m³, which revealed no adverse effects in the lung, liver, kidney, skin or hematopoietic and cardiovascular systems. In another report, acute toxicity was experienced by workers exposed to 2-nitropropane via inhalation in a plant in the United States. Daily exposure of workers to 2-nitropropane concentrations of 73–164 mg/m³ resulted in severe headaches in those least exposed and anorexia, nausea, vomiting and diarrhea in those most intimately exposed. However, it was also reported that two workers in another plant who were exposed during about one-quarter of their work week to concentrations of 36–108 mg/m³ experienced no adverse effects (Skinner 1947). In a case study, Harrison et al. (1987) reported on two construction workers who were exposed to 2-nitropropane while applying epoxy resin coating. One man died 10 days after exposure from fulminant hepatitis, and the other man had persistently elevated serum aminotransferase activity. Serum concentrations of 2-nitropropane on admission were 13 mg/L in the man who died and 8.5 mg/L in his co-worker. In another case study, fatalities following exposure to 2-nitropropane were reported. Four workers who used a 2-nitropropane-containing surface coating in a confined area died 6–10 days after exposure. All had hepatic damage. Concurrent exposure to other solvents may have contributed (Hine et al. 1978).

In summary, 2-nitropropane induced liver tumours in rats via both oral and inhalation exposures. Metastases were also observed in the lungs of exposed animals. Positive genotoxicity results from both in vitro and in vivo tests were obtained in hepatocytes or in the liver of exposed animals as well as other test systems. Studies on the underlying mechanism of the genotoxicity and carcinogenicity of 2-nitropropane suggested that sulfotransferase-mediated formation of DNA-reactive nitrenium ions produced from 2-nitropropane may be the cause of its adverse effects, although one study suggested a non-genotoxic carcinogenicity pathway. Studies further showed that human sulfotransferase is also capable of activating 2-nitropropane to form DNA-reactive nitronium. Exposure to 2-nitropropane has also induced non-cancer effects, mainly on the liver, in experimental animals. In addition, human case studies revealed that workers died from liver damage after exposure to high concentration of 2-nitropropane or solvents containing 2-nitropropane.

The confidence in the toxicity database for 2-nitropropane is considered to be moderate, as information was available to identify critical endpoints for risk characterization, although no reproductive toxicity studies were identified and there were no human cancer data. In addition, there was a lack of dermal studies for carcinogenicity and repeated-dose toxicity and a lack of oral, inhalation and dermal studies for developmental toxicity. Furthermore, only limited epidemiological studies were available.

**Characterization of Risk to Human Health**

Based principally on the weight of evidence assessments of international and other national agencies (IARC, European Commission and US NTP), a critical effect for characterization of risk to human health for 2-nitropropane is carcinogenicity. Increased incidences of liver tumours were observed in experimental animals from various studies.
2-Nitropropane induced benign and malignant liver tumours in rats in a 16-week oral study. Multiple hepatocellular carcinomas were observed in rats exposed to 2-nitropropane via inhalation for 6 months. Metastases were also observed in the lungs of exposed animals. In addition, 2-nitropropane showed initiating activity in rat liver following intraperitoneal injection or inhalation exposure.

In light of the clear evidence in the in vitro and in vivo genotoxicity assays in the liver of rats, where it causes tumours, and the evidence that the underlying mechanisms of the genotoxicity of 2-nitropropane in rodent cells and in human cells are apparently identical, it cannot be precluded that 2-nitropropane induces tumours via a mode of action involving direct interaction with genetic material both in experimental animals and in humans.

With respect to non-cancer effects, the lowest LOAEL for oral exposure to 2-nitropropane was 26 mg/kg-bw per day, based on increased hepatic lipid peroxidation, oxidative DNA damage and cell proliferation in the liver of rats in a 2-week study. Comparison of this effect level with the estimated intake from vegetable fats and oils for children aged 6–8 (0.0078 µg/kg-bw per day) results in a predicted margin of exposure of approximately $3.3 \times 10^6$. This margin is considered to be adequately protective against the induction of non-cancer effects in the general population in Canada in light of the very conservative nature of the exposure estimate.

Cigarette smoke represents a significant source of exposure to 2-nitropropane. Although smoking does not provide an appropriate basis on which to assess the risk to the general population, the additional intake of 2-nitropropane as a result of exposure to cigarette smoke would further reduce the margin of exposure for non-cancer effects.

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

This screening assessment does not include a full analysis of the mode of induction of effects, including cancer, associated with exposure to 2-nitropropane, nor does it take into account possible differences between humans and experimental species with respect to effects induced by this substance. There were no human cancer data available.

The data available with which to characterize human exposure were very limited. No environmental monitoring data were identified. Thus, environmental concentrations were estimated using a model based on physicochemical properties and an area sources release estimate available for one region of Canada. There is uncertainty regarding the possible use of 2-nitropropane in consumer products (e.g., paints), and regarding the potential for residual concentrations in therapeutic products.

**Conclusions**

Based on the information presented in this screening assessment, it is concluded that 2-nitropropane 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.

2-Nitropropane 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 carcinogenicity of 2-nitropropane, for which there may be a probability of harm at any level of exposure, it is concluded that 2-nitropropane should be considered a substance that may be entering the environment in a quantity or concentration or under conditions that constitute or may constitute a danger in Canada to human life or health.

It is therefore concluded that 2-nitropropane meets one or more criteria under 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.
References


ANGUS Chemical Company. 2009. SYNTHATANE\textsuperscript{TM} NP 200. ANGUS Chemical Company, a subsidiary of The Dow Chemical Company. [cited 2009 Apr 7]. Available from: http://www.dow.com/PublishedLiterature/dh_004f/0901b8038004ff2c.pdf?filepath=/PublishToInternet/InternetDOWCOM/angus/pdfs/noreg/319-00637.pdf&fromPage=BasicSearch


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Appendix 1: Estimates of potential exposure from foods based on assumed 2-nitropropane concentration in vegetable fats and oils of 10 μg/kg

<table>
<thead>
<tr>
<th>Age group (years)</th>
<th>Mean vegetable fat and oil intake from all food sources (^1) (g/kg-bw per day)</th>
<th>Concentration of 2-nitropropane (^2) (μg/kg)</th>
<th>Estimated intake (μg/kg-bw per day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6–8</td>
<td>0.78</td>
<td></td>
<td>0.0078</td>
</tr>
<tr>
<td>9–13</td>
<td>0.56</td>
<td></td>
<td>0.0056</td>
</tr>
<tr>
<td>14–18</td>
<td>0.46</td>
<td></td>
<td>0.0046</td>
</tr>
<tr>
<td>19–30</td>
<td>0.32</td>
<td>10</td>
<td>0.0032</td>
</tr>
<tr>
<td>31–50</td>
<td>0.29</td>
<td></td>
<td>0.0029</td>
</tr>
<tr>
<td>51–70</td>
<td>0.24</td>
<td></td>
<td>0.0024</td>
</tr>
<tr>
<td>70+</td>
<td>0.23</td>
<td></td>
<td>0.0023</td>
</tr>
</tbody>
</table>

\(^1\) Data generated by the Division of Statistics and Epidemiology, Bureau of Biostatistics and Computer Applications, Health Products and Food Branch, Health Canada. Unpublished document using data from Health Canada and Canadian Heart Health Initiative, Federal–Provincial Nutritional Surveys (1990s). Vegetable fat and oil intake values are presented for females, as intake is higher per unit body weight. Children 6–8 years of age have the highest intake of vegetable fats and oils per unit body weight. As 2-nitropropane is permitted for use only in the processing of vegetable oils, intake estimates based on consumption of all vegetable fats and oils are expected to be conservative.

\(^2\) The concentration of 2-nitropropane is based on the limit of detection reported in WHO (1990a). The limit of detection was used as the basis for exposure characterization, as procedures at the time for processing vegetable oils did not lead to detectable levels of 2-nitropropane in the finished product.
### Appendix 2: Estimates of potential exposure to 2-nitropropane in cigarette smoke

<table>
<thead>
<tr>
<th>Age group (years)</th>
<th>Smoking frequency(^1) (no. of cigarettes/day)</th>
<th>2-Nitropropane content per cigarette(^2) (µg/cigarette)</th>
<th>Mean body weight(^3) (kg)</th>
<th>Estimated intake (µg/kg-bw per day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Youth (15–19)</td>
<td>12.2</td>
<td>1.2</td>
<td>59.4</td>
<td>0.25</td>
</tr>
<tr>
<td>Young adults (20–24)</td>
<td>12.2</td>
<td></td>
<td>70.9</td>
<td>0.21</td>
</tr>
<tr>
<td>Adults (25+)</td>
<td>14.9</td>
<td></td>
<td>70.9</td>
<td>0.25</td>
</tr>
</tbody>
</table>

\(^1\) Mean cigarette consumption per CTUMS (2008).

\(^2\) 2-Nitropropane content based on Hoffman et al. (2001).

\(^3\) Mean body weight values based on Health Canada (1998).
Appendix 3. Summary of health effects information for 2-nitropropane

<table>
<thead>
<tr>
<th>Endpoints</th>
<th>Lowest effect levels^/Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laboratory animals and <em>in vitro</em></td>
<td></td>
</tr>
<tr>
<td>Acute toxicity</td>
<td>Lowest oral LD$_{50}$ (mice) = 400 mg/kg-bw (Hite and Skeggs 1979).</td>
</tr>
<tr>
<td></td>
<td>Lowest inhalation LC$_{50}$ (male rats) = 1460 mg/m$^3$ (Lewis <em>et al.</em> 1979).</td>
</tr>
<tr>
<td></td>
<td>Dermal LD$_{50}$ (rabbits) = &gt;2000 mg/kg-bw (ECB 2005).</td>
</tr>
<tr>
<td>Short-term repeated-dose toxicity</td>
<td>Lowest oral LOAEL = 26 mg/kg-bw per day based on significant increase in hepatic lipid peroxidation in liver of male F344 rats (five per group) exposed to 2-nitropropane by gavage at 60 mg/kg-bw given 6 times over 2 weeks (low dose, equivalent to 26 mg/kg-bw per day) or 90 mg/kg-bw given twice followed by 120 mg/kg-bw given 4 times over 2 weeks (high dose, equivalent to 47 mg/kg-bw per day). In the high dose group, a significant elevation of serum glutamic–oxaloacetic transaminase was observed. There was also a dose-related increase in oxidative DNA damage and cell proliferation in the liver (Sai <em>et al.</em> 1998).</td>
</tr>
<tr>
<td></td>
<td>Lowest inhalation LOAEC = 365 mg/m$^3$ based on enhanced total glutathione and increased activities of glutathione S-transferase and uridine 5'-diphosphate-glucuronosyltransferase in the liver of male Sprague-Dawley rats exposed to 2-nitropropane via whole-body inhalation, 7 h/day, for 4 days (Haas-Jobelius <em>et al.</em> 1992).</td>
</tr>
<tr>
<td></td>
<td>Other:</td>
</tr>
<tr>
<td></td>
<td>Oral LOAEL = 40 mg/kg-bw per day based on increased hepatic DNA synthesis and moderate signs of cholestasis and hepatotoxicity observed in a dose-dependent manner in the liver of male Fischer 344 rats exposed to 2-nitropropane by gavage at 20, 40 or 80 mg/kg-bw per day, 5 days/week, for 2 weeks (Cunningham and Matthews 1991).</td>
</tr>
<tr>
<td></td>
<td>Oral LOEL = 17 mg/kg-bw per day based on slight elevation in liver weights in male Fischer 344 rats exposed to 2-nitropropane in drinking water at doses of 0, 0.1, 1.0, 10, 100 or 1000 mg/L for 4 weeks (equivalent to 128 and 99 mg/kg-bw per day for female and male rats in the 1000 mg/L group, respectively; and 17 and 14 mg/kg-bw per day for male and female rats in the 100 mg/L group, respectively). Reduced food and fluid consumption and reduced body weight gain as well as elevated organ weights were observed in the highest dose (1000 mg/L) group. There were no treatment-related effects at 10 mg/L (estimated to be equivalent to 1–2 mg/kg-bw per day) (Griffin and Coulston 1986).</td>
</tr>
<tr>
<td></td>
<td>Oral LOAEL = 200 mg/kg-bw per day based on reduced body weight gain, higher alanine aminotransferase, aspartate aminotransferase and total bilirubin, and lower serum total protein and albumin levels in the surviving female Wistar rats exposed to 2-nitropropane by gavage at 0, 20, 200 or 400 mg/kg-bw per day for 28 days (all male rats died within 7 days after exposure) (Berryman and Wilson 1989).</td>
</tr>
</tbody>
</table>

No dermal studies were identified.
### Screening Assessment

<table>
<thead>
<tr>
<th>Endpoints</th>
<th>Lowest effect levels/Results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Subchronic toxicity</strong></td>
<td><strong>Oral NOAEL = 38 mg/kg-bw per day.</strong> Male Eker rats (15) were administered 2-nitropropane by gavage at a dose of 89 mg/kg-bw, 3 days/week (equivalent to 38 mg/kg-bw per day), for 4 or 6 months. No consistent effect on numbers of preneoplastic or neoplastic renal lesions was observed in the exposed animals. No neoplasms in the expected target organ (liver) were found (Morton et al. 2002).</td>
</tr>
<tr>
<td></td>
<td><strong>Lowest inhalation LOAEC = 130 mg/m³ based on liver effects.</strong> Sprague-Dawley rats (125 per sex) inhaled 200 ppm (624 mg/m³) of 2-nitropropane, 7 h/day, 5 days/week (duration-adjusted to 130 mg/m³), for up to 6 months. Group of 10 rats per sex were sacrificed at 10 days, 1 month, 3 months and 6 months. Increased serum glutamic–pyruvic transaminase (SGPT, 4.5-fold over controls) was observed after 6 months of exposure in male rats. A significant elevation (p = 0.01) in the relative liver weights was observed at 3 and 6 months for both sexes and at 1 month in females compared with the controls. Vacuolization and necrosis of hepatocytes were observed after 10 days and 1 month of exposure (Griffin et al. 1978; ANGUS Chemical Company 1985).</td>
</tr>
<tr>
<td></td>
<td><strong>Other inhalation LOAEC = 755 mg/m³ based on liver cellular damage and pulmonary lesions in male Sprague-Dawley rats exposed to 2-nitropropane via inhalation at 0, 98 or 755 mg/m³, 7 h/day, 5 days/week, for 3 and 6 months for the liver toxicity and for 1, 3 and 6 months for the lung toxicity. Hepatic lesions were considered to be preneoplastic and included marked elevation of SGPT levels, pale colour and necrotic foci, and hypertrophic areas with distorted architecture of the acini. No adverse effects were observed at 755 mg/m³ in rabbits (Lewis et al. 1979).</strong></td>
</tr>
<tr>
<td></td>
<td><strong>No dermal studies were identified.</strong></td>
</tr>
<tr>
<td><strong>Chronic toxicity/ carcinogenicity</strong></td>
<td><strong>Oral carcinogenicity in rats:</strong> Groups of 22 male Sprague-Dawley rats were administered 2-nitropropane by gavage at 0 or 1 mmol/kg-bw, 3 times/week (estimated to be 0 or about 40 mg/kg-bw per day), for 16 weeks. All of the rats (22/22) treated with 2-nitropropane developed benign (4/22) and/or malignant (22/22) liver tumours. Control animals developed 1 benign and no malignant liver tumours (p &lt; 0.001). Metastases were also observed in the lungs of four of the treated rats (Fiala et al. 1987).</td>
</tr>
<tr>
<td></td>
<td><strong>Inhalation carcinogenicity in rats:</strong> Male Sprague-Dawley rats were administered 2-nitropropane via inhalation at 0, 98 or 755 mg/m³, 7 h/day, for 2 days, 10 days, 1, 3 or 6 months (groups of 10 were killed at each time point). All of the 10 rats exposed to 755 mg/m³ for 6 months developed multiple hepatocellular carcinomas. Although there were no tumours seen in the rats exposed to 755 mg/m³ for 3 months, hyperplastic changes in the liver were reported. No tumours were noted in rats exposed to 98 mg/m³ (Lewis et al. 1979).</td>
</tr>
<tr>
<td></td>
<td><strong>Additional studies:</strong> In addition to the cancer data described above, it was reported that inhalation or intraperitoneal exposure to 2-nitropropane had an initiating action in rats also treated with established promoters (Denk et al. 1990; Astorg et al. 1994).</td>
</tr>
</tbody>
</table>
### Non-neoplastic effects:

**Lowest inhalation LOAEC**^3^ = 91 mg/m^3^ based on slightly increased focal vacuolization of the cytoplasm of hepatocytes and focal areas of hepatocellular nodules in Sprague-Dawley rats exposed to 2-nitropropane via inhalation, 7 h/day, 5 days/week, for 22 months (58/125 for exposed males vs. 22/125 for control males; and 19/124 for exposed females vs. 18/125 for control females). No incidence of benign or malignant tumours or any lesion was observed that could be attributed to the exposure to 2-nitropropane. The distribution of tumours and other lesions was similar in control and exposed groups of rats (Griffin *et al.* 1980, 1981).

No dermal studies were identified.

### Reproductive toxicity

No studies were identified.

### Developmental toxicity

**Lowest LOAEL** = 170 mg/kg-bw per day based on significantly reduced pre- or post-implantation survival and reduced fetal body weight or length when female Sprague-Dawley rats (numbers not specified) were exposed to 2-nitropropane via intraperitoneal injection at 0 or 170 mg/kg-bw per day on days 1–15 of pregnancy. There was no evidence of maternal toxicity (Hardin *et al.* 1981).

No oral, inhalation or dermal studies were identified.

### Gene mutation

**Positive:** C57BL/6 mice were administered 2-nitropropane via intraperitoneal injection with a single dose of 100 mg/kg-bw. An increase of mutant frequency in the $LacI$ gene (2- to 3-fold) in the liver of treated mice was observed (Cabelof *et al.* 2002).

### DNA damage

**Positive:** Male F344 rats were administered 2-nitropropane orally by gavage or via intraperitoneal injection with a single dose of 1 mmol/kg-bw (about 90 mg/kg-bw). An induction of aryl sulfotransferase-mediated liver DNA and ribonucleic acid (RNA) base modifications was observed in treated rats (Sodum and Fiala 1998).

**Positive:** Male Sprague-Dawley rats were administered 2-nitropropane orally with a single dose of 0.5, 2 or 8 mmol/kg-bw (about 45, 180 or 720 mg/kg-bw). DNA fragmentation in the liver of rats was observed at all dose

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^3^ This concentration level was converted from the reported level of 25 ppm based on the IARC conversion factor. In the Griffin study, considering the specific altitude of the experiment site (1350 m) and at 25 °C, the concentration level of 25 ppm is equivalent to 78 mg/m^3^. The USEPA used the value of 78 mg/m^3^.
levels and in the bone marrow at the highest dose (8 mmol/kg-bw). However, negative results were obtained in rat lung, kidney and brain (Robbiano et al. 1991).

Oxidative DNA damage

**Positive:** F344 rats were administered 2-nitropropane orally by gavage at doses of 60 mg/kg-bw given 6 times over 2 weeks (low dose) or 90 mg/kg-bw given twice followed by 120 mg/kg-bw given 4 times over 2 weeks (high dose). Significant increases (p < 0.01) in hepatic 8-hydroxydeoxyguanosine levels at both doses were observed in treated rats (Sai et al. 1998).

**Positive:** Male F344 rats were administered 2-nitropropane via intraperitoneal injection with a single dose of 100 mg/kg-bw. Significant increases (p < 0.05) in 8-hydroxydeoxyguanosine adducts in liver DNA were observed in treated rats. However, negative results were observed in the lymphocytes of treated rats (Toraason et al. 1999).

**Positive:** Sprague-Dawley rats were administered 2-nitropropane via intraperitoneal injection with a single dose of 100 mg/kg-bw (1.12 mmol/kg-bw). Significantly increased amounts (p < 0.01) of 8-hydroxydeoxyguanosine in liver DNA of treated rats were observed, and the increase was remarkably higher in male rats than in female rats. However, negative results were found in the kidney of treated rats (Guo et al. 1990).

Comet assay

**Positive:** Male Wistar rats (six per group) were administered 2-nitropropane via intraperitoneal injection with a single dose of 100 mg/kg-bw. DNA damage was observed in bone marrow cells of treated rats 24 h after the administration (Deng et al. 1997).

**Positive:** Male ddY mice (four per group) were administered 2-nitropropane via intraperitoneal injection with a single dose of 500 mg/kg-bw. Sample times were 3, 8 and 24 h after treatment. DNA damage was observed in the stomach, colon and liver 8 h after treatment. No detectable effects on the kidney, urinary bladder, lung, brain or bone marrow were found (Sasaki et al. 2000).

Unscheduled DNA synthesis (UDS)

**Positive:** Sprague-Dawley rats were administered 2-nitropropane orally at a single dose of 25, 50 or 100 mg/kg-bw. UDS in the hepatocytes of the rats was observed, with a dose–effect relationship between 50 and 100 mg/kg-bw. At the dose of 25 mg/kg-bw, 2-nitropropane did not induce UDS (George et al. 1989).

Micronucleus

**Positive:** Sprague-Dawley rats were administered 2-nitropropane orally at a single dose of 25, 50 or 75 mg/kg-bw. Induced micronuclei in the hepatocytes of the rats were observed. The effect was statistically significant at 25 and 50 mg/kg-bw. In the high dose group (75 mg/kg-bw), however, the effect was not significant (George et al. 1989).
### Equivocal: Sprague-Dawley rats were administered 2-nitropropane orally at a single dose of 50, 100 or 300 mg/kg-bw. A slightly increased mean micronucleus frequency in the bone marrow of rats treated with the highest dose (300 mg/kg-bw) was obtained, which was not statistically significant. Cytotoxicity was also observed in this group. However, negative results were obtained in all other dose groups (George et al. 1989).

### Negative: Male CD-1 mice (5 per dose group) were administered 2-nitropropane twice via intraperitoneal injection at doses of 125, 250 or 500 mg/kg-bw. Micronuclei were scored at 0, 24, 48 and 72 h in peripheral blood. No induction of either micronucleated polychromatic erythrocytes or micronucleated reticulocytes was observed up to the highest dose (Morita et al. 1997).

### Genotoxicity and related endpoints: in vitro

<table>
<thead>
<tr>
<th>Mutagenicity in bacteria</th>
<th>Positive in <em>Salmonella typhimurium</em> TA98, TA100 and TA102 with or without metabolic activation (IARC 1999).</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative</td>
<td><em>Salmonella typhimurium</em> TA1535 and TA1537 (IARC 1999).</td>
</tr>
<tr>
<td>Chromosomal aberration</td>
<td>Positive in human lymphocytes with metabolic activation (Bauchinger et al. 1987; Göggelmann et al. 1988).</td>
</tr>
<tr>
<td>Unscheduled DNA synthesis</td>
<td>Positive in human primary hepatocytes (Davies et al. 1993).</td>
</tr>
<tr>
<td>Positive</td>
<td>Positive in rat primary hepatocytes (Davies et al. 1993; Kohl et al. 1994; Fiala et al. 1995).</td>
</tr>
<tr>
<td>Positive</td>
<td>Positive in mouse primary hepatocytes (Davies et al. 1993).</td>
</tr>
<tr>
<td>Sister chromatid exchange</td>
<td>Positive in human lymphocytes with metabolic activation (Bauchinger et al. 1987; Göggelmann et al. 1988).</td>
</tr>
<tr>
<td>Negative</td>
<td>Negative in Chinese hamster ovary cells with or without metabolic activation (Galloway et al. 1987).</td>
</tr>
<tr>
<td>Micronucleus</td>
<td>Positive in H4IIEC3/G− cell line, 2sFou rat hepatoma cell line and C5Rev7 rat hepatoma cell line without metabolic activation (Roscher et al. 1990).</td>
</tr>
<tr>
<td>Negative</td>
<td>Negative in Chinese hamster lung V79 cells without metabolic activation (Roscher et al. 1990).</td>
</tr>
<tr>
<td>Endpoints</td>
<td>Lowest effect levels/Results</td>
</tr>
<tr>
<td>-----------</td>
<td>-----------------------------</td>
</tr>
<tr>
<td>Humans</td>
<td>Several human studies were identified.</td>
</tr>
</tbody>
</table>

A retrospective mortality study was conducted to determine if there were any unusual cancer or other disease mortality patterns among workers exposed to 2-nitropropane through handling the chemical at a plant in Sterlington, Louisiana. The initial study included 1815 employees who had worked at the plant from 1946 to 1977, and an updated study included 1915 employees who had been employed from 1946 to 1981. Production of 2-nitropropane at the plant began in early 1955. Employees were divided into three cohorts, covering those with direct, indirect or no exposure to 2-nitropropane, and the number of employees was 372, 366 and 743, respectively. Monitoring of workplace concentrations after 1962 revealed periodic exposures above 25 ppm (91 mg/m³). Data were expressed as standardized mortality ratios (SMRs). The authors concluded that there were no unusual cancer or other disease mortality patterns among the workers (either before or after the beginning of 2-nitropropane production in 1955). However, since the cohort was small and the period of latency was short for most of the subjects, the study did not prove that 2-nitropropane was not carcinogenic to humans (Miller and Temple 1979; Bolender 1983).

An employee health examination including workers exposed to 2-nitropropane was conducted in a chemical plant in the United States. A total of about 50 employees were associated with the process, about 40 of whom worked in the plant and 18 were considered to be potentially exposed to 2-nitropropane. The workforce studied was almost entirely male, the majority of whom had served the company for 16–35 years and were in the age group 45–64 years. Personal time-weighted average exposure levels were below 25 ppm (91 mg/m³). Body systems evaluated included lungs, liver, kidney, blood, skin and cardiovascular. The examination protocol included medical history questionnaire, clinical tests such as hematology, urinalysis, etc. No significant adverse health effects were found that could be attributed to the workplace. Specifically, there were no indications of cancer or liver dysfunction. There were also no significant differences between the group of 18 employees believed to have had potential contact with 2-nitropropane and the remaining employees (Crawford et al. 1985).

Acute toxicity experienced by workers exposed to 2-nitropropane via inhalation in a plant in the United States was reported. Daily exposure of five or six workers to concentrations of 20–45 ppm (73–164 mg/m³) resulted in severe headaches in those least exposed and anorexia, nausea, vomiting and diarrhea in those most intimately exposed. However, it was also reported that two workers in another plant who were exposed during about one-quarter of their work week to concentrations of 10–30 ppm (36–108 mg/m³) experienced no adverse effects (Skinner 1947).

Two construction workers became ill after applying an epoxy resin coating containing 2-nitropropane in the confined space of an underground concrete vault. One man died 10 days later from fulminant hepatic failure. The second man recovered but had persistently elevated serum aminotransferase activity.
Endpoints | Lowest effect levels¹/Results
--- | ---
The serum concentrations of 2-nitropropane on admission were 13 mg/L in the man who died and 8.5 mg/L in his co-worker (Harrison et al. 1987).

Fatalities following exposure to 2-nitropropane were reported in another case study. Four workers who used a 2-nitropropane-containing surface coating in a confined area died 6–10 days after exposure. All had hepatic damage. Concurrent exposure to other solvents may have contributed (Hine et al. 1978).

¹ LC₅₀, median lethal concentration; LD₅₀, median lethal dose; LOAEC, lowest-observed-adverse-effect concentration; LOAEL, lowest-observed-adverse-effect level; LOEL, lowest-observed-effect level.