# FINAL

# Report on Carcinogens Background Document for

# Nitromethane

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Prepared for the:
**U.S. Department of Health and Human Services**
**Public Health Service**
**National Toxicology Program**
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# FOREWORD

The Report on Carcinogens (RoC) is prepared in response to Section 301 of the Public Health Service Act as amended. The RoC contains a list of all substances (i) that either are known to be human carcinogens or may reasonably be anticipated to be human carcinogens; and (ii) to which a significant number of persons residing in the United States are exposed. The Secretary, Department of Health and Human Services (DHHS) has delegated responsibility for preparation of the RoC to the National Toxicology Program (NTP) who prepares the Report with assistance from other Federal health and regulatory agencies and non-government institutions.

Nominations for listing in or delisting from the RoC are reviewed by a formal process that includes a multi-phased, scientific peer review and multiple opportunities for public comment. The review groups evaluate each nomination according to specific RoC listing criteria. This Background Document was prepared to assist in the review of the nomination of nitromethane. The scientific information in this document comes from publicly available, peer reviewed sources. Any interpretive conclusions, comments or statistical calculations, etc made by the authors of this document that are not contained in the original citation are identified in brackets [ ]. If any member(s) of the scientific peer review groups feel this Background Document does not adequately capture and present the relevant information they will be asked to write a commentary for this Background Document that will be included as an addendum to the document. In addition, a meeting summary that contains a brief discussion of the respective review group's review and recommendation for the nomination will be added to the Background Document, also as an addendum.

A detailed description of the RoC nomination review process and a list of all nominations under consideration for listing in or delisting from the RoC can be obtained by accessing the NTP Home Page at http://ntp-server.niehs.nih.gov. The most recent RoC, the 9th Edition, was published in May, 2000 and may be obtained by contacting the NIEHS Environmental Health Information Service (EHIS) at http://ehis.niehs.nih.gov (800-315-3010).

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## Criteria for Listing Agents, Substances or Mixtures in the Report on Carcinogens

**U.S. Department of Health and Human Services**
**National Toxicology Program**

### Known to be Human Carcinogens:

There is sufficient evidence of carcinogenicity from studies in humans, which indicates a causal relationship between exposure to the agent, substance or mixture and human cancer.

### Reasonably Anticipated to be Human Carcinogens:

There is limited evidence of carcinogenicity from studies in humans, which indicates that causal interpretation is credible but that alternative explanations such as chance, bias or confounding factors could not adequately be excluded; or

There is sufficient evidence of carcinogenicity from studies in experimental animals which indicates there is an increased incidence of malignant and/or a combination of malignant and benign tumors: (1) in multiple species, or at multiple tissue sites, or (2) by multiple routes of exposure, or (3) to an unusual degree with regard to incidence, site or type of tumor or age at onset; or

There is less than sufficient evidence of carcinogenicity in humans or laboratory animals, however; the agent, substance or mixture belongs to a well defined, structurally-related class of substances whose members are listed in a previous Report on Carcinogens as either a *known to be human carcinogen, or reasonably anticipated to be human carcinogen* or there is convincing relevant information that the agent acts through mechanisms indicating it would likely cause cancer in humans.

Conclusions regarding carcinogenicity in humans or experimental animals are based on scientific judgment, with consideration given to all relevant information. Relevant information includes, but is not limited to dose response, route of exposure, chemical structure, metabolism, pharmacokinetics, sensitive sub populations, genetic effects, or other data relating to mechanism of action or factors that may be unique to a given substance. For example, there may be substances for which there is evidence of carcinogenicity in laboratory animals but there are compelling data indicating that the agent acts through mechanisms which do not operate in humans and would therefore not reasonably be anticipated to cause cancer in humans.

# Executive Summary

**Introduction**

Nitromethane is a nitroalkane used as a synthesis intermediate for nitromethane derivatives, as a solvent, as an explosive, and as fuel or fuel additive. Nitromethane was nominated by the National Institute of Environmental Health Sciences for listing in the Report on Carcinogens based on the results of a National Toxicology Program (NTP) two-year inhalation study of nitromethane, which concluded that there was clear evidence of carcinogenicity in female F344/N rats and male and female B6C3F$_1$ mice. There was no evidence of carcinogenicity in male F344/N rats.

**Human Exposure**

*Use.* Nitromethane's primary use is in the synthesis of nitromethane derivatives used as pharmaceuticals, agricultural soil fumigants, and industrial antimicrobials. Nitromethane also is used as a fuel or fuel additive with methanol in racing cars, boats, and model engines, which accounts for less than 20% of the market for nitromethane. Past uses of nitromethane include its use as a chemical stabilizer to prevent the decomposition of various halogenated hydrocarbons, such as metal degreasers and aerosol propellants; as an additive for 1,1,1-trichloroethane; and in the explosive industry as a component in a binary explosive formulation with ammonium nitrate and in shaped charges.

*Production.* Nitromethane is produced commercially by high-temperature vapor-phase nitration of propane, a reaction that also yields nitroethane, 1-nitropropane, and 2-nitropropane. Nitromethane was produced commercially in the United States by Angus Chemical Co. (Buffalo Grove, IL) and W.R. Grace and Company (Columbia, MD); however, Angus Chemical Co. has reported that it is the only current commercial producer of nitromethane and produces 16 million pounds domestically per year.

*Environmental exposure.* Nitromethane has been detected in air, in surface water, and in drinking water. The general population can be exposed to nitromethane by inhalation from motor vehicle exhaust and cigarette smoke. Estimated nitromethane concentrations in motor vehicle exhaust in a simulated city driving study ranged from less than 0.8 to 5.0 ppm depending on the conditions. Nitromethane also may be released in air and wastewater during the manufacture of the munitions cyclotrimethylenetrinitramine and cyclotetramethylenetetranitramine. Maximum ground-level air concentrations of nitromethane at three plants on the boundary of an ammunition plant were 0.21, 2.0, and 2.0 $\mu g/m^3$. Nitromethane was identified, but not quantified, as a pollutant in drinking water in two of five cities (Philadelphia, PA, and Cincinnati, OH) tested in a 1975 United States Environmental Protection Agency survey. Human exposure also may occur through dermal contact or accidental ingestion of methanol-nitromethane fuel mixture; however, products containing nitromethane are not widely used by consumers.

*Occupational exposure.* Approximately 135,000 male and 46,500 female workers in the United States were potentially exposed to nitromethane from 1981 through 1983. Angus Chemical Co. reported that in its facility where nitromethane was produced, occupational exposure was in the 1.0-ppm range (8-h time-weighted average [TWA]). Occupational

exposure to nitromethane may have occurred in the past as a consequence of exposure to other chemicals, such as 1,1,1-trichloroethane, that may contain nitromethane as a contaminant.

*Regulations.* The Occupational Safety and Health Administration nitromethane exposure limit is 100 ppm, or 250 mg/m$^3$. The American Conference of Governmental Industrial Hygienists has set a TWA threshold limit value for nitromethane of 20 ppm, or 50 mg/m$^3$. Nitromethane is considered immediately dangerous to life or health at a concentration of 750 ppm (NIOSH 1997). Nitromethane also is regulated by the United States Environmental Protection Agency, with standards and record-keeping requirements for industrial facilities that produce nitromethane.

**Human Cancer Studies**

No studies have been reported on the relationship between human cancer and exposure to nitromethane.

**Studies in Experimental Animals**

The International Agency for Research on Cancer (IARC) concluded that there was sufficient evidence for the carcinogenicity of nitromethane in experimental animals, based on the NTP inhalation study in mice and rats. Increased incidences of harderian gland adenoma and adenoma or carcinoma (combined) occurred in male and female mice exposed to nitromethane by inhalation at a concentration of 375 or 750 ppm. Increased incidences of lung carcinoma occurred in males exposed at 750 ppm and females exposed at 375 ppm. Female mice exposed at 750 ppm had a significantly increased incidence of lung adenoma or carcinoma (combined). In addition, the incidences of hepatocellular adenoma and adenoma or carcinoma (combined) were significantly increased in female mice at 188 or 750 ppm. The NTP concluded that there was clear evidence for carcinogenicity of nitromethane in both male and female B6C3F$_1$ mice. In female F344/N rats exposed to nitromethane at 188 or 375 ppm for two years, the incidences of mammary gland fibroadenoma and fibroadenoma, adenoma, or carcinoma (combined) were significantly increased, and at 375 ppm, the incidence of mammary gland carcinoma was significantly increased. The NTP concluded that there was clear evidence that nitromethane was carcinogenic to female F344/N rats. There was no evidence that nitromethane was carcinogenic in male or female Long-Evans rats exposed to nitromethane by inhalation at 100 or 200 ppm for two years or in male F344/N rats exposed at 94, 188, or 375 ppm for two years. Evidence of only mild to moderate toxicity was observed in rabbits exposed to nitromethane at a concentration of 98 or 745 ppm by inhalation for 6 months.

**Genotoxicity**

Nitromethane was not mutagenic *in vitro* or *in vivo*. It did not induce reverse mutation in *Salmonella typhimurium* strains TA98, TA100, TA1535, or TA1537 with or without induced rat liver S9; chromosomal aberrations or sister chromatid exchange in Chinese hamster ovary cells; or micronuclei in Syrian hamster embryo cells or mouse bone marrow cells or peripheral erythrocytes.

**Other Relevant Data**

Nitromethane has been shown to produce toxic effects in animals, including neurologic and reproductive effects. Relatively few reports have been published on the absorption, distribution, metabolism, and excretion of nitromethane. The available data suggest that absorption may occur by inhalation but that the amount absorbed after dermal exposure is negligible. Although nitromethane may be metabolized to formaldehyde by rat liver microsomes *in vitro*, no published reports have characterized the metabolism of nitromethane *in vivo*. Nitromethane is structurally related to other nitro compounds (i.e., 2-nitropropane and tetranitromethane) that have been evaluated by IARC and considered to be possibly carcinogenic to humans. The mechanism of carcinogenicity for nitromethane and these other nitro compounds is not known; however, it has been hypothesized that reactive radicals may play a key role in their carcinogenicity.

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# 1 Introduction

Nitromethane is a nitroalkane used as a synthesis intermediate for nitromethane derivatives, agricultural fumigants, biocides, and other products; as a solvent; and, in mixtures with ammonium nitrate, as an explosive in mining, oil-well drilling, and seismic exploration. Nitromethane also is used as a fuel or fuel additive to increase the power output of rockets, racing cars, boats, and model engines. Nitromethane has been found in air, surface and drinking water, and cigarette smoke and as a byproduct of hydrocarbon combustion and munitions manufacture. It is structurally related to two other nitroalkanes, 2-nitropropane and tetranitromethane, that are known animal carcinogens and are listed in the 9th Report on Carcinogens (NTP 2000) as *reasonably anticipated to be a human carcinogen*.

Nitromethane was nominated by the National Institute of Environmental Health Sciences for listing in the Report on Carcinogens based on the results of a National Toxicology Program (NTP) two-year inhalation study of nitromethane that concluded there was clear evidence of carcinogenicity in female F344/N rats (mammary gland fibroadenoma and carcinoma), female B6C3$F_1$ mice (liver neoplasms and harderian gland adenoma and carcinoma), and male B6C3$F_1$ mice (harderian gland adenoma and carcinoma) (NTP 1997). There was no evidence of carcinogenicity in male F344/N rats. Increased incidences of alveolar/bronchiolar adenoma and carcinoma in male and female mice also were observed and considered related to nitromethane exposure.

## 1.1 Chemical identification

Nitromethane ($CH_3NO_2$, mol wt 61.04, CASRN 75-52-5) is a colorless, oily liquid with a mild fruity or disagreeable odor (Budavari 1996). It is also known as nitrocarbol, nitrometan, NMT, and NM. Its RTECS number is PA9800000, and its Department of Transportation number and hazard class are UN 1261, flammable liquid. The structure of nitromethane is given in Figure 1-1.

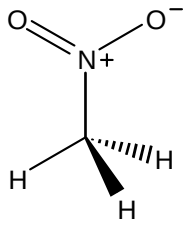


**Figure 1-1. Structure of nitromethane**

## 1.2 Physical-chemical properties

Nitromethane is a flammable liquid that may explosively decompose on shock, friction, concussion, or heating. Although nitromethane is relatively insensitive to detonation by shock at ordinary temperatures, it becomes more sensitive as the temperature increases. At 55°C to 60°C (130°F to 140°F), nitromethane has a 50% probability of detonation with a No. 8 blasting cap. Heating of nitromethane vapor results only in slow

decomposition even at temperatures above the critical point of 315°C (599°F). (The critical point is the temperature above which a liquefied gas will vaporize almost instantaneously if heat is added.) Heating nitromethane in the liquid phase, therefore, may be hazardous, as rapid expansion of confined volumes may result in ignition and explosion (Angus 2000).

Nitromethane reacts with alkalis and reacts violently with strong oxidants and strong reducing agents, causing fire and explosion hazards. The vapor is heavier than air and may travel along the ground; thus, distant ignition is possible. Nitromethane will slowly corrode steel and copper when wet (NIOSH 1998). The hazardous decomposition products of nitromethane are toxic fumes of nitrogen oxides (Ash and Ash 1996). The physical and chemical properties of nitromethane are summarized in Table 1-1.

**Table 1-1. Physical and chemical properties of nitromethane**

| Property | Information | Reference |
|---|---|---|
| Molecular weight | 61.04 | ChemFinder 2001, Budavari 1996 |
| Color | colorless | ChemFinder 2001, Budavari 1996, NTP 2001 |
| Odor | mild fruity or disagreeable | NTP 2001, ChemFinder 2001 |
| Physical state | oily liquid | ChemFinder 2001, Budavari 1996 |
| Melting point ($^{o}$C) | -29 | ChemFinder 2001, Budavari 1996 |
| Boiling point ($^{o}$C) | 101.2 | ChemFinder 2001, Budavari 1996 |
| Evaporation rate | 1.39 | ChemFinder 2001, NTP 2001 |
| Flash point ($^{o}$C) | 35 | ChemFinder 2001, NTP 2001 |
| Density | 1.1371 | ChemFinder 2001 |
| Vapor density | 2.1 | ChemFinder 2001, NTP 2001 |
| Vapor pressure (mm Hg at 20$^{o}$C) | 27.8 | ChemFinder 2001, NTP 2001 |
| Solubility (at 23$^{o}$C): | | |
| water | 9.50 g/100 mL | ChemFinder 2001 |
| acetone | soluble | HSDB 2000 |
| alcohol | soluble | Budavari 1996 |
| ether | soluble | HSDB 2000 |
| Henry's law constant (calc.) (atm-m$^{3}$/mol) | 2.68 x $10^{-5}$ | (SRC 2001) |

## 1.3 Other nitroparaffins

Four nitroparaffins, also called nitroalkanes or aliphatic nitro compounds ($RNO_3$), are available commercially as solvents and chemical intermediates in the synthesis of a variety of compounds (Kirk-Othmer 2001, Archer 1996, Markofsky 1991, Budavari 1996). These four compounds, nitromethane (Figure 1-1), nitroethane (Figure 1-2), 1-nitropropane (Figure 1-3), and 2-nitropropane (Figure 1-4), sometimes are referred to as the lower mononitroparaffins. Polynitro compounds include tetranitromethane (Figure 1-

5). The four mononitroparaffins and tetranitromethane all are liquids at room temperature, and all five compounds are slightly soluble in water and insoluble in alkanes but are soluble in most other organic solvents, including ethanol and ethyl ether. In addition, all five compounds are flammable, and some (nitromethane and tetranitromethane) are explosive. 2-Nitropropane and tetranitromethane have been reviewed by both an International Agency for Research on Cancer (IARC) Working Group and the NTP for potential carcinogenicity (see Section 6.4).

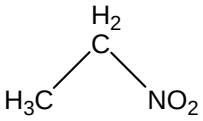


**Figure 1-2. Structure of nitroethane**

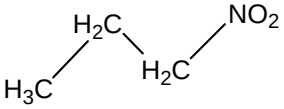


**Figure 1-3. Structure of 1-nitropropane**

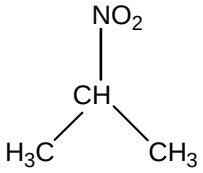


**Figure 1-4. Structure of 2-nitropropane**

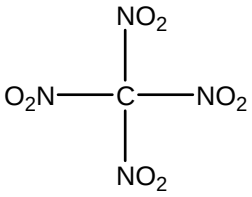


**Figure 1-5. Structure of tetranitromethane**

# 2 Human Exposure

## 2.1 Use

Nitromethane's primary use is in the synthesis of nitromethane derivatives used as pharmaceuticals, agricultural soil fumigants, and industrial antimicrobials. Table 2-1 summarizes the major nitromethane derivatives, their formation, and their uses (Markofsky 1991).

**Table 2-1. Nitromethane derivatives**

| Derivative | Formation | Uses |
|---|---|---|
| Chloropicrin | reaction of nitromethane with sodium hypochlorite | fungicide and nematocidal fumigant |
| Tris(hydroxymethyl)nitromethane | reaction of formaldehyde and nitromethane (3:1 molar ratio) via the Henry reaction | biocide |
| Tris(hydroxymethyl) aminomethane | reduction of tris(hydroxymethyl) nitromethane | buffer and a component of resins and adhesives |
| Di(hydroxymethyl)nitromethane | reaction of formaldehyde and nitromethane (2:1 molar ratio) via the Henry reaction | chemical intermediate in the synthesis of the X-ray contrast agent iopamidol |
| 2-Bromo-2-nitro-1,3-propanediol | bromination of di(hydroxymethyl)nitromethane | widely used biocide (bronopol) |
| β-nitrostyrene | reaction of benzaldehyde and nitromethane and dehydration | used as a chain transfer agent (lowers molecular weights of polymers in their free radical initiated states) |
| Bromonitrostyrene | treatment of β-nitrostyrene with bromine followed by dehydrobromination | slimicide |
| Nizatidine | commercial process | anti-ulcer drug |
| Ranitidine | commercial process | anti-ulcer drug |
| Sulpiride | commercial process | psychotropic agent |

Source: Markofsky 1991.

In public comments in response to the nomination of nitromethane for listing in the Report on Carcinogens, Angus Chemical Company, a subsidiary of Dow Chemical Company, reported that 85% to 90% of the domestically produced nitromethane is used in the above industrial settings (Angus 2001). Angus Chemical Co. has estimated that use of nitromethane as a fuel or fuel additive with methanol in racing cars, boats, and model engines accounts for less than 20% of the market for nitromethane. Angus Chemical Co. also has reported that use of nitromethane as a chemical stabilizer to prevent the decomposition of various halogenated hydrocarbons, such as metal degreasers and aerosol propellants, has diminished to virtually zero. Nitromethane previously was used as an additive for 1,1,1-trichloroethane; however, the mandatory phase-out of 1,1,1-

trichloroethane in 1995 ended this use of nitromethane (Angus 2001). Nitromethane also was used in the explosive industry as a component in a binary explosive formulation with ammonium nitrate and in shaped charges (IARC 2000, NTP 1997). Angus Chemical Co. (2001) has reported that as of 2000, it no longer sells nitromethane for explosive-industry applications.

## 2.2 Production

Nitromethane is produced commercially by high-temperature vapor-phase nitration of propane, a reaction that also yields nitroethane, 1-nitropropane, and 2-nitropropane. Nitromethane was produced commercially in the United States by Angus Chemical Co. (Buffalo Grove, IL) and W.R. Grace and Company (Columbia, MD) (SRI 1992); however, Angus Chemical Co. has reported that it is the only current commercial producer of nitromethane (Angus 2001). Nitromethane also can be prepared by the reaction of sodium nitrite with sodium chloroacetate (Budavari 1996).

In its public comments, Angus Chemical Co. (2001) submitted a statement that approximately 16 million pounds of nitromethane are produced domestically per year. No information from the U.S. International Trade Commission on domestic nitromethane production was found.

## 2.3 Analysis

Nitromethane can be determined in workplace air by adsorption on Chromosorb, desorption with ethyl acetate, and analysis by gas chromotography with a nitrogen-specific detector. The applicable working range of this method (National Institute for Occupational Safety and Health [NIOSH] method 2527) is 60 to 360 ppm (150 to 900 $mg/m^3$) for a 2-L air sample (IARC 2000).

## 2.4 Environmental occurrence

Nitromethane has been detected in air, in surface water, and in drinking water. It also has been found in cigarette smoke and as a byproduct of hydrocarbon combustion and munitions manufacture (IARC 2000, NTP 1997).

## 2.5 Environmental fate

### *2.5.1 Atmospheric fate*

Nitromethane does not persist in the environment, having a half-life of 4 to 9 hours in air; degradation is by photolysis. Reaction with photochemically produced hydroxyl radicals is not considered an important atmospheric fate, as this reaction is very slow, with a half-life of 100 days (HSDB 2000).

### *2.5.2 Aquatic fate*

Nitromethane in water will be lost by volatilization. Nitromethane is slightly soluble in water (9.5 g/100 mL) and evaporates at about the same rate as water; thus, the aquatic half-life of nitromethane depends on the rate of evaporation (NTP 1997). The half-life of nitromethane was found to be 28.7 hours in a model river and 13 days in a model pond. The importance of biodegradation or photodegradation in the removal of nitromethane

from surface water has not been studied. Nitromethane is not expected to adsorb to sediment or particulate matter or to bioconcentrate in aquatic organisms (HSDB 2000).

### *2.5.3 Terrestrial fate*

Nitromethane is expected to volatilize rapidly in soil because of its high vapor pressure, high calculated Henry's Law constant (which defines the equilibrium between the concentration of a solute gas in solution and the partial pressure of that gas above the solution), and low adsorptivity to soil. It may leach into soil, and degradation is expected to be low. In terrestrial studies, more nitromethane was lost as volatile products than through conversion to carbon dioxide (NTP 1997, HSDB 2000).

## 2.6 Environmental exposure

### *2.6.1 Atmospheric exposure*

Vaporization of nitromethane in the atmosphere can lead to human exposure via inhalation. Nitromethane can be absorbed into the body by inhalation and by ingestion (NIOSH 1998). The general population will be exposed to nitromethane by inhalation from motor vehicle exhaust and cigarette smoke (HSDB 2000). Nitromethane concentrations in exhaust from automobiles using nine hydrocarbon test fuels were estimated under simulated city driving conditions. Estimated concentrations ranged from < 0.8 to 5.0 ppm. Environmental exposure to nitromethane also would occur in the use of specialty fuel blends for drag racing and hobby fuel (Angus 2001). Nitromethane also is a byproduct in the manufacture of the munitions cyclotrimethylenetrinitramine (RDX) and cyclotetramethylenetetranitramine (HMX) and may be released in air emissions and wastewaters during their manufacture (HSDB 2000, IARC 2000).

### *2.6.2 Drinking water*

Nitromethane was identified, but not quantified, as a pollutant in drinking water in two of five cities tested (Philadelphia, PA, and Cincinnati, OH) in a 1975 U.S. Environmental Protection Agency (EPA) survey (HSDB 2000).

### *2.6.3 Other exposure*

Human exposure may occur through dermal contact or accidental ingestion of methanol-nitromethane fuel mixtures (IARC 2000). Products containing nitromethane are not widely used by consumers; therefore, consumer exposure is presumed to be low (NTP 1997). In a study to evaluate the utility of human milk in specific pollutant studies, environmental pollutants in milk were identified by gas chromatography/mass spectrometry. In each of four urban areas selected based on the probability of emissions of various halogenated pollutants (Bridgeville, PA, Bayonne and Jersey City, NJ, and Baton Rouge, LA), up to 12 women were selected from various health clinics and hospitals. Nitromethane was detected by qualitative analysis in 1 of the 12 samples from one unspecified site. No quantitative analysis was done (Pellizzari *et al.* 1982).

In 1984, the munitions RDX and HMX (see Section 2.6.1) were manufactured only in one plant in Kingsport, TN (ATSDR 1995). Maximum ground-level air concentrations of

nitromethane at three sites on the boundary of this ammunition plant were 0.21, 2.0, and 2.0 $\mu g/m^3$ (HSDB 2000).

## 2.7 Occupational exposure

It was reported that approximately 135,000 male and 46,500 female workers in the United States were potentially exposed to nitromethane from 1981 through 1983 (NTP 1997). Angus Chemical Co. reported that in its facility where nitromethane was produced, occupational exposure was in the 1.0-ppm range (8-h time-weighted average [TWA]). No information on peak exposure to nitromethane was provided (Angus 2001). Exposure could have occurred in the past as a consequence of exposure to other chemicals, such as 1,1,1-trichloroethane, that may contain nitromethane as a contaminant (Henschler *et al.* 1980).

## 2.8 Biological indices of exposure

The acute symptoms of inhalation exposure to nitromethane are cough, drowsiness, headache, nausea, sore throat, unconsciousness, and vomiting (NIOSH 1998).

## 2.9 Regulations

The Occupational Safety and Health Administration (OSHA) nitromethane exposure limit is 100 ppm, or 250 $mg/m^3$ (OSHA 2001). The American Conference of Governmental Industrial Hygienists (ACGIH) has set a TWA threshold limit value for nitromethane of 20 ppm, or 50 $mg/m^3$ (ACGIH 1999). Nitromethane is considered immediately dangerous to life or health at a concentration of 750 ppm (NIOSH 1997).

Nitromethane is also regulated by the U.S. EPA requiring standards and record-keeping requirements for industrial facilities that produce nitromethane.

**Table 2-2. EPA regulations**

| Regulatory action | Effect of regulation or other comments |
|---|---|
| 40 CFR 60.480 – Subpart VV – Standards of Performance for Equipment Leaks of VOC in the Synthetic Organic Chemicals Manufacturing Industry. Promulgated: 48 FR 48335, 10/18/83. | The provisions of this subpart apply to affected facilities in the synthetic organic chemicals manufacturing industry that produce, as intermediates or final products, nitromethane. This subpart identifies standards, test methods, procedures, and record-keeping requirements for affected facilities. |

Source: The regulations in this table have been updated through the 2001 Code of Federal Regulations 40 CFR, 1 July 2001.

## Table 2-3. OSHA Regulations

| Regulatory action | Effect of regulation or other comments |
|---|---|
| 29 CFR 1910.119 – Sec. 1910.119. Process safety management of highly hazardous chemicals. U.S. Codes: 29 U.S.C. 653, 655, 657. | Nitromethane is listed as a toxic and reactive highly hazardous chemical that presents a potential for a catastrophic event at or above the threshold quantity of 2,500 lb. |
| 29 CFR 1915.1000 – Subpart Z – Air contaminants. TABLE Z-1 Limits for Air Contaminants. | An employee's personal exposure level (PEL) for nitromethane shall be limited to 100 ppm (8-h TWA) or 250 $mg/m^3$ (8-h TWA). |
| 29 CFR 1915.1000 – Subpart Z – Air contaminants. Toxic and Hazardous Substances. | An employee's PEL for nitromethane in shipyards shall be limited to 100 ppm (8-h TWA) or 250 $mg/m^3$ (8-h TWA). |
| 29 CFR 1926.50ff – Subpart D – Occupational Health and Environmental Controls. | Exposure of employees to inhalation, ingestion, skin absorption, or contact with any material or substance at concentrations above those specified in the ACGIH "Threshold Limit Values of Airborne Contaminants for 1970" shall be avoided. |

Source: The regulations in this table have been updated through the 2001 Code of Federal Regulations 29 CFR, 1 July 2001.

# 3 Human Cancer Studies

No studies have been reported on the relationship between human cancer and exposure to nitromethane.

# 4 Studies of Cancer in Experimental Animals

An IARC Working Group (2000) reviewed three animal cancer studies and several relevant metabolism and toxicity studies of nitromethane. Cancer studies were conducted with Long-Evans rats (Griffin *et al.* 1996), F344/N rats (NTP 1997), and B6C3F$_1$ mice (NTP 1997). The IARC Working Group concluded that there was sufficient evidence for the carcinogenicity of nitromethane in experimental animals. No carcinogenicity studies in experimental animals have been published since the IARC (2000) monograph. In addition, results from several subchronic toxicity studies in mice, rats, and rabbits are presented in Sections 4.1 through 4.3.

## 4.1 Rabbits

Male New Zealand white rabbits (15 per group) were exposed to nitromethane vapor at a concentration of 0, 98, or 745 ppm by inhalation, 7 hours/day, 5 days/week, for 24 weeks (Lewis *et al.* 1979). Five rabbits from each group were sacrificed after 1, 3, or 6 months of exposure. Evidence of only mild to moderate toxicity was observed in rabbits exposed to nitromethane at 98 or 745 ppm for 6 months. Growth rates and organ weights were not affected except for thyroid weight. Thyroid weight increased after 6 months of exposure at 745 ppm, and lower serum thyroxine levels were observed after exposure at 98 or 745 ppm after 1, 3, and 6 months. In addition, there was some evidence of pulmonary edema and other pulmonary abnormalities in rabbits exposed to either level of nitromethane for 1 month. However, no exposure-related gross or microscopic effects were seen in any of the tissues examined.

## 4.2 Mice

Nitromethane was selected for a two-year carcinogenicity bioassay in B6C3F$_1$ mice (NTP 1997) based on its potential for human exposure and its relationship to the known animal carcinogens 2-nitropropane and tetranitromethane. Inhalation studies first were conducted in the same strain of mice for 16 days (see Section 6) and 13 weeks. Results from the 13-week subchronic toxicity study and two-year carcinogenicity study are summarized here.

Three lots of nitromethane were obtained from W.R. Grace and Company (Lexington, MA) and analyzed for identity, purity, and stability by Midwest Research Laboratory (Kansas City, MO). Lot 1F-13-06 (used for the 16-day study, described in Section 6.1.3, and the beginning of the 13-week study) had a purity of approximately 99%, with 0.4% propionitrile and 0.017% 2-nitropropane. Lot 1-H-0501 (used for the remainder of the 13-week study and the beginning of the two-year study) had a purity of approximately 98%, with 1.71% total impurities. Lot 1-H-1004 (used for the remainder of the two-year study) had a purity of approximately 98%, with 1.5% total impurities (NTP 1997).

### *4.2.1 Subchronic toxicity*

The 13-week study was conducted to evaluate the cumulative toxic effects of repeated exposure to nitromethane and to determine the exposure concentrations to be used in the two-year study (NTP 1997). Groups of B6C3F$_1$ mice (10 of each sex) were exposed to nitromethane vapor at a concentration of 0, 94, 188, 375, 750, or 1,500 ppm by inhalation, 6 hours/day, 5 days/week, for 13 weeks. Animals were housed individually;

water was available *ad libitum*; and feed was available *ad libitum* except during exposure periods. Clinical observations were recorded weekly, and animals were weighed initially, weekly, and at the end of the study. At the end of the study, samples were collected for sperm motility or vaginal cytology evaluations from all mice in all groups. Complete necropsies were performed on all animals and included histopathologic examination of all major organs and tissues. The heart, right kidney, liver, lungs, right testis, and thymus were weighed.

All mice survived to the end of the study. The final mean body weights and weight gains of exposed mice were generally similar to those of the controls. There were no treatment-related clinical findings. The absolute kidney weights of all groups of exposed male mice except the 1,500-ppm group and of all groups of female mice exposed at 188 ppm or more were significantly greater than those of the controls. The relative kidney weights also were significantly greater than those of controls in all males and females in the 750- and 1,500-ppm groups. The absolute liver weight of male mice in the 750-ppm group and the relative liver weights of males exposed at 375 ppm or more were significantly greater than those of the controls. Olfactory epithelial degeneration and respiratory epithelial hyaline droplets were observed microscopically in all male and female mice exposed at 375 ppm or more. Degeneration also occurred in females in the 188-ppm group, and hyaline droplets occurred in females in the 94- and 188-ppm groups. The average severity of the nasal lesions ranged from minimal to mild in males and from minimal to moderate in females. All males and 9 females in the 1,500-ppm groups also had minimal extramedullary hematopoiesis of the spleen.

#### *4.2.2 Two-year carcinogenicity study*

Exposure levels were based on the incidence and severity of nasal lesions and the presence of extramedullary hematopoiesis of the spleen in the 1,500-ppm groups in the subchronic toxicity study (see Section 4.2.1). Groups of seven-week-old B6C3$F_1$ mice (50 of each sex) were exposed to nitromethane vapor at a concentration of 0, 188, 375, or 750 ppm by inhalation, 6 hours/day, 5 days/week, for 103 weeks (NTP 1997). Water was available *ad libitum*, and feed was available *ad libitum* except during exposure periods. All animals were observed twice daily. Clinical findings were recorded monthly through week 91, then every two weeks until the end of the study. Animals were weighed initially, weekly through week 12, monthly from week 15 through week 91, every two weeks thereafter, and at the end of the study. Complete necropsies and microscopic examinations were performed on all tissues and organs of all animals.

Nitromethane exposure did not significantly affect survival, and the survival rate of females in the 750-ppm group was marginally greater than that of the controls (see Appendix B, pp. B-40 and B-41, Table 14 and Figure 3 in NTP 1997). The mean body weights of exposed females were generally slightly greater than the mean body weight of the controls during the study but generally similar to that of the controls at the end of the study. The mean body weights of exposed and control males were similar throughout the study (see Appendix B, pp. B-42 to B-44, Tables 15 and 16 and Figure 4 in NTP 1997). Clinical findings included swelling around the eyes and exophthalmos (abnormal protrusion of the eyeball) in exposed males and females. These findings were coincident with harderian gland neoplasms.

The incidences of harderian gland adenoma and adenoma or carcinoma (combined) in exposed mice increased with increasing exposure concentration and were significantly greater in males and females in the 375- and 750-ppm groups than in the controls (Table 4-1). The incidences of these neoplasms in all exposed groups of male mice were greater than the historical incidences for chamber-control mice in two-year NTP inhalation studies; however, the incidences in control males also exceeded the range of historical control incidences. Incidences of adenoma and adenoma or carcinoma (combined) in all exposed groups of female mice also exceeded the historical control incidences, except for adenoma in the low-dose group. The incidences of carcinoma in males and females in the 375- and 750-ppm groups also were slightly greater than the incidences in the controls. Although the differences were not statistically significant, the incidences of carcinoma in the 375- and 750-ppm groups were outside the historical control incidence range of 0% to 4%. The incidences of harderian gland hyperplasia in males and females in the 375-ppm groups were similar to those in the controls. A significant positive dose-related trend was observed for all harderian gland neoplasms except for carcinoma in female mice.

**Table 4-1. Harderian gland tumor incidence in B6C3F$_1$ mice following inhalation exposure to nitromethane for up to two years**

| Sex | Exposure conc. (ppm) | Harderian gland tumor incidence[a] (%) | | |
|---|---|---|---|---|
| | | Adenoma | Carcinoma | Combined |
| Male | 0 | 9/50 (18) | 1/50 (2) | 10/50 (20) |
| | 188 | 10/50 (20) | 1/50 (2) | 11/50 (22) |
| | 375 | 19/50 (38)* | 6/50 (12) | 25/50 (50)*** |
| | 750 | 32/50 (64)*** | 5/50 (10) | 37/50 (74)*** |
| | Hist. control | 47/950 (0–14) | 2/950 (0–4) | 49/950 (0–14) |
| | Trend | $P < 0.001$ | $P = 0.036$ | $P < 0.001$ |
| Female | 0 | 5/50 (10) | 1/50 (2) | 6/50 (12) |
| | 188 | 7/50 (14) | 2/50 (4) | 9/50 (18) |
| | 375 | 16/50 (32)** | 4/50 (8) | 20/50 (40)** |
| | 750 | 19/50 (38)** | 3/50 (6) | 21/50 (42)** |
| | Hist. control | 26/941 (0–16) | 6/941 (0–4) | 32/941 (0–16) |
| | Trend | $P < 0.001$ | $P = 0.305$ | $P < 0.001$ |

Source: NTP 1997.

*$P \leq 0.05$, **$P \leq 0.01$, ***$P \leq 0.001$ (logistic regression test).

[a]Number of mice with tumors/number of mice examined.

Female mice in the 188- and 750-ppm groups had significantly greater incidences of hepatocellular adenoma and adenoma or carcinoma (combined) than the controls (Table 4-2). The incidences of these neoplasms exceeded the historical control ranges of 0% to 40% for hepatocellular adenomas and 3% to 54% for hepatocellular adenomas or carcinomas (combined) for two-year NTP inhalation studies. Incidences of multiple hepatocellular adenomas also were higher in female mice in the 188-ppm (13/49, 27%)

and 750-ppm (13/50, 26%) groups than in the controls (3/50, 6%). The incidences of eosinophilic focus increased with increasing exposure concentration, and the incidences in the 375- and 750-ppm groups were significantly greater than the control incidence.

**Table 4-2. Liver tumor incidence in B6C3F$_1$ mice following inhalation exposure to nitromethane for up to two years**

| Sex | Exposure conc. (ppm) | Liver tumor incidence[a] (%) | | |
|---|---|---|---|---|
| | | Adenoma | Carcinoma | Combined |
| Male | 0 | 17/50 (34) | 16/50 (32) | 29/50 (58) |
| | 188 | 14/50 (28) | 14/50 (28) | 24/50 (48) |
| | 375 | 13/50 (26) | 10/50 (20) | 22/50 (44) |
| | 750 | 17/50 (34) | 9/50 (18) | 26/50 (52) |
| | Hist. control | not reported | not reported | not reported |
| | Trend | $P = 0.484$ | $P = 0.032$[b] | $P = 0.319$[b] |
| Female | 0 | 14/50 (28) | 10/50 (20) | 19/50 (38) |
| | 188 | 25/49 (51)* | 14/49 (29) | 34/49 (69)*** |
| | 375 | 17/49 (35) | 8/49 (16) | 22/49 (45) |
| | 750 | 35/50 (70)*** | 12/50 (24) | 40/50 (80)*** |
| | Hist. control | 114/937 (0–40) | 103/937 (0–30) | 200/937 (3–54) |
| | Trend | $P < 0.001$ | $P = 0.329$ | $P = 0.001$ |

Source: NTP 1997.

*$P \leq 0.05$, **$P \leq 0.01$, ***$P \leq 0.001$ (logistic regression test).

[a]Number of mice with tumors/number of mice examined.

[b]Negative trend.

The incidences of alveolar/bronchiolar carcinoma in male and female mice in the 750-ppm groups were significantly greater than those in the controls and exceeded the historical control range of 0% to 16% for these neoplasms in two-year NTP inhalation studies. The incidence of alveolar/bronchiolar carcinoma in females in the 375-ppm group was significantly greater than in controls but was within the historical control range of 0% to 12%. The incidence of alveolar/bronchiolar adenomas in females in the 750-ppm group also exceeded the historical control range of 0% to 14%. Females in the 375-ppm group had a significantly greater incidence of cellular infiltration of histiocytes than the controls. The incidences of alveolar epithelial hyperplasia in exposed males and females were similar to those of the controls. The lung tumor incidence data are summarized in Table 4-3.

**Table 4-3. Lung tumor incidence in B6C3F$_1$ mice following inhalation exposure to nitromethane for up to two years**

| Sex | Exposure conc. (ppm) | Alveolar/bronchiolar tumor incidence[a] (%) | | |
|---|---|---|---|---|
| | | Adenoma | Carcinoma | Combined |
| Male | 0 | 11/50 (22) | 2/50 (4) | 13/50 (26) |
| | 188 | 10/50 (20) | 3/50 (6) | 13/50 (26) |
| | 375 | 9/50 (18) | 3/50 (6) | 12/50 (24) |
| | 750 | 12/50 (24) | 11/50 (22)** | 20/50 (40) |
| | Hist. control | 141/947 (6–36) | 75/947 (0–16) | 205/947 (10–42) |
| | Trend | $P$ = 0.422 | $P$ = 0.001 | $P$ = 0.059 |
| Female | 0 | 3/50 (6) | 0/50 (0) | 3/50 (6) |
| | 188 | 3/50 (6) | 3/50 (6) | 6/50 (12) |
| | 375 | 2/49 (4) | 5/49 (10)* | 6/49 (12) |
| | 750 | 9/50 (18) | 3/50 (6) | 12/50 (24)* |
| | Hist. control | 61/939 (0–14) | 38/939 (0–12) | 97/939 (0–16) |
| | Trend | $P$= 0.022 | $P$ = 0.149 | $P$ = 0.007 |

Source: NTP 1997.

*$P \leq 0.05$, **$P \leq 0.01$ (logistic regression test).

[a]Number of mice with tumors/number of mice examined.

## 4.3 Rats

### *4.3.1 Subchronic toxicity*

#### *4.3.1.1 Sprague-Dawley rats*

Male Sprague-Dawley rats (50 per group) were exposed to nitromethane vapor at a concentration of 0, 98, or 745 ppm (Lewis *et al.* 1979). The nitromethane had a reported purity of 96.5%. Animals were housed in inhalation chambers 24 hours/day but were exposed to nitromethane 7 hours/day, 5 days/week, for up to 24 weeks. Ten animals in each group were sacrificed and necropsied after 2 days, 10 days, 1 month, 3 months, and 6 months. The only effects of nitromethane exposure occurred at the high concentration and included decreased body-weight gain after 8 weeks, lowered hematocrit and hemoglobin level from 10 days through 6 months, and increased thyroid weight after 6 months. No compound-related macroscopic or microscopic lesions were observed.

#### *4.3.1.2 F344/N rats*

The NTP (1997) conducted a 13-week study to evaluate the cumulative toxic effects of repeated exposure to nitromethane and to determine the exposure concentrations to be used in the two-year study (see Section 4.2.2.1). Nitromethane was selected for study based on its potential for human exposure and its relationship to the known animal carcinogens 2-nitropropane and tetranitromethane.

Groups of F344/N rats (10 of each sex) were exposed to nitromethane vapor at a concentration of 0, 94, 188, 375, 750, or 1,500 ppm by inhalation, 6 hours/day, 5 days/week, for 13 weeks. Additional groups of rats (10 of each sex) designated for clinical pathology evaluations received the same exposure concentrations as the core study rats. Animals were housed individually; water was available *ad libitum,* and feed was available *ad libitum*; except during exposure periods. Clinical observations were recorded weekly. The core study animals were weighed initially, weekly, and at the end of the study. Neurobehavioral tests included forelimb and hindlimb grip strength measurements, response to stimulus (tail-flick latency), and startle response. Clinical pathology and clinical chemistry analyses were performed on rats designated for clinical pathology evaluation on days 3 and 23 and on core study rats at the end of the study. Samples also were collected for sperm motility and vaginal cytology evaluations from all rats in all groups at the end of the study. Complete necropsies were performed on all core study animals and included histopathologic examination of all major organs and tissues. The heart, right kidney, liver, lungs, right testis, thymus, and thyroid gland were weighed.

All rats survived to the end of the study. The final mean body weight and weight gain of male rats in the 1,500-ppm group were significantly less than those of the controls. Clinical findings included hindlimb paralysis in rats in the 750- and 1,500-ppm groups. Inhalation exposure of rats to nitromethane resulted in an exposure concentration–dependent, microcytic, responsive anemia; anemia was most pronounced in males and females exposed at 375 ppm or more. The presence of schistocytes, Heinz bodies, and spherocytes and increased mean cell hemoglobin and methemoglobin concentrations were evidence that a hemolytic process was occurring, which could have accounted, in part, for the anemia. Thrombocytosis accompanied the anemia and would be consistent with a reactive bone marrow or could have been due to the erroneous inclusion of small erythrocyte fragments in the platelet count. On day 23, transient decreases in serum triiodothyronine, thyroxine, and free thyroxine were observed in male rats exposed at 375 ppm or more and female rats in the 750- and 1,500-ppm groups. There was little or no pituitary response to the thyroid hormone decreases, as evidenced by the lack of significantly increased concentrations of thyroid-stimulating hormone in exposed rats. No biologically significant differences in organ weights were observed. The forelimb and hindlimb grip strengths of males in the 1,500-ppm group and the hindlimb grip strengths of females in the 750- and 1,500-ppm groups were significantly less than those of the controls. Minimal to mild hyperplasia of the bone marrow was observed microscopically in male rats in the 750- and 1,500-ppm groups and in females exposed at 188 ppm or more. Nasal lesions included olfactory epithelial degeneration in males and females exposed at 375 ppm or more and in one female in the 188-ppm group and respiratory epithelial hyaline droplets and goblet cell hyperplasia in males and females in the 750- and 1,500-ppm groups; the severity of nasal lesions in males and females was minimal to mild. Males and females exposed at 375 ppm or more had minimal to mild degeneration of the sciatic nerve and the lumbar spinal cord.

### *4.3.2 Chronic studies*

#### *4.3.2.1 F344/N rats*

Although several effects were considered treatment related in the subchronic toxicity study (see Section 4.3.1.2), most were not severe or common enough for determination of exposure concentrations for the two-year study. Exposure concentrations for the two-year study were based on the neurotoxicologic findings of hindlimb paralysis at 750 and 1,500 ppm and sciatic nerve and spinal cord lesions at 375 ppm or more. Groups of seven-week-old F344/N rats (50 of each sex) were exposed to nitromethane at a concentration of 0, 94, 188, or 375 ppm by inhalation, 6 hours/day, 5 days/week, for 103 weeks. The animals were housed individually; water was available *ad libitum*, and feed was available *ad libitum* except during exposure periods. All animals were observed twice daily. Clinical findings were recorded monthly through week 91, then every two weeks until the end of the study. Animals were weighed initially, weekly through week 12, monthly from week 15 through week 91, every two weeks thereafter, and at the end of the study. Complete necropsies and microscopic examinations were performed on all tissues and organs.

Survival rates did not differ significantly between exposed and control male or female rats (see Appendix B, pp. B-27 and B-28, Table 6 and Figure 1 in NTP 1997). From week 23 to the end of the study, the mean body weight of females in the 375-ppm group was slightly greater than that of the control group. The mean body weights of exposed and control males were generally similar throughout the study (see Appendix B, pp. B-29 to B-31, Figure 2 and Tables 7 and 8 in NTP 1997).

Clinical findings (masses on shoulder and torso) consistent with mammary gland neoplasms were observed in females in the 188- and 375-ppm groups during the course of the study. There were no indications of hindlimb paralysis or other treatment-related clinical findings. The incidences of mammary gland fibroadenoma and fibroadenoma, adenoma, or carcinoma (combined) increased with increasing exposure concentration, and the incidences in the 188- and 375-ppm groups were significantly greater than those of the controls (Table 4-4). Additionally, the incidences of carcinoma and adenoma or carcinoma (combined) in the 375-ppm group were significantly greater than those of the controls. The incidences of fibroadenoma in the 188- and 375-ppm groups and carcinoma in the 94- and 375-ppm groups exceeded the historical ranges for these neoplasms (16% to 42% and 0% to 8%, respectively) in chamber-control female rats in two-year NTP inhalation studies. No treatment-related mammary gland neoplasms were observed in male rats.

**Table 4-4. Mammary tumor incidence in female F344/N rats following inhalation exposure to nitromethane for up to two years**

| Exposure conc. (ppm) | Mammary tumor incidence[a] | | | | |
|---|---|---|---|---|---|
| | Fibroadenoma | Adenoma | Carcinoma | Adenoma or carcinoma | All combined |
| 0 | 19/50 (38) | 2/50 (4) | 2/50 (4) | 4/50 (8) | 21/50 (42) |
| 94 | 21/50 (42) | 0/50 (0) | 7/50 (14) | 7/50 (14) | 25/50 (50) |
| 188 | 33/50 (66)** | 0/50 (0) | 1/50 (2) | 1/50 (2) | 34/50 (68)** |
| 375 | 36/50 (72)*** | 2/50 (4) | 11/50 (22)* | 13/50 (26)* | 41/50 (82)*** |
| Hist. control | 180/653 (16–42) | 8/653 (0–4) | 25/653 (0–8) | NR[b] | 202/653 (16–46) |
| Trend | $P < 0.001$ | NS | $P = 0.009$ | $P = 0.01$ | $P < 0.001$ |

Source: NTP 1997.

*$P \leq 0.05$, **$P \leq 0.01$, ***$P \leq 0.001$, logistic regression test. NS = not significant.

[a]Number of rats with tumor/number of rats examined.

[b]NR = not reported in NTP 1997.

Histopathologic evaluation of sections of spinal cords and sciatic nerves from approximately 15 rats of each sex from the control and 375-ppm groups revealed no significant differences between exposed and control rats.

#### *4.3.2.2 Long-Evans rats*

A chronic inhalation study of nitromethane in Long-Evans rats, conducted as one of a series of inhalation studies of nitroparaffins, was reported (Griffin *et al.* 1996). Previous investigations of carcinogenic potential were performed on similar rats exposed to 1-nitropropane, 2-nitropropane, or nitroethane. Of these three nitroparaffins, only 2-nitropropane exhibited carcinogenic potential, in male rats only. Griffin *et al.* (1996) exposed groups of Long-Evans rats (40 of each sex) to nitromethane vapor at a concentration of 0, 100, or 200 ppm. The low concentration corresponds to the occupational exposure limit established by OSHA. The nitromethane had a reported purity of 96.26%, with 2.79% nitroethane and 0.62% nitropropane. Animals were housed in the inhalation chambers and exposed to nitromethane 7 hours/day, 5 days/week, for two years. Animals were observed daily for signs of toxic effects. Moribund animals were sacrificed, and dead animals were necropsied and thoroughly examined for macroscopic and microscopic lesions. At the end of the study, all surviving animals were sacrificed and received thorough clinical and pathological examinations.

The proportion of male rats surviving to the end of the study was approximately the same in the control and the two exposed groups. Among female rats, survival was lower in the 200-ppm group; however, no statistical test was performed. Survival rates of controls were 62.5% for males and 75% for females, and survival rates in the 200-ppm groups were 62.5% for males and 60% for females. Body weight was not significantly affected in males, but in females it was slightly depressed after 9 months and significantly reduced during the last year of the study. There were no statistically significant differences in

hematology, serum chemistry, and organ weights between the exposed and the control groups. Further, the data suggest no exposure-related differences in non-neoplastic or neoplastic pathology.

## 4.4 Summary

IARC (2000) concluded that there was sufficient evidence for the carcinogenicity of nitromethane in experimental animals, based on the NTP (1997) study.

### *4.4.1 Rabbits*

Evidence of only mild to moderate toxicity was observed in rabbits exposed to nitromethane at a concentration of 98 or 745 ppm by inhalation for 6 months.

### *4.4.2 Mice*

Increased incidences of harderian gland adenoma and adenoma or carcinoma (combined) occurred in male and female mice exposed to nitromethane by inhalation at 375 or 750 ppm. Increased incidences of lung carcinoma occurred in males exposed at 750 ppm and females exposed at 375 ppm. Female mice exposed at 750 ppm had a significantly increased incidence of lung adenoma or carcinoma (combined). In addition, the incidences of hepatocellular adenoma and adenoma or carcinoma (combined) were significantly increased in female mice at 188 or 750 ppm. The NTP concluded that there was clear evidence for carcinogenicity of nitromethane in both male and female $B6C3F_1$ mice.

### *4.4.3 Rats*

There was no evidence that nitromethane was carcinogenic in male or female Long-Evans rats exposed to nitromethane by inhalation at 100 or 200 ppm for two years or in male F344/N rats exposed at 94, 188, or 375 ppm for two years. In female F344/N rats exposed to nitromethane at 188 or 375 ppm for two years, the incidences of mammary gland fibroadenoma and fibroadenoma, adenoma, or carcinoma (combined) were significantly increased, and at 375 ppm, the incidence of mammary gland carcinoma was significantly increased. The NTP concluded that there was clear evidence that nitromethane was carcinogenic to female F344/N rats.

# 5 Genotoxicity

The genotoxicity of nitromethane was reviewed by the IARC Working Group (2000), which concluded that nitromethane was not genotoxic in any short-term tests except the Syrian hamster embryo (SHE) cell transformation assay (discussed in Section 6). No new studies on the genotoxicity of nitromethane have been published since the IARC (2000) monograph; the available literature is summarized below.

## 5.1 Prokaryotic systems: Reverse mutations in *Salmonella typhimurium*

In a study examining the mutagenicity of nitroaromatic and nitroheterocyclic compounds, Chiu *et al*. (1978) found that exposure to 0.1, 1, or 10 μmol of nitromethane did not induce reverse mutation in *Salmonella typhimurium* strains TA98 or TA100 in the absence of induced rat liver S9 metabolic activation. Similar results were obtained in studies by Löfroth *et al*. (1986) (20,000 to 50,000 μg [328 to 819 μmol), Mortelmans *et al*. (1986) (100 to 10,000 μg), Dayal *et al*. (1989) (50 to 200 μmol), Dellarco and Prival (1989) (0.3 to 100 μmol), and the NTP (1997) (100 to 10,000 μg[1.6-164 μmol). Nitromethane was not mutagenic in strains TA98 and TA100 in the presence of induced rat liver S9 (Mortelmans *et al.* 1986, Dellarco and Prival 1989, NTP 1997), strain TA1535 in the absence (Löfroth *et al.* 1986, Mortelmans *et al.* 1986, NTP 1997) or presence of induced rat liver S9 (Mortelmans *et al.* 1986, NTP 1997), or strain TA1537 in the presence or absence of induced rat liver S9 (Mortelmans *et al.* 1986, NTP 1997).

## 5.2 Non-mammalian eukaryotic systems: Sex-linked recessive lethal mutations in *Drosophila melanogaster*

Adult *Drosophila melanogaster* were given food spiked with nitromethane (125 mM), and sex-linked lethal mutations were scored in each of three successive broods (Gocke *et al.* 1981). Nitromethane did not induce sex-linked lethal mutations.

## 5.3 Mammalian systems

### *5.3.1* In vitro *assays*

The genotoxicity of nitromethane was assessed in tests that measure chromosomal and DNA damage.

#### *5.3.1.1 Chromosomal aberrations*

Chromosomal aberrations were not induced in Chinese hamster ovary (CHO) cells exposed to nitromethane at concentrations of 1,077 to 4,980 μg/mL in the presence or absence of induced rat liver S9 (NTP 1997).

#### *5.3.1.2 Micronucleus test*

Micronuclei were not induced in SHE cells exposed to nitromethane at concentrations of up to 5,000 μg/mL (Gibson *et al*. 1997).

#### *5.3.1.3 Sister-chromatid exchange*

The number of sister-chromatid exchanges (SCEs) per cell was not increased in CHO cells exposed to nitromethane at concentrations of 497 to 4,965 μg/mL in the presence or absence of induced rat liver S9 (NTP 1997).

### *5.3.2* In vivo *assays: Micronucleus test*

Micronucleus formation was not induced in bone-marrow erythrocytes of NMRI mice given nitromethane by intraperitoneal (i.p.) injection at a cumulative dose of 410, 1,830, or 3,660 mg/kg b.w. (Gocke *et al.* 1981) or in peripheral blood erythrocytes of $B6C3F_1$ mice exposed to nitromethane by inhalation at a concentration of 94 to 1,500 ppm for 13 weeks (NTP 1997).

## 5.4 Summary

Table 5-1 summarizes the data on nitromethane genotoxicity. Nitromethane was not mutagenic *in vitro* or *in vivo*. It did not induce reverse mutations in *S. typhimurium* strains TA98, TA100, TA1535, or TA1537 with or without induced rat liver S9; chromosomal aberrations or SCEs in CHO cells; or micronuclei in SHE cells or mouse bone marrow cells or peripheral erythrocytes.

**Table 5-1. Summary of genotoxicity studies of nitromethane**

| Test system | Endpoint | Results[a] | | Reference |
|---|---|---|---|---|
| | | without metabolic activation | with metabolic activation | |
| *S. typhimurium* TA98, TA100 | reverse mutation | – | – | Mortelmans *et al.* 1986, NTP 1997 |
| *S. typhimurium* TA98, TA100 | reverse mutation | – | NR | Chiu *et al.* 1978, Löfroth *et al.* 1986, Dayal *et al.* 1989 |
| *S. typhimurium* TA98, TA100 | reverse mutation | NR | – | Dellarco and Prival 1989 |
| *S. typhimurium* TA1535, TA1537 | reverse mutation | – | – | Mortelmans *et al.* 1986, NTP 1997 |
| *S. typhimurium* TA1535 | reverse mutation | – | NR | Löfroth *et al.* 1986 |
| *D. melanogaster* | sex-linked lethal mutations | – | NA | Gocke *et al.* 1981 |
| CHO cells | chromosomal aberrations, SCEs | – | – | NTP 1997 |
| SHE cells | micronuclei | – | NR | Gibson *et al.* 1997 |
| Mouse bone marrow cells (i.p.) | micronuclei | – | NA | Gocke *et al.* 1981 |
| Mouse peripheral erythrocytes (inhalation) | micronuclei | – | NA | NTP 1997 |

[a]NR = not reported, NA = not applicable.

# 6 Other Relevant Data

For the IARC (2000) review, no data were available on the toxicity, absorption, distribution, metabolism, or excretion of nitromethane in humans.

## 6.1 Toxicity

### *6.1.1 IARC review*

IARC (2000) reviewed eight studies in which rats, mice, or rabbits were exposed to nitromethane by i.p. or subcutaneous injection or by inhalation. Toxic effects included histidinemia, neurologic effects, degeneration of the olfactory epithelia, and hyperplasia of the bone marrow. Reproductive toxicity was manifested in a dose-related decrease in sperm motility in rats and mice and a dose-related increase in the length of the estrus cycle in mice.

Injection of Wistar rats with nitromethane at lethal doses did not result in detectable methemoglobin in the blood; the heart, lungs, kidney, and spleen, but not the liver, contained low concentrations of nitrite. The only tissue containing detectable nitromethane after inhalation of a lethal concentration (33 $g/m^3$) for 6 hours was the liver.

### *6.1.2 Hepatotoxicity*

The hepatotoxicity of nitroalkanes, including nitromethane, was studied in male and female BALB/c mice (Dayal *et al.* 1989). Nitromethane and nitroethane were administered by i.p. injection at 9 mmol/kg (549 and 675 mg/kg body weight [b.w.], respectively), and 2-nitropropane was administered at 4.5, 6.7, and 9 mmol/kg (400, 596, and 801 mg/kg b.w.). The animals were sacrificed after 24, 48, 72, or 96 hours, and blood samples were collected by cardiac puncture. The plasma activities of the hepatic enzymes sorbitol dehydrogenase, alanine aminotransferase, and aspartate aminotransferase were unchanged in male and female mice treated with either nitromethane or nitroethane. The activities of all three enzymes were significantly elevated in male mice at 48, 72, and 96 hours after administration of the high dose of 2-nitropropane, but not at 24 hours and not after administration of smaller doses. Hepatotoxicity was observed in female mice only at the middle dose of 2-nitropropane (6.7 mmol/kg, or 596 mg/kg b.w.).

The biochemical results were supported by histopathological evaluation of the livers of exposed mice. No significant abnormalities were observed in the livers of mice exposed to nitromethane or nitroethane. However, the livers of mice given 2-nitropropane at 9 mmol/kg (801 mg/kg b.w.) showed disruption of the normal parenchyma, together with extensive hemorrhagic necrosis. Apoptosis was a common feature of livers affected to varying degrees. The authors reported that 2-nitropropane was hepatotoxic at a dose of 9 mmol/kg, but that nitromethane and nitroethane were not hepatotoxic at this dose.

### *6.1.3 Miscellaneous toxicity studies*

#### *6.1.3.1 16-Day studies in rats and mice*

The NTP (1997) carried out 16-day inhalation toxicity studies in male and female F344/N rats and $B6C3F_1$ mice. Groups of animals (5 of each sex) were exposed to nitromethane

at a concentration of 0, 94, 188, 375, 750, or 1,500 ppm, 6 hours/day, 5 days/week, for a total of 12 exposures. All rats and mice survived to the end of the study.

In rats of both sexes, clinical findings of toxicity at 1,500 ppm included increased preening, rapid breathing, hyperactivity at the beginning of the study, and hypoactivity and loss of coordination in the hindlimbs near the end of the study. Degeneration of the sciatic nerve, ranging in severity from minimal to moderate, was present in all rats exposed to nitromethane at 375 ppm or more. The nerve lesion increased in severity with increasing exposure concentration and was characterized by prominent, diffuse vacuolization and dilatation of the axonal sheaths and increased cellularity. In addition, significantly less myelin was present around the sciatic axons in rats exposed to nitromethane at 750 or 1,500 ppm than in control rats. Degeneration of the olfactory epithelium of the nasal turbinates (minimal to mild severity) was observed in all males exposed at 375 ppm or more, in all females in the 750- and 1500-ppm groups, and in four females in the 375-ppm group. No exposure-related lesions were found in the lungs of exposed rats of either sex. In all exposed groups of male rats, relative liver weights were significantly higher than those of controls, and absolute and relative liver weights were significantly increased in female rats at 375, 750, and 1,500 ppm. Also significantly increased were the relative kidney weights of male rats at 750 and 1,500 ppm and female rats at 1,500 ppm.

In mice of both sexes, clinical findings included hypoactivity and tachypnea at 1,500 ppm, near the end of the study. The absolute and relative liver weights of male mice at 750 and 1,500 ppm and female mice at all exposure levels and the relative liver weight of male mice at 375 ppm were significantly greater than in controls. Degeneration of the olfactory epithelium was observed microscopically in all males (minimal severity) and females (minimal to mild severity) exposed at 375 ppm or more.

A series of acute inhalation exposures of groups of 2 to 4 rats to nitromethane (2 hours) or simulated hair sprays containing nitromethane (15 minutes) was conducted (EPA 1989, 1992). When observed for up to 10 days after exposure, the rats showed signs of eye irritation, respiratory impairment, and central nervous system depression. The approximate lethal dose was 6,000 ppm, indicating low toxicity.

#### *6.1.3.2 Bacterial luminescence toxicity test*

Median effective concentrations ($EC_{50}$s) for nitroparaffins were determined with the Microtox test, a commercial system for toxicity testing with a luminescent bacterium, a strain of *Vibrio fischeri* (previously known as *Photobacterium phosphoreum*) (Thumm *et al.* 1992, AZUR Environmental 2001). Inhibition of cellular activity by a toxic substance results in decreased respiration and correspondingly decreased bioluminescence, which is a byproduct of cellular respiration. The test substances included nitromethane, nitroethane, 1-nitropropane, 2-nitropropane, 1-nitrobutane, tert-nitrobutane (2-nitro-2-methylpropane), 1-nitropentane, 1-nitrohexane, 2-nitrobutane, and iso-nitrobutane (1-nitro-2-methylpropane). From these data, quantitative structure-activity relationships were deduced suggesting that toxicity depends on the number of methyl and methylene groups in a molecule. Nitromethane was the least toxic material tested.

## 6.2 Mammalian absorption, metabolism, and excretion

### *6.2.1 Human studies*

Gabrielli and Hammett-Stabler (1998) reported absorption of nitromethane by a patient as a result of accidental exposure to nitromethane fuel following a racing crash. The authors suggested that absorption was both dermal and by inhalation, but did not provide any quantitative data. Evidence for absorption was the apparent interference of nitromethane with a standard assay for serum creatinine; no evidence for a toxic effect was reported.

### *6.2.2 Animal studies*

#### *6.2.2.1 Dermal absorption in monkeys*

A single dose of radiolabeled nitromethane (300 μL of an ether/ethanol solution containing 5.5% [$^{14}$C]nitromethane, for a total dose of 18.8 μg) was applied to the skin of two female adult rhesus monkeys (*Macaca fascicularis*) for 12 hours (EPA 1990). After 72 hours, blood, urine, feces, skin, and subcutaneous fat were collected and tested for radioactivity, and the skin samples were examined histologically.

There were no changes in general appearance, behavior, weight, or appetite or signs of toxicity or irritation throughout the study. After 72 hours, an average of 15.39 μg of nitromethane was excreted, of which 11.44 μg (0.062% of the total dose) was excreted in the urine. The plasma contained an average of 1.53 μg of nitromethane (0.008% of the total dose), and the skin contained an average of 3.49 μg (0.018% of the total dose). No nitromethane was found in subcutaneous fat, indicating that nitromethane and its metabolites are absorbed only in negligible amounts through the skin, with absorption to subcutaneous fat also negligible (EPA 1990).

#### *6.2.2.2 Metabolism*

No published reports of *in vivo* metabolism of nitromethane were available for this review.

Metabolism of nitromethane by liver microsomes from Fischer 344 rats resulted in formation of only trace amounts of formaldehyde (IARC 2000).

Wade *et al.* (1977) reported that nitromethane interacted with sodium dithionite-reduced rabbit liver microsomes and competed with carbon monoxide for binding to cytochrome P-450. These data suggested that the interaction of nitromethane with reduced hepatic microsomes was different from that of aromatic nitro compounds.

Formaldehyde released by metabolic reactions may be a factor in the irritancy of inhaled compounds, and a role for metabolically generated formaldehyde in the tumorigenicity of some compounds has been suggested. Dahl and Hadley (1983) tested 32 potential substrates for cytochrome P-450-dependent monooxygenases, including nitromethane, with rat nasal mucosal and liver microsomes. The formation of formaldehyde, which is a known nasal carcinogen in animal models, was detected after incubation of nitromethane with rat liver, but not nasal mucosal, microsomes.

### 6.3 Transformation potential in Syrian hamster embryo cells

The SHE cell transformation assay has been proposed as a model for testing chemical agents for their neoplastic transformation potential. SHE cells can metabolically activate many chemicals and follow a progressive, multistage pattern of neoplastic transformation that has been compared to *in vivo* carcinogenesis. Kerckaert *et al.* (1996) exposed SHE cell cultures to nitromethane (98% purity) at six concentrations (2,000, 2,500, 3,000, 3,500, 4,000, and 5,000 μg/mL) for 24 hours, followed by 6 to 7 days of growth. The two highest concentrations (4,000 and 5,000 μg/mL) produced significant increases in the morphological transformation frequency ($P = 0.0291$ and $P = 0.0027$, respectively; Fisher's exact test), and the trend test also was statistically significant ($P = 0.001$). Based on these results, the authors predicted that nitromethane is likely to be a carcinogen in rodents.

### 6.4 Carcinogenicity and mutagenicity of related compounds

Nitromethane belongs to the class of nitroparaffins, of which the four commercially important members are nitromethane, nitroethane, 1-nitropropane, and 2-nitropropane (Kirk-Othmer 2001). No evidence exists in the published literature for the carcinogenicity of either nitroethane or 1-nitropropane.

IARC (1999) lists 2-nitropropane as possibly carcinogenic to humans (Group 2B), based on occurrence of benign and malignant liver tumors in rats. 2-Nitropropane also is listed in the 9th Report on Carcinogens (NTP 2000) as *reasonably anticipated to be a human carcinogen,* based on sufficient evidence of carcinogenicity in experimental animals; when administered through inhalation, 2-nitropropane induced hepatocellular carcinoma in male rats and hepatocellular nodules in rats of both sexes. The IARC Working Group (1999) also reported that 2-nitropropane was mutagenic to bacteria (with and without exogenous metabolism) and was genotoxic to a wide range of organisms *in vitro* and *in vivo*.

Another nitroalkane, tetranitromethane, has been evaluated for potential carcinogenicity by both an IARC Working Group (1996) and the NTP (2000). The IARC Working Group (1996) concluded that tetranitromethane is possibly carcinogenic to humans (Group 2B) based on a marked increase in the incidence of alveolar/bronchiolar adenoma and carcinoma in mice and rats and of squamous-cell carcinoma of the lung in rats. The NTP (1990) concluded that there was clear evidence of carcinogenicity of tetranitromethane in male and female F344/N rats and male and female B6C3$F_1$ mice, based on increased incidences of alveolar/bronchiolar neoplasms in both species and squamous-cell carcinoma of the lung in rats. Tetranitromethane is listed in the Report on Carcinogens as *reasonably anticipated to be a human carcinogen*. The IARC Working Group (1996) also reported that tetranitromethane is genotoxic in bacteria and in cultured mammalian cells and that a GC:AT transition in the second base of codon 12 of the K-*ras* oncogene was identified in tumors from tetranitromethane-exposed rats and mice.

Dayal *et al.* (1989) investigated the mutagenicity of nitromethane (see Section 5), 2-nitropropane, and nitroethane and their nitronates (the nitronate, or anionic form, of nitromethane is ($H_2C{=}NO_2^-$) in *S. typhimurium* strains TA98, TA100, and TA102.

Nitromethane, nitroethane, and their nitronates were not mutagenic, but 2-nitropropane and its anionic form, propane-2-nitronate, were mutagenic, with the anionic form being the more potent mutagen.

There is no consensus on why tumor sites and mutagenicity test results have differed among the individual nitroparaffin compounds. The 2-nitroalkanes, including 2-nitropropane, produce electrochemically active species; therefore, it is possible that the metabolites, and not the compounds themselves, are responsible for the positive results in genotoxicity studies for some of the compounds. Other studies have shown that the enzymatic denitrification of 2-nitropropane to acetone results in the formation of free radicals, superoxide, and hydrogen peroxide. Chemicals with the aliphatic nitro group ($-C-NO_2$) are on an NTP list of DNA-reactive subgroups that should be considered for possible carcinogenic activity. It is not known whether these reactive radicals may be involved, either directly or indirectly, in the mechanism of carcinogenicity for nitromethane and other nitroparaffins (NTP 1997).

## 6.5 Summary

Nitromethane has been shown to produce toxic effects in animals, including neurologic and reproductive effects. Relatively few reports have been published on the absorption, distribution, metabolism, and excretion of nitromethane. The available data suggest that absorption may occur by inhalation, but that the amount absorbed after dermal exposure is negligible. Although nitromethane may be metabolized to formaldehyde by rat liver microsomes *in vitro*, no published reports have characterized the metabolism of nitromethane *in vivo*. Nitromethane is structurally related to other nitro compounds (i.e., 2-nitropropane and tetranitromethane) that have been evaluated by IARC and considered to be possibly carcinogenic to humans. The mechanism of carcinogenicity for nitromethane and these other nitro compounds is not known; however, it has been hypothesized that reactive radicals may play a key role in their carcinogenicity.

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