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SECOND DRAFT

Information Profiles on Potential Occupational Hazards: Nitroparaffins

Center for Chemical Hazard Assessment
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16. Abstract (Limit: 200 words)

Profiles of information were presented for the following nitroparaffins chosen because of their commercial importance: nitroethane (79243), nitromethane (75525), 1-nitropropane (108032), 2-nitropropane (79469), tetranitromethane (509148), and trinitromethane (517259). Oral and inhalation toxicities and the degree of histological damage increase with increasing molecular weight of the compounds. The primary effects included histological liver damage and central nervous system depression, both atactic and narcotic changes, regardless of the route of administration or the duration of exposure. Vapor exposures also caused respiratory tract and conjunctival irritation and pulmonary edema. 1-Nitropropane, 2-nitropropane, tetranitromethane, and trinitromethane have been shown to be methemoglobinic poisons in animals. The development of precancerous lesions in the liver and hepatocellular cancer in rats have followed chronic inhalation exposure to 2-nitropropane. 2-Nitropropane gave a positive mutagenicity test result using the Ames Salmonella assay. Negative results were obtained for limited Salmonella and micronucleus testing of the other nitroparaffins. Symptoms of exposure in humans included headache, nausea, damage to the respiratory tract and liver damage. Most of the exposures to nitroparaffins resulting from occupational pursuits have been to 2-nitropropane.

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I. SCOPE OF DOCUMENT AND SUMMARY OF MAJOR FINDINGS

A. CLASS IDENTIFICATION

Nitroparaffins (or nitroalkanes) are derivatives of the alkanes in which one hydrogen or more is replaced by the electronegative nitro group ($-NO_2$), which is attached to carbon through nitrogen (Martin and Baker, 1969).

Appendix A contains a listing of all the nitroparaffins considered by this class definition.

B. CHEMICALS TO BE ADDRESSED

Individual profiles have been prepared for the following nitroparaffins:

Nitroethane
Nitromethane
1-Nitropropane
2-Nitropropane
Tetranitromethane
Trinitromethane

Profiles have been prepared for all the nitroparaffins identified as having commercial importance. Here, commercial importance means an annual production in the thousands of pounds and a specific industrial or commercial use as opposed to a reagent or laboratory use.

The four major nitroparaffins of commerce are nitromethane, nitroethane, 1-nitropropane, and 2-nitropropane. All are produced in multimillion pound quantities and have diversified applications.

C. SUMMARY OF BIOLOGICAL ACTIVITY

The clinical and pathological changes, in animals, resulting from exposure to nitromethane, nitroethane, 1-nitropropane, 2-nitropropane, trinitromethane, and tetranitromethane are similar in nature although different in degree. Comparative studies have indicated that oral and inhalation toxicity and the degree of histologic damage increases with increasing molecular weight of the compound; nitromethane and nitroethane (rat oral LD50s > 1000 mg/kg) are less toxic than 1- or 2-nitropropane (500-700 mg/kg), which in turn are less toxic than tetra- and trinitromethane (≈300 mg/kg). Histologic liver damage and central nervous system depression (atactic and narcotic changes) are the primary effects in animals of exposure to these nitroparaffins regardless of the route of administration or duration of exposure, and respiratory tract and conjuctival irritation and pulmonary edema have consistently been associated with vapor exposures. The four higher molecular weight nitroparaffins (1- and 2-nitropropane, tetra- and trinitromethane) additionally have been demonstrated to be methemoglobinic poisons in animals. Chronic inhalation exposure to 2-nitropropane has been associated with the development of precancerous lesions in the liver and hepatocellular cancer in rats, and 2-nitropropane was a positive mutagen in the Ames Salmonella assay. Limited Salmonella and micronucleus testing of the other nitroparaffins (including micronucleus testing of 2-nitropropane) were negative.

In humans, the symptoms of exposure for all six nitroparaffins are similar; these include headache and nausea and, at high concentrations, damage to the respiratory tract and liver. The majority of reports of worker exposure are related to exposure to 2-nitropropane.

II. INFORMATION PROFILES

A. NITROETHANE

1. Chemical Name: Nitroethane

2. Chemical Structure: $CH_3-CH_2-NO_2$

3. Synonyms: Ethane, nitro-
NE

4. Chemical Abstracts Service (CAS) Number: 79-24-3

5. Registry of Toxic Effects of Chemical Substances (RTECS) Number:
KI5600000

6. Chemical and Physical Properties:

Description:	colorless oily liquid; pleasant odor
Molecular Weight:	75.07
Boiling Point:	114.07°C
Melting Point:	-50°C
Vapor Pressure:	15.8 mm Hg (20°C)
Solubility:	4.5 ml/100 ml water; miscible with ethanol, methanol, ether; soluble in chloroform, acetone, and aqueous solutions of alkalis
Specific Gravity:	1.052^{20}_{20}
Stability:	combustible; decomposes when subjected to high temperatures; autoignition temp.: 779°F; Flash point: 82°F

7. Production

Nitroethane is produced in multimillion-pound quantities (Martin and Baker, 1969). Specific production ranges are not available from the U.S. EPA (1980).

8. Use

Nitroethane is most useful as a chemical intermediate for organic synthesis (IMC, n.d.). The nitroparaffins, including nitroethane, are used in the production of derivatives such as nitroalcohols, alkanolamines, and polynitro compounds. Production of these derivatives consumes several million pounds of nitroparaffins annually (Martin and Baker, 1969). Nitroethane, for example, is used to produce the nitroalcohol 2-nitro-2-methyl-1,3-propanediol which is reduced to the alkanolamine 2-amino-2-methyl-1,3-propanediol (IMC, n.d.).

As an intermediate, nitroethane is also used in the synthesis of the insecticide Prolan and can be used to synthesize the insecticide methomyl. Nitroethane is used in the synthesis of a wide variety of pharmaceuticals, insecticides, herbicides, and other specialty chemicals. Among these useful derivatives of nitroethane are phenylpropanolamine, amphetamine, amphetaminil, and phenylacetone (IMC, n.d.).

One of the largest volume uses of nitroparaffins consumed _per se_ is as solvents. Solvent applications include use in polymers and coatings, as extraction or partition solvents, as reaction media, and as widely used solvents in crystallization of organic compounds (Martin and Baker, 1969). Nitroethane is an excellent solvent for a wide variety of organic compounds and for resins such as acrylic and vinyl resins used in coatings and inks. It can be used as a solvent for the extraction of resin from wood and in separation systems such as fractionating petroleum distillate oils and for the dewaxing of diesel fuels. Nitromethane is a solvent for aluminum chloride which forms a complex used as a Friedel-Crafts catalyst (IMC, n.d.).

Nitroethane is also used as a stabilizer for halogenated hydrocarbon solvents to help prevent release of HCl (IMC, n.d.), and as an additive to diesel fuels to increase power and to reduce smoke in exhaust (IMC, 1980). It can be used as a battery electrolyte (Gu and Bennion, 1978).

9. Manufacturers and Distributors

Nitroethane is manufactured by International Minerals and Chemical (IMC) Corp. in Sterlington, LA (SRI International, 1980; U.S. EPA, 1980).

The manufacturer may be the only major distributor.

Other distributors include (Chem Sources--USA, 1980):

Aldrich Chem.
Alfa Prod.
Anachemia Chem.
Atomergic Chemetals
J.T. Baker Chem.
Chem. Services
Eastern Chem.
EM Labs
Lachat Chem.
LaPine Sci.
Mallinckrodt
MCB Reagents
Pfaltz and Bauer
Polysciences, Inc.
Tridom Chem.

10. Manufacturing Process

The four lower mononitroparaffins--nitroethane, nitromethane, 1-nitropropane, and 2-nitropropane--are made on a large scale at the Sterlington, LA, plant of the IMC Chemical Group. The manufacturing process consists of oxidizing an excess of vapor-phase propane with nitric acid at a temperature range of 370-450°C and pressure of 8 to 12 atmospheres. Approximately 40% of the nitric acid is converted to nitroparaffins; the remainder acts as an oxidizing agent to produce the oxygenated by-products and is, in turn, reduced to nitric oxide.

Yields of the four nitroparaffins can be varied by temperature adjustments and additions of oxygenated sulfur compounds.

The nitroparaffins and condensable by-products (ketones and aldehydes) are condensed upon leaving the reactor; the unreacted propane and nitric oxide remain in the gas phase. The propane is separated and recycled, while the NO is oxidized to NO_2, absorbed in water to form HNO_3, concentrated, and recycled to the process. The ketones and aldehydes are separated from the nitroparaffins by solvent extraction with chlorinated aromatics. The individual nitroparaffins are then separated and purified by fractional distillation (Martin and Baker, 1969; Leipins <u>et al</u>., 1977). Figure 1 outlines the basic process operations.

The four lower mononitroparaffins formed during propane nitration at 500°C are produced in the following percentages (Martin and Baker, 1969):

nitroethane	16.6 mole %
nitromethane	22.0 mole %
1-nitropropane	13.2 mole %
2-nitropropane	48.2 mole %

These commercial nitroalkanes are 92.5-95% pure by individual compound and are 99% nitroparaffins by weight (Martin and Baker, 1969).

11. Impurities or Additives

Commercial nitroethane has the following specifications (IMC, 1980):

Nitroethane content, by wt. (min.)	92.5%
Total nitroparaffins, by wt. (min.)	99%
Acidity as acetic acid, by wt. (max.)	0.1%
Water, by wt. (max.)	0.1%
Color, APHA (max.)	20

12. Occupational Exposure

The National Occupational Hazard Survey indicates that 824,404 workers are potentially exposed to nitroethane.

13. Control Technology and Work Practices

Specific factors that may contribute to or prevent employee exposure to nitroethane were not found in the literature searched. IMC (1977) has noted that general mechanical ventilation or hoods at point of use are normally required to control the atmospheric vapor concentrations of the four lower mononitroparaffins at levels below that of the established Threshold Limit Values (TLVs). For short exposure to concentrations of nitroparaffin vapors of less than 2% and where sufficient oxygen is present (>16%), industrial-type gas masks

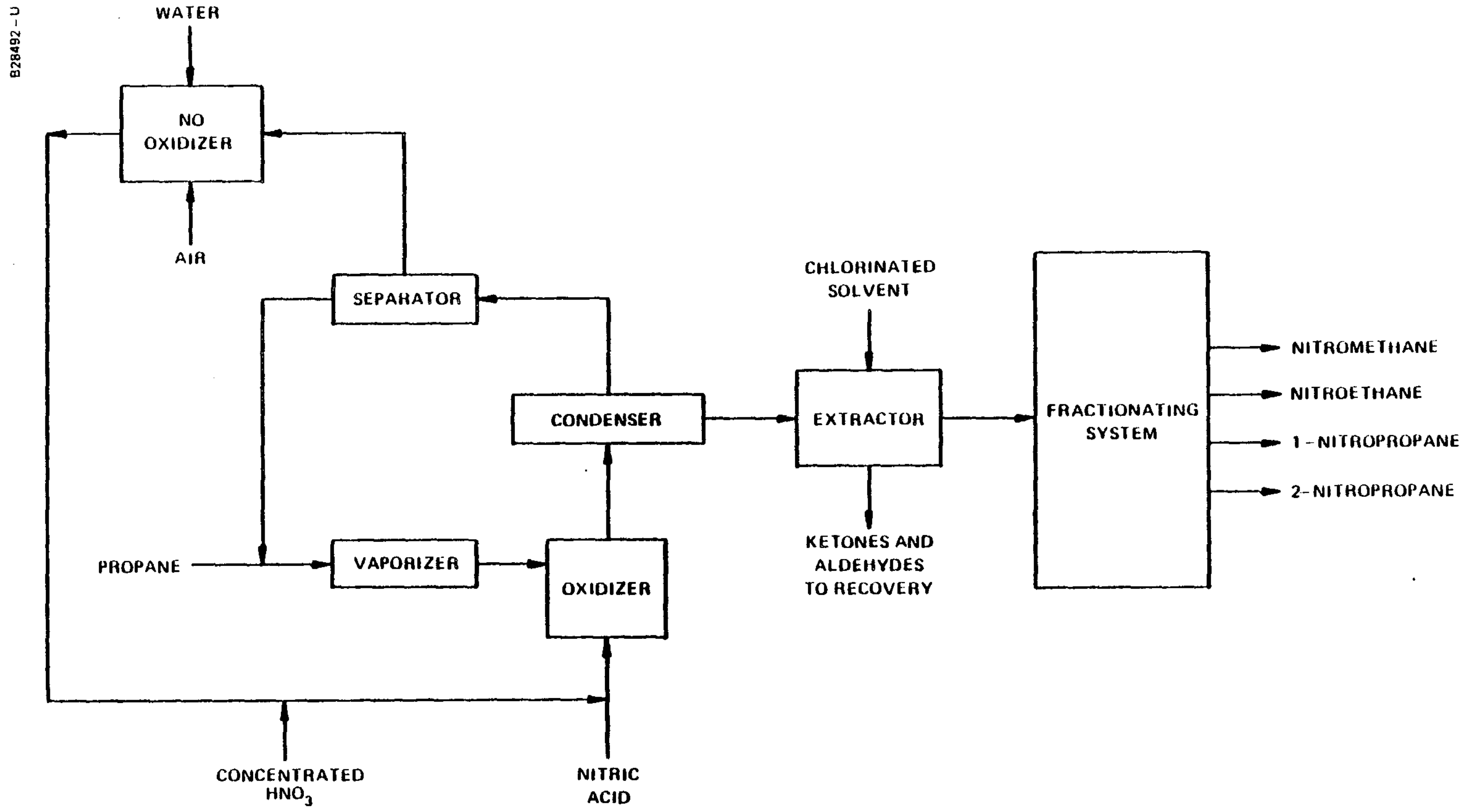


Figure 1. Manufacture of Nitromethane, Nitroethane, and Nitropropane (adopted from Martin and Baker, 1969; Leipins _et al._, 1977)

provided with recommended organic vapor canisters were deemed satisfactory (IMC, 1977). A fresh air mask or a self-contained breathing apparatus is recommended for use in situations where prolonged exposure to vapors of nitroparaffins above the TLV is anticipated.

14. Biological Effects

a. Animal Studies

(1) Acute Exposures

The acute toxic effects of nitroethane are summarized in Table 1. Oral administration of 500 to 750 mg/kg nitroethane to rabbits caused progressive weakness and collapse, unsteadiness and incoordination ending in complete ataxia, and changes in respiration evidenced first by slowed breathing and later by rapid breathing (Machle et al., 1940). Oral administration of the chemical at these levels caused no changes in blood chemistry and no methemoglobin formation. At necropsy, severe congestion of the enteric tract was observed. Liver damage was present in all animals that died from administration of the chemical (Machle et al., 1940).

Inhalation experiments with rabbits, guinea pigs, and monkeys were also performed by Machle et al. (1940). Mortality was dose related. Rabbits and guinea pigs (2 of each species) survived exposures to 2500 ppm for 3 hours or 1000 ppm for 6 hours, but exposure to 1000 ppm for 12 hours or 30,000 ppm for 30 minutes resulted in the death of 1 of 2 rabbits. At 500 ppm, the lowest concentration used in this study, 2 rabbits and 1 monkey survived an extended exposure period as described under subchronic exposures (Machle et al., 1940). Based on mortality, nitroethane was more toxic to rabbits than to guinea pigs.

Exposure to nitroethane in air caused irritation of the respiratory tract and conjunctival irritation; eyelids were reddened, discharges

Table 1. Acute Effects of Nitroethane

Route	Species	Dose (mg/kg)	Response	Reference
oral	rats	1625 + 193	LD50	Martin and Baker, 1967
oral	rats	1100	LD50	Dorigan _et_ _al_., 1976
oral	mice	2150	LD50	Hite and Skeggs, 1979
oral	mice	860	LD50	Dorigan _et_ _al_., 1976
oral	rabbits	500	LDLo	Machle _et_ _al_., 1940
inhalation	rabbits	5000 ppm x 2 h[a]	LCLo	Machle _et_ _al_., 1940

[a] h = hour.

appeared, and the eyes were kept closed (Machle et al., 1940). Central nervous system symptoms, manifested as jerking or twitching movements of the extremities, also were observed, but were of minimal intensity. Nitroethane differed from nitromethane in that it exhibited anesthetic properties; stupor, narcosis, or light general anesthesia appeared in animals exposed to 30,000 ppm in air for longer than 1 hour or to 1000 ppm for 5 or 6 hours (Machle et al., 1940). The intensity of the symptoms of nitroethane poisoning paralleled the severity and duration of exposure. Machle et al. (1940) also noted that there was no distinct latent period before the onset of symptoms induced by nitroethane (unlike nitromethane), and that lethal concentrations of nitroethane were lower than narcotic concentrations (like nitromethane).

At necropsy, all exposed animals were found to have some liver damage; fatty infiltration was seen in a number of animals (Machle et al., 1940). Animals that died from nitroethane inhalation also exhibited general visceral and cerebral congestion, severe congestion of the upper respiratory tract, and pulmonary congestion with edema (Machle et al., 1940).

Dequidt et al. (1972) reported that single intraperitoneal injections of 1100 mg/kg nitroethane were not lethal to rats. Rats also survived 7 daily intraperitoneal injections of 110 mg/kg nitroethane administered over 10 days. The authors also found that rats survived five 6-hour inhalation periods at 2200 ppm nitroethane. No methemoglobin was detected in the blood after inhalation of 2200 ppm nitroethane.

Application of nitroethane (dose not specified) to the clipped skin of rabbits caused neither skin irritation nor illness (Machle et al., 1940).

(2) Subchronic Exposures

In a short-term subchronic study, 2 rabbits and 1 monkey survived 6-hour periods of inhalation of 500 ppm nitroethane for a total exposure period of 140 hours (Machle et al., 1940).

(3) Chronic Exposures

No information was found in the literature searched.

(4) Carcinogenicity

No information was found in the literature searched.

(5) Mutagenicity

Nitroethane was not mutagenic in the Ames test for Salmonella typhimurium strains TA1537, TA92, TA98, or TA100, when tested with or without mammalian microsome activation (Hite and Skeggs, 1979). Nitroethane was also non-mutagenic in the micronucleus test with mice (Hite and Skeggs, 1979); in this study, mice were given 2 consecutive daily oral doses of 282, 565, or 1130 mg/kg nitroethane.

(6) Teratogenicity

Beliles et al. (1978) exposed 24 pregnant mice by inhalation to a combination of 14.3 ppm nitroethane and 8.9 ppm diethylhydroxylamine on days 6 to 17 of gestation. Exposures were for 8.25 hours/day, including weekends. Exposure to this combination of chemicals produced no compound-induced terata, variation in sex ratio, embryotoxicity, or inhibition of fetal growth and development.

(7) Reproductive Effects

No embryotoxicity was produced by the inhalation regimen described in Section 6 (Beliles et al., 1978).

(8) Other Relevant Information

Nitroethane is oxidatively degraded in rabbits to yield acetaldehyde and nitrite (Scott, 1942). The nitrite apparently is converted rapidly to nitrate (Scott, 1943). Scott (1943) measured the levels of nitroethane, nitrite, and nitrate in the blood of rabbits exposed to nitroethane by inhalation or oral administration. There was a definite correlation between the concentrations of nitrate and nitroethane in the blood of animals exposed by inhalation. The concentration of nitrate and nitrite increased gradually in the blood of rabbits during the exposure period; urinary excretion of nitrate was slow (Scott, 1943).

Dequidt *et al*. (1972) concluded that nitroethane was a relatively weak methemoglobinic poison compared to 1- or 2-nitropropane. Small quantities of nitrite were detected in all organs, except the liver, of rats exposed by inhalation or intraperitoneal injection. Unchanged nitroethane, however, was detected in no organs other than the liver. After 5 daily 6-hour exposure sessions to 2200 ppm nitroethane in air, the level of unchanged nitroethane in the liver was 0.1 mg/100 g (Dequidt *et al*., 1972).

A fairly rapid breakdown, with nearly complete elimination of nitroethane in 30 hours' time, was indicated in experiments with rats and rabbits (Machle *et al*., 1942). The total amount of nitroethane in the tissues of rabbits injected with 1 g of nitroethane decreased from 0.147 g at 20 minutes to 0.014 g at 30 hours. In rats, 79% of a 13.6 mg dose was recovered as unchanged nitroethane 1.6 minutes after injection, but only 14% was recovered after 3 hours (Machle *et al*., 1942).

Nitroethane is partially eliminated from the body via the lungs. During a 30-hour period following an intravenous injection of 1 g of nitroethane, 0.171 g of nitroethane was recovered in the expired air of rabbits

(Machle et al., 1942). Dequidt et al. (1972) recovered 10% of the injected dose of nitroethane in the expired air of rats.

b. Human Studies

(1) Pharmacokinetics

No information was found in the literature searched.

(2) Health Effects

Early symptoms of nitroparaffin intoxication include headache and nausea, which clear when exposure is reduced (Martin and Baker, 1969).

Mild skin irritation following frequent contact with nitroparaffins has been reported by workers (IMC, 1977), but no allergies or other adverse physiological effects have been reported as a result of skin exposure (Martin and Baker, 1969).

(3) Target Organ Toxicity

The most common route of exposure to nitroethane in the workplace is by inhalation of vapors (IMC, 1977). Inhalation of high concentrations of vapor will cause damage to the respiratory tract and to other internal organs, primarily the liver (IMC, 1977). Animal studies indicate that, regardless of the route of exposure, the liver is the organ that suffers the most severe damage from nitroethane poisoning.

(4) Epidemiology

The International Minerals and Chemical Corporation (IMC) plant at Sterlington, LA, is the sole commerical manufacturer of nitroethane. Nitromethane, nitroethane, 1-nitropropane, and 2-nitropropane are all made simultaneously in this plant; hence, workers are exposed to all four compounds. Because it has been suggested that 2-nitropropane may be a human carcinogen (Finklea, 1977), IMC initiated a retrospective mortality study to deter mine if there were any unusual disease mortality patterns among the workers of this plant. The study included 1815 employees who had worked at the plant during the period from January 1, 1946 through June 30, 1977 (Miller and Temple, 1979). Death certificates of 180 employees were examined. Eleven past employees could not be accounted for, but 7 of those had terminated prior to 1955, the year that nitroparaffin production began. Employee exposure was categorized on the basis of the department in which the employee worked. The cohorts were (1) "direct exposure," consisting of 372 employees from laboratories, research, production, derivatives, and warehouses, (2) "indirect exposure," consisting of 366 employees from the machine shop, electric shop, maintenance, and related services, and (3) "no exposure," consisting of 743 employees from all non-nitroparaffin departments such as plant offices and other processes. IMC provided the original data on 1481 individuals employed after January 1, 1955 and 334 employees terminated prior to that date to Drs. Monson and McMahon at the Harvard School of Public Health for analysis and interpretation.

A review of the deaths caused by cancer revealed that no deaths had resulted from cancer of the liver, including hepatocellular carcinoma (Miller and Temple, 1979). No cases were reported indicating benign neoplasms of the liver. The analysis of the data did not suggest any unusual cancer or other disease mortality patterns among the workers at the Sterlington plant, either before or after the start of nitroparaffin production in 1955. Monson and McMahon noted, however, that because the cohort is small and because the period of latency is, in most cases, relatively short, one cannot conclude from these data that 2-nitropropane is noncarcinogenic in humans (Miller and Temple, 1979). Although nitroethane was not specifically addressed in this study, the results and limitations of this study are applicable to nitroethane since simultaneous exposure to all four nitroparaffins occurs in this plant.

The statements of Drs. Monson and McMahon regarding the limitations of this study are in agreement with the conclusions of a study by Brown and Dobbin (1977). Following an industrial survey at the Sterlington plant which was conducted to determine the feasibility of a health effects study on nitroparaffin workers, Brown and Dobbin (1977) concluded that the population exposed was too small and the length of time since onset of exposure was too short to conduct a retrospective cohort mortality study, pregnancy outcome study, or cross-sectional medical study.

15. Ongoing Studies

Microbial mutagenesis and genetic toxicity testing of nitroethane is scheduled to be completed by the National Toxicology Program in fiscal year 1981 (NTP, 1981b).

16. Exposure Standards

The current occupational exposure standards recommended by the ACGIH (1981) for nitroethane are a Threshold Limit Value-Time Weighted Average (TLV-TWA) of 100 ppm (310 mg/m^3) and a Threshold Limit Value-Short-Term Exposure Limit (TLV-STEL) of 150 ppm (465 mg/m^3). OSHA (1976) has adopted the TLV-TWA of 100 ppm for nitroethane.

17. Sources of Additional Relevant Information

No sources of additional relevant information were identified.

18. Other Pertinent Data

No other information that would aid in the assessment of nitroethane as an occupational hazard was found in the literature searched.

B. NITROMETHANE

1. Chemical Name: Nitromethane

2. Chemical Structure: CH_3NO_2

3. Synonyms: Nitrocarbol
   Methane, nitro-
   NM

4. Chemical Abstracts Service (CAS) Number: 75-52-5

5. Registry of Toxic Effects of Chemical Substances (RTECS) Number:

   PA9800000

6. Chemical and Physical Properties:

Description:	colorless oily liquid
Molecular Weight:	61.04
Boiling Point:	101.20°C
Melting Point:	-28.55°C
Vapor Pressure:	27.3 mm Hg (20°C)
Solubility:	≈11 g/100 g water (25°C); soluble in alcohol, ether, dimethyl formanide, acetone, and alkali; 10.5% by weight in water (200°C)
Specific Gravity:	1.13
Stability:	dangerous fire and explosion risk; autoignition temp.: 785°F; Flash point: 95°F

7. Production

Nitromethane is produced in multimillion-pound quantities (Martin and Baker, 1969). Specific production figures or ranges are not available from the U.S. EPA (1980).

8. Use

One of the most important uses for the nitroparaffins, including nitromethane, is the production of derivatives such as nitroalcohols, alkanolamines, and polynitro compounds. Production of these derivatives consumes several million pounds of nitroparaffins annually (Martin and Baker, 1969). Specifically, nitromethane is used to prepare tris(hydroxymethyl) nitromethane, 2-nitroethanol, and 2-nitro-1,3-propanediol nitroalcohols (Dewey, 1969). Reduction of these nitroalcohols yields the corresponding alkanolamines.

One of the largest volume uses of nitroparaffins consumed per se is as solvents. Solvent applications include use in polymers and coatings, as extraction or partition solvents, as reaction media, and as widely used solvents in crystallization of organic compounds (Martin and Baker, 1969). Nitromethane is the best known solvent for x-cyanoacrylates; solvent blends containing nitromethane are recommended for consumer or industiral end-product use (IMC, 1980). In general, nitromethane is miscible with high proportions of aromatic hydrocarbons and only miscible with aliphatic hydrocarbons at low concentrations. It is therefore a suitable solvent for the separation of aromatics from aliphatics by solvent-extraction techniques (IMC, 1980).

Nitromethane is used commercially as a chemical stabilizer to prevent the decomposition of various chlorinated and fluorinated solvents which are used as metal degreasers and aerosol propellants. The addition of a small percentage of a mixture of nitromethane and oxygenated solvent (e.g., dioxane, butylene oxide) to solvents such as 1,1,1-trichloroethane inhibits decomposition and prevents corrosive attack of the halogenated solvent on metals (IMC, 1980).

As a fuel, nitromethane is used as a specialty fuel in racing cars and model engines (IMC, 1980). It is commonly used in mixtures with methanol for this purpose. IMC Markets this mixture as Comsol NM-55. Nitromethane may also be incorporated into diesel fuels up to 2% by weight to help increase power and to reduce exhaust smoke (IMC, 1980).

Nitromethane also has commercial applications as an explosive and propellent, as a battery electrolyte, and as a chemical intermediate for a variety of syntheses (IMC, 1980; Martin and Baker, 1969; Gu and Bennion, 1978).

9. Manufacturers and Distributors

Nitromethane is manufactured by International Minerals and Chemical (IMC) Corp. in Sterlington, LA (SRI International, 1980; U.S. EPA, 1980).

Distributors include (*1980-81 OPD Chemical Buyers Directory*, 1980; *Chemical Week: 1980 Buyers' Guide Issue*, 1980; *Chem Sources--USA*, 1980):

Aldrich Chem.
Alfa Prod.
Anachemia Chem.
Ashland Chem.
Atomergic Chemetals
J.T. Baker Chem.
Bio-Clinical Labs
Chem Services
Columbia Organics
EM Labs
Eastman Kodak
Fisher Sci.
Jonas Chem.
Kum Yang Co. Ltd.
Lachat Chem.
LaPine Sci.
Mallinckrodt
MCB Reagents
Pfaltz and Bauer
Tridom Chem.

10. Manufacturing Processes

The four lower mononitroparaffins--nitroethane, nitromethane, 1-nitropropane, and 2-nitropropane--are made on a large scale at the Sterlington, LA, plant of the IMC Chemical Group. The manufacturing process consists of oxidizing an excess of vapor-phase propane with nitric acid at a temperature range of 370-450°C and pressure of 8 to 12 atmospheres. Approximately 40% of the nitric acid is converted to nitroparaffins; the remainder acts as an oxidizing agent to produce the oxygenated by-products and is, in turn, reduced to nitric oxide.

Yields of the four nitroparaffins can be varied by temperature adjustments and additions of oxygenated sulfur compounds.

The nitroparaffins and condensable by-products (ketones and aldehydes) are condensed upon leaving the reactor; the unreacted propane and nitric oxide remain in the gas phase. The propane is separated and recycled, while the NO is oxidized to NO_2, absorbed in water to form HNO_3, concentrated, and recycled to the process. The ketones and aldehydes are separated from the nitroparaffins by solvent extraction with chlorinated aromatics. The individual nitroparaffins are then separated and purified by fractional distillation (Martin and Baker, 1969; Leipins et al., 1977). Figure 2 outlines the basic process operations.

The four lower mononitroparaffins formed during propane nitration at 500°C are produced in the following percentages (Martin and Baker, 1969):

nitroethane	16.6 mole %
nitromethane	22.0 mole %
1-nitropropane	13.2 mole %
2-nitropropane	48.2 mole %

These commercial nitroalkanes are 92.5-95% pure by individual compound and are 99% nitroparaffins by weight (Martin and Baker, 1969).

11. Impurities or Additives

Commercial nitromethane has the following specifications (IMC, 1980):

Purity, by wt. (min.)	95%
Total nitroparaffins, by wt. (min.)	99%
Acidity as acetic acid, by wt. (max.)	0.1%
Water, by wt. (max.)	0.1%
Color, APHA (max.)	20

12. Occupational Exposure

The National Occupational Hazard Survey indicates that 838,491 workers are potentially exposed to nitromethane.

13. Control Technology and Work Practices

Specific factors that may contribute to or prevent employee exposure to nitromethane were not found in the literature searched. IMC (1977) has noted that general mechanical ventilation or hoods at point of use are normally required to control the atmospheric vapor concentrations of the four lower mononitroparaffins at levels below that of the established Threshold Limit Values (TLVs). For short exposure to concentrations of nitroparaffin vapors of less

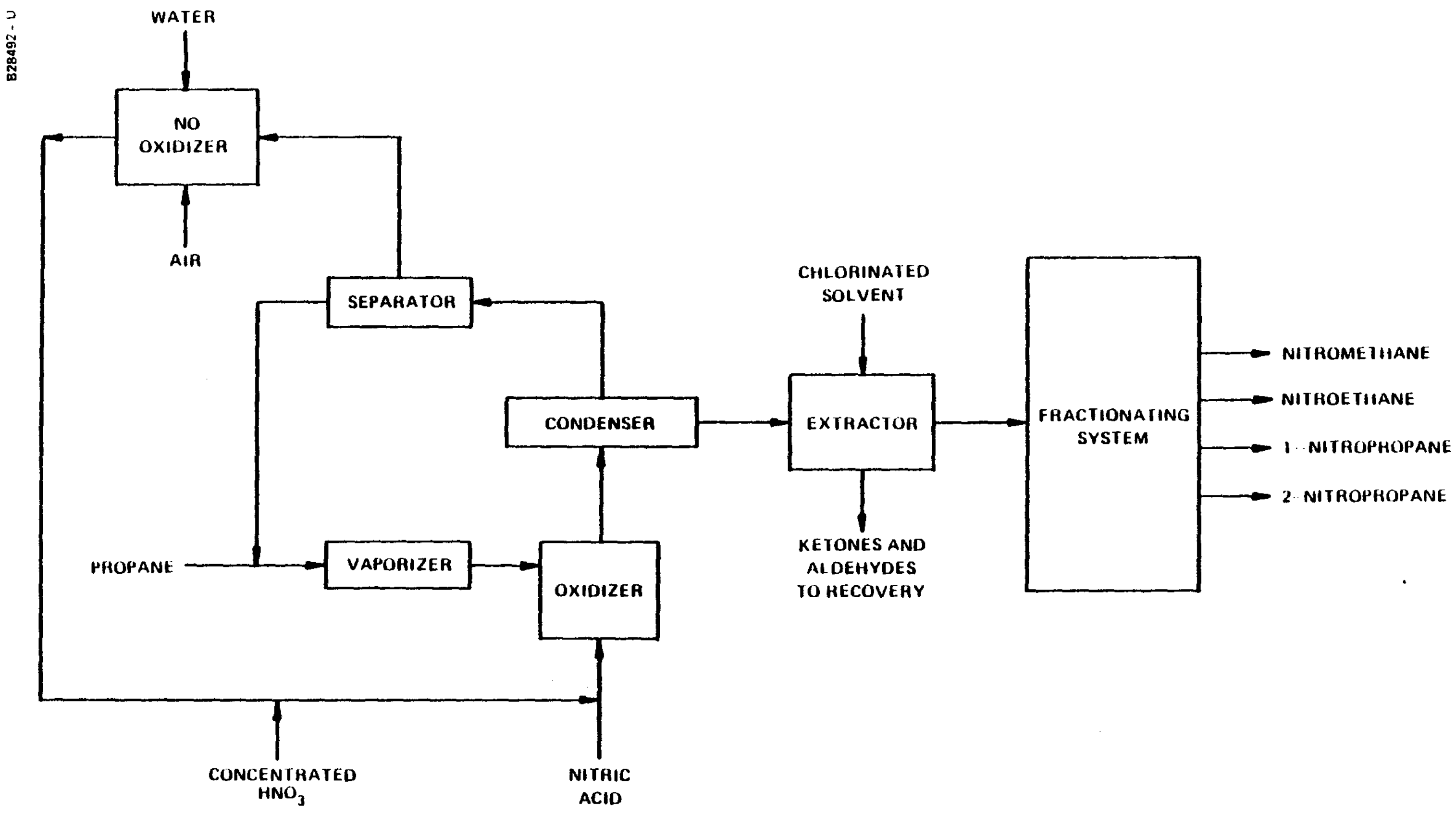


Figure 2. Manufacture of Nitromethane, Nitroethane, and Nitropropane (adopted from Martin and Baker, 1969; Leipins *et al.*, 1977)

than 2% and where sufficient oxygen is present (>16%), industrial-type gas masks provided with recommended organic vapor canisters were deemed satisfactory (IMC, 1977). A fresh air mask or a self-contained breathing apparatus is recommended for use in situations where prolonged exposure to vapors of nitroparaffins above the TLV is anticipated.

14. Biological Effects

a. Animal Studies

(1) Acute Exposures

The acute toxic effects of nitromethane are summarized in Table 2. One of the earliest studies on nitromethane toxicity was performed in 1891 by Gibbs and Reichert (1891). They reported a minimum lethal dose for dogs of 565 to 1130 mg/kg. Injection of nitromethane caused lassitude, drowsiness, weakness, salivation, urination, defecation, and vomiting. Nitromethane first accelerated, then retarded, the dogs' pulse rate. Treated dogs exhibited progressive weakness, coma, paralysis, and terminal convulsions. Death by respiratory failure usually occurred within 24 hours of injection (Gibbs and Reichert, 1891).

Machle et al. (1940) observed similar symptoms of nitromethane poisoning in rabbits receiving oral doses of 750 to 1000 mg/kg; administration of the chemical caused progressive weakness and collapse, unsteadiness and incoordination ending in complete ataxia, and changes in respiration evidenced first by slowed breathing and later by rapid breathing. There were no changes in blood chemistry and no methemoglobin formation. At necropsy, severe congestion of the enteric tract was observed. Liver damage was present in all animals that died from administration of the chemical (Machle et al., 1940).

Table 2. Acute Effects of Nitromethane

Route[a]	Species (mg/kg)	Dose	Response	Reference
oral	rats	1210 + 322	LD50	Martin and Baker, 1967
oral	rats	940	LD50	Dorigan _et_ _al_., 1976
oral	mice	1440	LD50	Weatherby, 1955
oral	mice	950	LD50	Dorigan _et_ _al_., 1976
oral	rabbits	750	LDLo	Machle _et_ _al_., 1940
oral	dogs	125	LDLo	Weatherby, 1955; Dorigan _et_ _al_., 1976
s.c.	dogs	565	LDLo	Dorigan _et_ _al_., 1976
i.v.	rabbits	750-1000	LD50	Weatherby, 1955
i.v.	dogs	800	LDLo	Weatherby, 1955
inhalation	monkeys	1000 ppm	LCLo	Machle _et_ _al_., 1940
inhalation	monkeys	980 ppm	LCLo	Dorigan _et_ _al_., 1940

[a] s.c. = subcutaneous; i.v. = intravenous.

Weatherby (1955) also performed pathologic examinations on dogs that had received single oral doses of nitromethane. A dose of 125 mg/kg was not fatal to dogs and produced slight pathologic changes in the liver only. Mild fatty change of the hepatic parenchyma and a few lymphocytes in the portal areas were observed 24 hours after exposure. By 48 hours post-exposure regeneration of hepatic cells was observed. Liver damage became more severe as the dose was increased. Kidney damage was observed only in animals receiving doses of 1500 mg/kg. All other tissues of the dosed dogs were normal (Weatherby, 1955).

Inhalation experiments with rabbits and guinea pigs were also performed by Machle et al. (1940). Mortality was related to total dose (concentration of exposure multiplied by duration) at concentrations greater than 0.05% (≈500 ppm). Rabbits and guinea pigs (2 of each species) survived exposures to 30,000 ppm for 15 minutes or 10,000 ppm for 1 hour, but all died when exposed to 30,000 ppm for 2 hours or 10,000 ppm for 6 hours.

Machle et al. (1940) noted that there was a latent period before the onset of symptoms of nitromethane poisoning that was inversely related to the concentration of nitromethane in the air. Nervous system effects were observed within one-half to 1 hour after exposure to 30,000 or 50,000 ppm, but when animals were exposed to 10,000 ppm, central nervous system effects were not observed until 5 hours after the start of exposure. Machle et al. (1940) also noted that the lethal concentrations of nitromethane were lower than the narcotic concentrations which elicited the pronounced central nervous system effects.

The symptoms of nitromethane poisoning following inhalation were similar for all three animal species, although guinea pigs seemed to be somewhat more susceptible (Machle et al., 1940). Inhalation of nitromethane first caused restlessness and slight irritation of the respiratory tract. After the latent period, the animals began salivating, appeared ill, and showed signs of narcosis. As the exposure period progressed, the animals became weak, atactic, incoordinated, and often exhibited circus movements, convulsions, twitching, and cerebellar fits. At necropsy, all exposed animals were found to have some liver damage (Machle et al., 1940). Animals that died from nitromethane inhalation exhibited general visceral and cerebral congestion and acute pulmonary congestion with edema.

Application of nitromethane (dose not specified) to the clipped skin of rabbits caused neither skin irritation nor illness (Machle et al., 1940).

(2) Subchronic Exposures

Young male albino rats (10 for each dose) receiving 2500 or 1000 mg/kg nitromethane in their drinking water for a period of 15 weeks exhibited slower weight gain than did controls (Weatherby, 1955). At necropsy, mild pathologic changes were observed in the liver of 6 of 7 survivors in the 2500 mg/kg group. In this group, 2 animals were found to have minor pathologic changes in their spleen. Of 6 survivors in the 1000 mg/kg group, the only pathologic changes observed were large hepatic cells with prominent nuclei in 2 animals. In both groups, all other organs appeared normal (Weatherby, 1955).

In a short-term subchronic study, a monkey exposed to 1000 ppm nitromethane in air died after 8 daily 6-hour exposure periods (Machle et al., 1940). At 500 ppm, the lowest concentration used in this study, 2 rabbits and 1 monkey survived a total exposure period of 140 hours (administered in daily 6-hour periods). No evidence of specific hematological damage (percent hemoglobin, red blood cell, white blood cell, or differential count) was seen (Machle et al., 1940).

In a study for NIOSH conducted by the Huntingdon Research Center (reported by Lewis et al., 1979), groups of 50 Sprague-Dawley rats and 15 New Zealand white rabbits were exposed to air containing 98 or 745 ppm of nitromethane for 7 hours/day, 5 days/week, for periods up to 24 weeks. Groups of 10 rats were sacrificed after 2 days, 10 days, and 1, 3, and 6 months of exposure. All animals survived the exposure at both concentrations and only mild to moderate symptoms of toxicity were observed in the rats and rabbits. Effects of nitromethane exposure were decreased weight gain in rats following 8 weeks of exposure to 745 ppm and a thyroid effect in rabbits that was indicated by increased thyroid weight and decreased serum thyroxin levels. Lewis et al. (1979) observed no exposure-related gross or microscopic alterations in any of the tissues examined in the rats and rabbits exposed to either 98 or 745 ppm nitromethane.

(3) Chronic Exposures

No information was found in the literature searched.

(4) Carcinogenicity

In the NIOSH study reported by Lewis et al. (1979) and cited in the "Subchronic Exposures" section of this profile, histopathologic examinations of the liver, kidney, lungs and trachea, brain, and thyroid of rats and rabbits exposed to 98 or 745 ppm nitromethane in air for 6 months revealed no neoplasms that might implicate nitromethane as a carcinogen.

No other information on the possible carcinogenic action of nitromethane was found in the literature searched.

(5) Mutagenicity

Nitromethane was not mutagenic for *Salmonella typhimurium* TA98 or TA100 tester strains in the Ames mutation test without microsomal activation (Chiu et al., 1978).

(6) Teratogenicity

No information was found in the literature searched.

(7) Reproductive Effects

No information was found in the literature searched.

(8) Other Relevant Information

D-Amino acid oxidase isolated from hog kidney catalyzes the oxidation of nitromethane by oxygen *in vitro* to give formaldehyde, nitrite, and hydrogen peroxide (Porter *et al*., 1972).

Because of the potential for formation of large quantities of nitrite in animals exposed to nitromethane, Dequidt *et al*. (1973) determined the levels of nitrite in tissues and methemoglobin in blood of exposed animals. No methemoglobin formation occurred in any of the rats exposed to nitromethane after either intraperitoneal injection of 2400 mg/kg or inhalation for 6 hours of 13,000 ppm nitromethane (Dequidt *et al*., 1973). Nitrite was detected in the heart, lungs, kidney, and spleen, but not the liver, of animals treated by intraperitoneal injection or pulmonary intoxication. Following 4 daily 6-hour inhalation periods of 2500 ppm nitromethane, nitrite concentrations were 625, 372, 408, and 800 mg/100 g of heart, lung, kidney, and spleen tissue, respectively. Unchanged nitromethane was not detected in any of the organs of animals given intraperitoneal injections of nitromethane. Following exposure by inhalation, nitromethane was detected only in the liver (0.27 g/100 g) and then only after a 6-hour exposure to 13,000 ppm nitromethane (Dequidt *et al*., 1973).

Nomura (1975) found no evidence of methemoglobinemia in mice administered either 1 or 3 consecutive intraperitoneal injections of nitromethane. Sulfhemoglobinemia, however, was induced in mice by 3 consecutive intraperitoneal injections of nitromethane (dose not specified in abstract of this Japanese article).

Nitromethane has been demonstrated to be an inhibitor of the enzyme histidase in rats (Lee and Wang, 1975). Injection of 293 mg/kg every other day for 12 days reduced enzyme activity by 75% and produced symptoms of histidinemia in the rat similar to the genetic disorder that occurs in humans (Lee and Wang, 1975).

b. Human Studies

(1) Pharmacokinetics

No information was found in the literature searched.

(2) Health Effects

Accidental inhalation of nitromethane and nitrocellulose by a handyman caused severe hemolysis and methemoglobinemia, along with severe kidney damage and anuria. A respiratory emergency also occurred following inhalation (Kaiffer et al., 1972).

Mild skin irritation following frequent contact with nitroparaffins has been reported by workers (IMC, 1977).

(3) Target Organ Toxicity

The most common route of exposure to nitromethane in the workplace is by inhalation of vapors (IMC, 1977). Inhalation of high concentrations will cause damage to the respiratory tract and to other internal organs, primarily the liver (IMC, 1977). Animal studies indicate that, regardless of the route of exposure, the liver is the organ that suffers the most severe damage from nitromethane poisoning.

(4) Epidemiology

The International Minerals and Chemical Corporation (IMC) plant at Sterlington, LA, is the sole commercial manufacturer of nitromethane. Nitromethane, nitroethane, 1-nitropropane, and 2-nitropropane are all made simultaneously in this plant; hence, worker exposure is to all four compounds. Because it has been suggested that 2-nitropropane may be a human carcinogen (Finklea, 1977), IMC initiated a retrospective mortality study to determine if there were any unusual disease mortality patterns among the workers of this plant. The study included 1815 employees who had worked at the plant during the period from January 1, 1946 through June 30, 1977 (Miller and Temple, 1979). Death certificates of 180 employees were examined. Eleven past employees could not be accounted for, but 7 of those had terminated prior to 1955, the year that nitroparaffin production began. Employee exposure was categorized on the basis of the department in which the employee worked. The cohorts were (1) "direct exposure," consisting of 372 employees from laboratories, research, production, derivatives, and warehouses, (2) "indirect exposure," consisting of 366 employees from the machine shop, electric shop, maintenance, and related services, and (3) "no exposure," consisting of 743 employees from all non-nitroparaffin departments such as plant offices and other processes. IMC provided the original data on 1481 individuals employed after January 1, 1955 and 334 employees terminated prior to that date to Drs. Monson and McMahon at the Harvard School of Public Health for analysis and interpretation.

A review of the deaths caused by cancer revealed that no deaths had resulted from cancer of the liver, including hepatocellular carcinoma (Miller and Temple, 1979). No cases were reported indicating benign neoplasms of the liver. The analysis of the data did not suggest any unusual cancer or other disease mortality patterns among the workers at the Sterlington plant, either before or after the start of nitroparaffin production in 1955. Monson and McMahon noted, however, that because the cohort is small and because the period of latency is, in most cases, relatively short, one cannot conclude from these data that 2-nitropropane is noncarcinogenic in humans (Miller and Temple, 1979). Although nitromethane was not specifically addressed in this study, the results and limitations of this study are applicable to nitromethane since simultaneous exposure to all four nitroparaffins occurs in this plant.

The statements of Drs. Monson and McMahon regarding the limitations of this study are in agreement with the conclusions of a study by Brown and Dobbin (1977). Following an industrial survey at the Sterlington plant which was conducted to determine the feasibility of a health effects study on nitroparaffin workers, Brown and Dobbin (1977) concluded that the population exposed was too small and the length of time since onset of exposure was too short to conduct a retrospective cohort mortality study, pregnancy outcome study, or cross-sectional medical study.

15. Ongoing Studies

Microbial mutagenesis and genetic toxicity testing of nitromethane is scheduled to be completed by the National Toxicology Program in fiscal year 1981 (NTP, 1981b).

16. Exposure Standards

The current occupational exposure standards recommended by the ACGIH (1981) for nitromethane are a Threshold Limit Value-Time Weighted Average (TLV-TWA) of 100 ppm (250 mg/m^3) and a Threshold Limit Value-Short-Term Exposure Limit (TLV-STEL) of 150 ppm (375 mg/m^3). OSHA (1976) has adopted the TLV-TWA of 100 ppm for nitromethane.

17. Sources of Additional Relevant Information

No sources of additional relevant information were identified.

18. Other Pertinent Data

No other information that would aid in the assessment of nitromethane as an occupational hazard was found in the literature searched.

C. 1-NITROPROPANE

1. Chemical Name: 1-Nitropropane

2. Chemical Structure: $CH_3-CH_2-CH_2-NO_2$

3. Synonyms: NiPar S-10
   NiPar S-30
   1-NP
   Propane, 1-nitro-

4. Chemical Abstracts Service (CAS) Number: 108-03-2

5. Registry of Toxic Effects of Chemical Substances (RTECS) Number:

   TZ5075000

6. Chemical and Physical Properties:

Description:	colorless liquid
Molecular Weight:	89.09
Boiling Point:	131.18°C
Melting Point:	-108°C
Vapor Pressure:	7.5 mm Hg (20°C)
Solubility:	1.5 ml/100 ml water; miscible with many other solvents; soluble in alcohol, ether, chloroform
Specific Gravity:	0.9934
Stability:	combustible; hygroscopic Autoignition temp. 789°F; Flash point: 120°F

7. Production

1-Nitropropane is produced in multimillion-pound quantities (Martin and Baker, 1969). Specific production ranges are not available from the U.S. EPA (1980).

8. Use

One of the most important uses for the nitroparaffins, including 1-nitropropane, is the production of derivatives such as nitroalcohols, alkanolamines, and polynitro compounds. Production of these derivates consumes several million pounds of nitroparaffins annually (Martin and Baker, 1969).

1-Nitropropane, for example, is used to make the nitroalcohol 2-nitro-2-ethyl-1,3-propanediol (Dewey, 1969); this nitroalcohol is reduced to the alkanolamine 2-amino-2-ethyl-1,3-propanediol.

One of the largest volume uses of nitroparaffins consumed per se is as solvents. Solvent applications include use in polymers and coatings, as extraction or partition solvents, as reaction media, and as widely used solvents in crystallization of organic compounds (Martin and Baker, 1969). 1-Nitropropane is an outstanding solvent for inks and coatings based on resins of vinyl, epoxy, acrylic, polyurethane, and polyamid, and for nitrocellulose and chlorinated rubber. It is also used in automobile finishes (Chemical Week: 1981 Buyers' Guide Issue, 1980).

Other uses of 1-nitropropane include applications as a stabilizer for organics, in explosives and propellants, as a fuel additive in diesel fuel (Martin and Baker, 1969), as a grinding medium for aluminum powders to displace traces of water, and as a chemical intermediate (IMC, 1980).

9. Manufacturers and Distributors

1-Nitropropane is manufactured by International Mineral and Chemical (IMC) Corp. in Sterlington, LA (SRI International, 1980; U.S. EPA, 1980).

Thorson Chemical (NYC, NY) imported between 0 and 1000 pounds in 1977 (U.S. EPA, 1980). Other distributors include (Chemical Week: 1981 Buyers Guide Issue, 1980; Chem Sources--USA, 1980):

Anachemia Chem.
J.T. Baker Chem.
Bio-Clinical Labs
Chem Services
Eastern Chem.
Eastman Kodak
Fisher Sci.
Gill and Duffus Chem.
LaPine Sci.
MCB Reagents
Pfaltz and Bauer
Tridom Chem.

10. Manufacturing Processes

The four lower mononitroparaffins--nitroethane, nitromethane, 1-nitropropane, and 2-nitropropane--are made on a large scale at the Sterlington, LA, plant of the IMC Chemical Group. The manufacturing process consists of oxidizing an excess of vapor-phase propane with nitric acid at a temperature range of 370-450°C and pressure of 8 to 12 atmospheres. Approximately 40% of the nitric acid is converted to nitroparaffins, the remainder acts as an oxidizing agent to produce the oxygenated by-products and is, in turn, reduced to nitric oxide.

Yields of the four nitroparaffins can be varied by temperature adjustments and additions of oxygenated sulfur compounds.

The nitroparaffins and condensable by-products (ketones and aldehydes) are condensed upon leaving the reactor; the unreacted propane and nitric oxide remain in the gas phase. The propane is separated and recycled, while the NO is oxidized to NO_2, absorbed in water to form HNO_3, concentrated, and recycled to the process. The ketones and aldehydes are separated from the nitroparaffins by solvent extraction with chlorinated aromatics. The individual nitroparaffins are then separated and purified by fractional distillation (Martin and Baker, 1969; Leipins et al., 1977). Figure 3 outlines the basic process operations.

The four lower mononitroparaffins formed during propane nitration at 500°C are produced in the following percentages (Martin and Baker, 1969):

nitroethane	16.6 mole %
nitromethane	22.0 mole %
1-nitropropane	13.2 mole %
2-nitropropane	48.2 mole %

These commercial nitroalkanes are 92.5-95% pure by individual compound and are 99% nitroparaffins by weight (Martin and Baker, 1969).

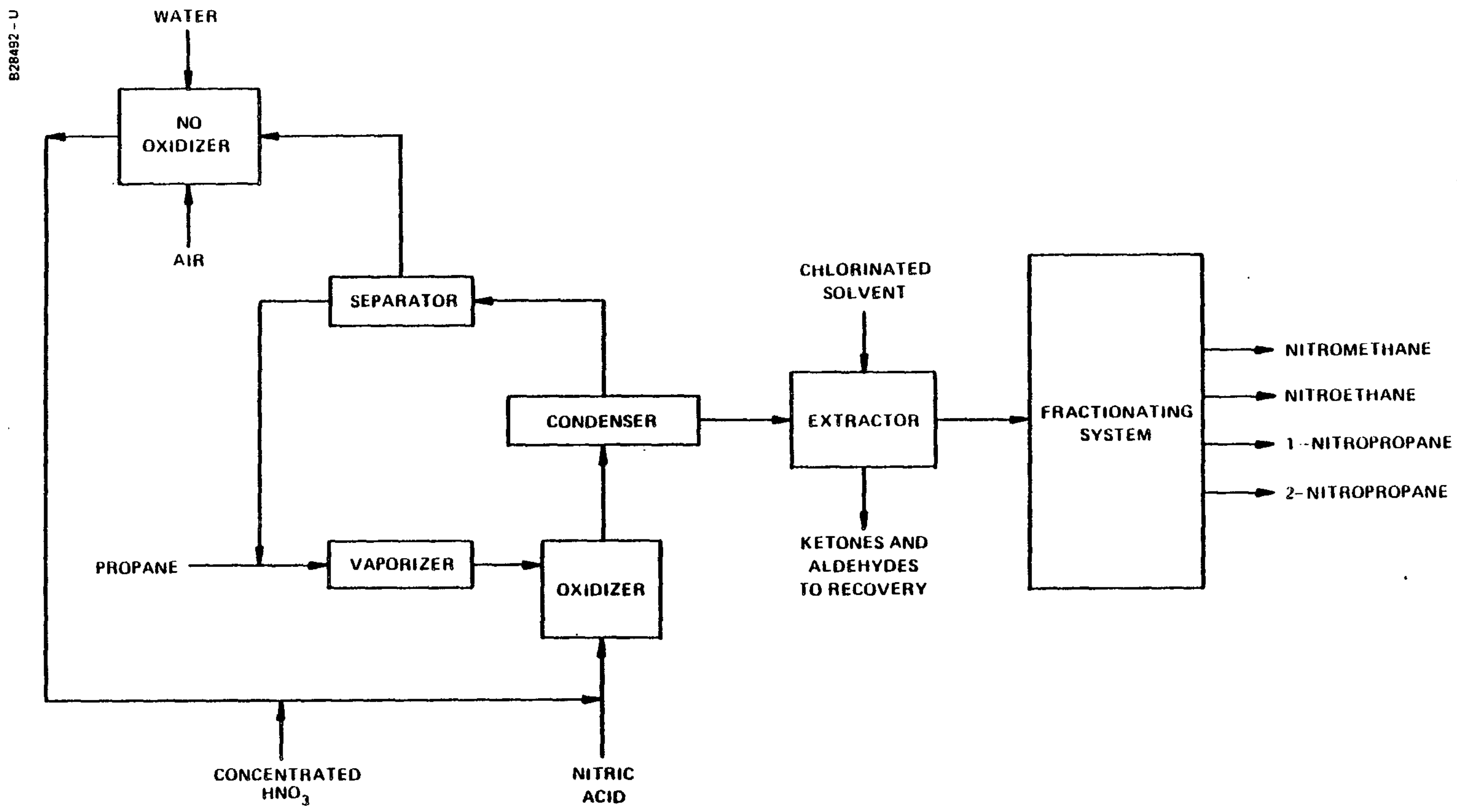


Figure 3. Manufacture of Nitromethane, Nitroethane, and Nitropropane (adopted from Martin and Baker, 1969; Leipins *et al.*, 1977)

11. Impurities or Additives

There is no evidence in the literature searched to indicate the presence of deliberate additives in commercially produced 1-nitropropane.

12. Occupational Exposure

The National Occupational Hazard Survey indicates that 9871 workers are potentially exposed to 1-nitropropane.

13. Control Technology and Work Practices

Specific factors that may contribute to or prevent employee exposure to 1-nitropropane were not found in the literature searched. IMC (1977) has noted that general mechanical ventilation or hoods at point of use are normally required to control the atmospheric vapor concentrations of the four lower mononitroparaffins at levels below that of the established Threshold Limit Values (TLVs). For short exposure to concentrations of nitroparaffin vapors of less than 2% and where sufficient oxygen is present (>16%), industrial-type gas masks provided with recommended organic vapor canisters were deemed satisfactory (IMC, 1977). A fresh air mask or a self-contained breathing apparatus is recommended for use in situations where prolonged exposure to vapors of nitroparaffins above the TLV is anticipated.

14. Biological Effects

a. Animal Studies

(1) Acute Exposures

The acute toxic effects of 1-nitropropane are summarized in Table 3. Oral administration of 250 to 500 mg/kg of 1-nitropropane to rabbits caused progressive weakness and collapse, unsteadiness and incoordination ending in complete ataxia, and changes in respiration evidenced first by slowed breathing and later by rapid breathing (Machle *et al.*, 1940). Oral administration of the chemical at these levels caused no changes in blood

Table 3. Acute Effects of 1-Nitropropane

Route	Species	Dose (mg/kg)	Response	Reference
oral	rats	455 + 75	LD50	Martin and Baker, 1967
oral	rats	1000	LDLo	Dorigan _et_ _al_., 1976
oral	mice	800	LD50	Dorigan _et_ _al_., 1976
oral	rabbits	250	LDLo	Machle _et_ _al_., 1940

chemistry and no methemoglobin formation. At necropsy, severe congestion of the enteric tract was observed. Liver damage was present in all animals that died from administration of the chemical (Machle et al., 1940).

In inhalation experiments by Machle et al. (1940), 2 rabbits and 1 of 2 guinea pigs survived exposure to 10,000 ppm 1-nitropropane for 1 hour. Exposure to 10,000 or 5000 ppm 1-nitropropane for 3 hours was, however, 100% lethal to groups of 2 rabbits and 2 guinea pigs per dose. Based on mortality, 1-nitropropane was more toxic than nitromethane or nitroethane. The symptoms of poisoning were similar and of a similar order of magnitude as those produced by nitroethane. Irritation of the respiratory tract and conjunctival irritation occurred. Central nervous system symptoms, manifested as jerking or twitching movements of the extremities, were also observed (Machle et al., 1940). Machle et al. (1940) noted that lethal concentrations were far lower than narcotic concentrations.

At necropsy, all exposed animals were found to have some liver damage; fatty infiltration was seen in a number of animals (Machle et al., 1940). Animals that died from 1-nitropropane inhalation exhibited general visceral and cerebral congestion, severe congestion of the upper respiratory tract, and pulmonary congestion with edema (Machle et al., 1940).

1-Nitropropane, when administered by intraperitoneal injection, was found to be more toxic than 2-nitropropane (Dequidt et al., 1972). The minimum dose required to kill rats in 4 hours was 550 mg/kg of 1-nitropropane compared to 1100 mg/kg of 2-nitropropane. By the respiratory route, however, 1-nitropropane was clearly less toxic than 2-nitropropane. One 8-hour exposure of 800 ppm 2-nitropropane caused the death of rats in 48 hours, but three 8-hour exposures of 800 ppm 1-nitropropane were necessary to cause death in a similar group of rats (Dequidt et al., 1972).

Application of 1-nitropropane (dose not specified) to the clipped skin of rabbits caused neither skin irritation nor illness (Machle *et al*., 1940).

(2) Subchronic Exposures

No information was found in the literature searched.

(3) Chronic Exposures

In a written communication from International Minerals and Chemical Corporation (IMC) (Purcell, 1980), SRC was advised that a lifetime inhalation study has been completed in which male and female rats were exposed to 100 ppm 1-nitropropane 7 hours/day, 5 days/week, for about 22 months. In an interim report following sacrifice at 18-months, it was stated that "no significant pathology was apparent in the treated group of animals as compared to the control." A significant increase in methemoglobin was noted in the exposed males ($P < 0.01$) relative to controls, but the investigators suggested waiting for analysis of remaining data before drawing conclusions (Griffin, 1980). The final report of this study will be completed by the end of September, 1981 (Purcell, 1981).

(4) Carcinogenicity

No information was found in the literature searched.

(5) Mutagenicity

1-Nitropropane was not mutagenic in the Ames test for *Salmonella typhimurium* strains TA1537, TA92, TA98, or TA100, when tested with or without mammalian microsome activation (Hite and Skeggs, 1979).

(6) Teratogenicity

No information was found in the literature searched.

(7) Reproductive Effects

No information was found in the literature searched.

(8) Other Relevant Information

1-Nitropropane has been shown to be oxidatively denitrified by bacteria to yield propionaldehyde and nitrite (Kido and Soda, 1976).

Dequidt _et_ _al_. (1972) detected nitrite in the heart, lungs, kidney, and spleen, but not the liver, of rats given single or repeated intraperitoneal injections of 1-nitropropane (110 to 1100 mg/kg). Methemoglobin was detected in the blood of rats that received 7 daily injections of 110 mg/kg or a single injection of 550 mg/kg 1-nitropropane. Nitrite was detected in all organs except the liver of animals exposed via inhalation to concentrations ranging from 80 ppm (8 hours/session for 8 sessions) to 13,000 ppm (one 5-hour session), but methemoglobin formation occurred only in rats exposed for 8 hours to 2500 ppm or 5 hours to 13,000 ppm (Dequidt _et_ _al_., 1972).

Unmetabolized 1-nitropropane was found only in the liver of animals exposed by the pulmonary or intraperitoneal routes (Dequidt _et_ _al_., 1972). A concentration of 1 mg/100 g liver tissue was detected 4 hours after injection of 550 mg/kg. Following exposure by inhalation, 1-nitropropane concentration in the liver ranged from 0.54 mg/100 g (at 800 ppm) to 1.2 mg/100 g (at 13,000 ppm 1-nitropropane in air) (Dequidt _et_ _al_., 1972).

b. Human Studies

(1) Pharmacokinetics

No information was found in the literature searched.

(2) Health Effects

Early symptoms of nitroparaffin intoxication include headache and nausea, which clear when exposure is reduced (Martin and Baker, 1969).

Silverman _et_ _al_. (1946) exposed 12 unconditioned subjects of both sexes to 1-nitropropane for 15-minute periods. The subjects found that exposure to 150 ppm was irritating to the eyes, and that concentrations (not stated) greater than 150 ppm were irritating to the nose and throat. The highest tolerable level for an 8-hour 1-nitropropane exposure was judged to be 100 ppm by the majority of the subjects. It should be noted that the concentration of 1-nitropropane in the exposure chamber was calculated (nominal) rather than measured analytically.

Mild skin irritation following frequent contact with nitroparaffins has been reported by workers (IMC, 1977), but no allergies or other adverse physiological effects have been reported as a result of skin exposure (Martin and Baker, 1969).

(3) Target Organ Toxicity

The most common route of exposure in the workplace is by inhalation of vapors (IMC, 1977). Inhalation of high concentrations will cause damage to the respiratory tract and to other internal organs, primarily the liver (IMC, 1977). Animal studies indicate that, regardless of the route of exposure, the liver is the organ that suffers the most severe damage from 1-nitropropane poisoning.

(4) Epidemiology

The International Minerals and Chemical Corporation (IMC) plant at Sterlington, LA, is the sole commercial manufacturer of 1-nitropropane. Nitromethane, nitroethane, 1-nitropropane, and 2-nitropropane are all made simultaneously in this plant; hence, worker exposure is to all four compounds. Because it has been suggested that 2-nitropropane may be a human carcinogen (Finklea, 1977), IMC initiated a retrospective mortality study to determine if there were any unusual disease mortality patterns among the workers of this plant. The study included 1815 employees who had worked at the plant during the period from January 1, 1946 through June 30, 1977 (Miller and Temple, 1979).

Death certificates of 180 employees were examined. Eleven past employees could not be accounted for, but 7 of those had terminated prior to 1955, the year that nitroparaffin production began. Employee exposure was categorized on the basis of the department in which the employee worked. The cohorts were (1) "direct exposure," consisting of 372 employees from laboratories, research, production, derivatives, and warehouses, (2) "indirect exposure," consisting of 366 employees from the machine shop, electric shop, maintenance, and related services, and (3) "no exposure," consisting of 743 employees from all non-nitroparaffin departments such as plant offices and other processes. IMC provided the original data on 1481 individuals employed after January 1, 1955 and 334 employees terminated prior to that date to Drs. Monson and McMahon at the Harvard School of Public Health for analysis and interpretation.

A review of the deaths caused by cancer revealed that no deaths had resulted from cancer of the liver, including hepatocellular carcinoma (Miller and Temple, 1979). No cases were reported indicating benign neoplasms of the liver. The analysis of the data did not suggest any unusual cancer or other disease mortality patterns among the workers at the Sterlington plant, either before or after the start of nitroparaffin production in 1955. Monson and McMahon noted, however, that because the cohort is small and because the period of latency is, in most cases, relatively short, one cannot conclude from these data that 2-nitropropane is noncarcinogenic in humans (Miller and Temple, 1979). Although 1-nitropropane was not specifically addressed in this study, the results and limitations of this study are applicable to 1-nitropropane since simultaneous exposure to all four nitroparaffins occurs in this plant.

The statements of Drs. Monson and McMahon regarding the limitations of this study are in agreement with the conclusions of a study by Brown and Dobbin (1977). Following an industrial survey at the Sterlington plant which was conducted to determine the feasibility of a health effects study on nitroparaffin workers, Brown and Dobbin (1977) concluded that the population exposed was too small and the length of time since onset of exposure was too short to conduct a retrospective cohort mortality study, pregnancy outcome study, or cross-sectional medical study.

15. Ongoing Studies

The long-term tumorigenicity of 1-nitropropane will be evaluated via the inhalation route at one dose level, using rats as the experimental subjects. This project is being conducted by T. Lewis of the U.S. Department of Health, Education, and Welfare, Public Health Service, Center for Disease Control, National Institute for Occupational Safety and Health, Division of Biomedical Behavorial Science, Cincinnati, OH (SSIE, 1980).

Microbial mutagenesis and genetic toxicity testing of 1-nitropropane is scheduled to be completed by the National Toxicology Program in fiscal year 1981 (NTP, 1981b).

16. Exposure Standards

The current occupational exposure standards recommended by the ACGIH (1980) for 1-nitropropane are a Threshold Limit Value-Time Weighted Average (TLV-TWA) of 25 ppm (90 mg/m^3) and a Threshold Limit Value-Short-Term Exposure Limit (TLV-STEL) of 35 ppm (135 mg/m^3). A notice of intended change to a TLV-TWA of 15 ppm and TLV-STEL of 25 ppm has been published by the ACGIH. OSHA (1976) has adopted the TLV-TWA of 25 ppm for 1-nitropropane.

17. Sources of Additional Relevant Information

No sources of additional relevant information were identified.

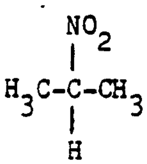
18. Other Pertinent Data

No other information that would aid in the assessment of 1-nitropropane as an occupational hazard was found in the literature searched.

D. 2-NITROPROPANE

1. **Chemical Name**: 2-Nitro~~pro~~propane

2. **Chemical Structure**:



$H_3C-C(NO_2)(H)-CH_3$

3. **Synonyms**: Dimethylnitromethane
Isonitropropane
Nitroisopropane
NiPar S-20
NiPar S-30
2-NP
Propane, 2-nitro-

4. **Chemical Abstracts Service (CAS) Number**: 79-46-9

5. **Registry of Toxic Effects of Chemical Substances (RTECS) Number**:

TZ5250000

6. **Chemical and Physical Properties**:

Description:	colorless liquid
Molecular Weight:	89.09
Boiling Point:	120.25°C
Melting Point:	-93°C
Vapor Pressure:	13 mm Hg (20°C)
Solubility:	1.7 ml/100 ml water; miscible with many organic solvents
Specific Gravity:	0.9821^{25}_{4}
Stability:	combustible; Autoignition temperature: 802°F; Flash point: 103°F

7. **Production**

2-Nitropropane is produced in multimillion-pound quantities (Martin and Baker, 1969). An estimated 30 million pounds are produced annually of which 12 million pounds are sold domestically and the remainder is used internally by the manufacturer or exported (Finklea, 1977). Manufacturing ranges are not available from the U.S. EPA (1980); however, Thorson Chem. imported 0 to 1000 pounds in 1977.

8. Use

One of the most important uses for the nitroparaffins, including 2-nitropropane, is the production of derivatives such as nitroalcohols, alkanolamines, and polynitro compounds. Production of these derivatives consumes several million pounds of nitroparaffins annually (Martin and Baker, 1969).

One of the largest volume uses of nitroparaffins consumed *per se* is as solvents. Solvent applications include use in polymers and coatings, as extraction or partition solvents, as reaction media, and as widely used solvents in crystallization of organic compounds (Martin and Baker, 1969).

Solvent systems containing 2-nitropropane are used in coatings (e.g., vinyl, epoxy, nitrocellulose, and chlorinated rubber), printing inks, and adhesives. 2-Nitropropane (in concentrations ranging from approximately 5 to 25%) is used in a number of solvent systems to contribute desirable properties such as improved drying time, more complete solvent release, better flow and film integrity, retardation of blushing, greater wetting ability, improved electrostatic spraying, and increased pigment dispersion (Finklea, 1977).

2-Nitropropane is used as a pesticide intermediate, in explosives and propellents, and as an additive in diesel fuels (Martin and Baker, 1969); and in a variety of chemical syntheses (IMC, 1980).

9. Manufacturers and Distributors

2-Nitropropane is manufactured by International Mineral and Chemical (IMC) Corp. in Sterlington, LA (SRI International, 1980).

Thorson Chemical (NYC, NY) imported between 0 and 1000 pounds in 1977 (U.S. EPA, 1980).

Distributors include (*Chemical Week: 1981 Buyers' Guide Issue*, 1980; *Chem Sources--USA*, 1980):

- Alfa Prod.
- Aldrich Chem.
- Anachemia Chem.
- Ashland Chem.
- Atomergic Chemetals
- J.T. Baker Chem.
- Bio-Clinical Labs.
- Chemical Dynamics
- Chem Services
- Eastman Kodak
- EM Labs
- Fisher Sci.
- Lachat Chem.
- MCB Reagents
- Pfaltz and Bauer
- Thompson-Hayward Chem.
- Tridom Chem.
- George Uhe Co.
- Union Chem.

10. Manufacturing Processes

The four lower mononitroparaffins--nitroethane, nitromethane, 1-nitropropane, and 2-nitropropane--are made on a large scale at the Sterlington, LA, plant of the IMC Chemical Group. The manufacturing process consists of oxidizing an excess of vapor-phase propane with nitric acid at a temperature range of 370-450°C and pressure of 8 to 12 atmospheres. Approximately 40% of the nitric acid is converted to nitroparaffins; the remainder acts as an oxidizing agent to produce the oxygenated by-products and is, in turn, reduced to nitric oxide.

Yields of the four nitroparaffins can be varied by temperature adjustments and additions of oxygenated sulfur compounds.

The nitroparaffins and condensable by-products (ketones and aldehydes) are condensed upon leaving the reactor; the unreacted propane and nitric oxide remain in the gas phase. The propane is separated and recycled, while the NO is oxidized to NO_2, absorbed in water to form HNO_3, concentrated, and recycled to the process. The ketones and aldehydes are separated from the nitroparaffins by solvent extraction with chlorinated aromatics. The individual nitroparaffins are then separated and purified by fractional distillation (Martin and Baker, 1969; Leipins *et al*., 1977). Figure 4 outlines the basic process operations.

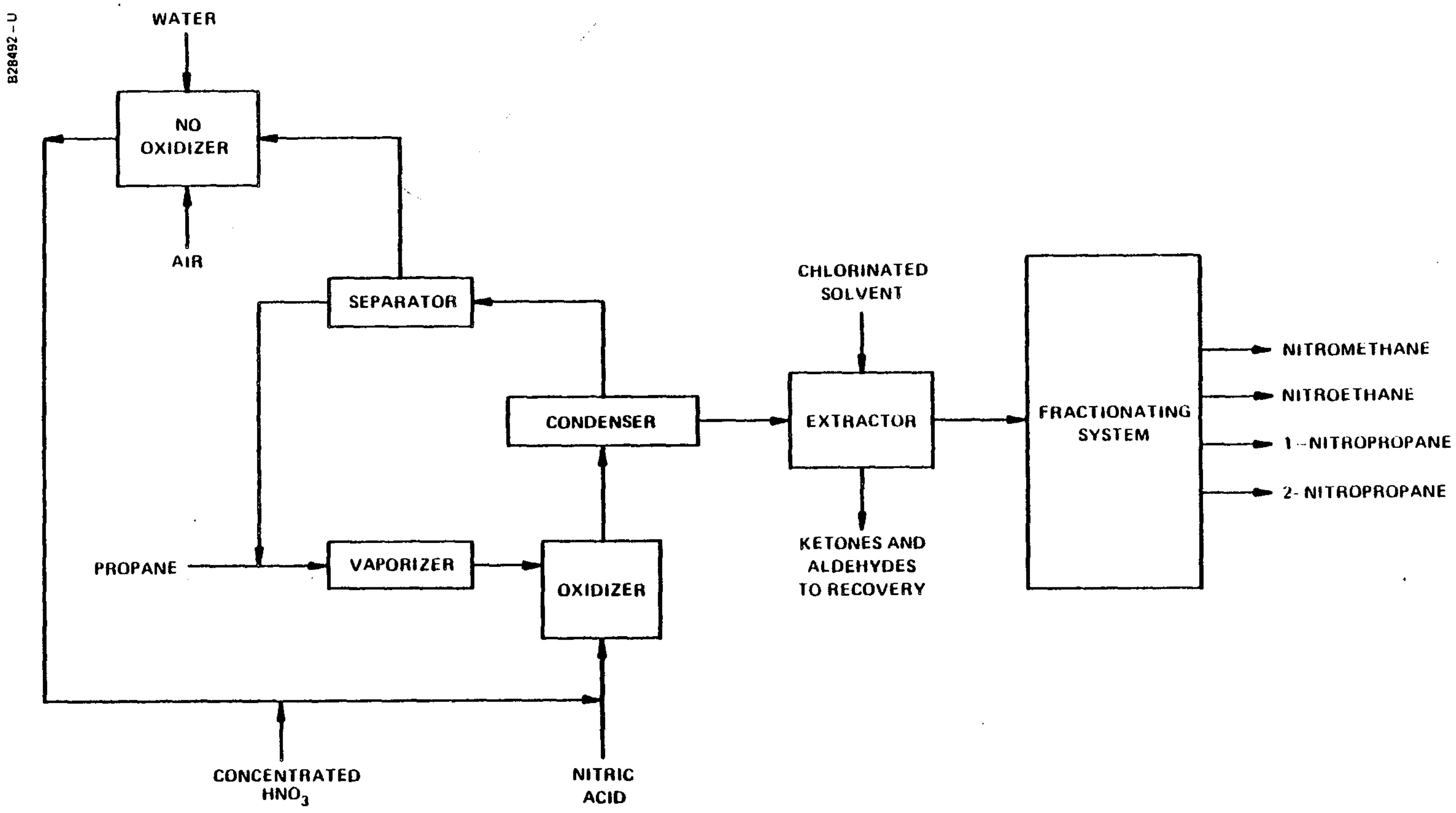


Figure 4. Manufacture of Nitromethane, Nitroethane, and Nitropropane (adopted from Martin and Baker, 1969; Leipins <u>et al</u>., 1977)

The four lower mononitroparaffins formed during propane nitration at 500°C are produced in the following percentages (Martin and Baker, 1969):

nitroethane	16.6 mole %
nitromethane	22.0 mole %
1-nitropropane	13.2 mole %
2-nitropropane	48.2 mole %

These commercial nitroalkanes are 92.5-95% pure by individual compound and are 99% nitroparaffins by weight (Martin and Baker, 1969).

11. Impurities and Additives

Typical analysis of commercial 2-nitropropane is as follows:

Component	% by wt.
2-nitropropane	95.65
1-nitropropane	3.63
Nitroethane	0.20
2-nitro-2-methylpropane	0.51
Water	0.01

NiPar S-30®, marketed by IMC, is a mixture of 1-nitro- and 2-nitropropanes and is used in solvent applications.

12. Occupational Exposure

The National Occupational Hazard Survey indicates that 160,603 workers are potentially exposed to 2-nitropropane

13. Control Technology and Work Practices

Specific factors that may contribute to or prevent employee exposure to 2-nitropropane were not found in the literature searched. IMC (1977) has noted that general mechanical ventilation or hoods at point of use are normally required to control the atmospheric vapor concentrations of the four lower mononitroparaffins at levels below that of the established Threshold Limit Values (TLVs). For short exposure to concentrations of nitroparaffin vapors of less than 2% and where sufficient oxygen is present (>16%), industrial-type gas masks provided with recommended organic vapor canisters were deemed satisfactory (IMC, 1977). A fresh air mask or a self-contained breathing apparatus is recommended for use in situations where prolonged exposure to vapors of nitroparaffins above the TLV is anticipated.

14. Biological Effects

a. Animal Studies

1. Acute Exposures

The acute toxic effects of 2-nitropropane are summarized in Table 4. Oral administration of 500-750 mg/kg 2-nitropropane to rabbits caused progressive weakness and collapse, unsteadiness and incoordination ending in complete ataxia, and changes in respiration evidenced first by slowed breathing and later by rapid breathing (Machle _et al._, 1940). Oral administration of the chemical at these levels caused no changes in blood chemistry and no methemoglobin formation. At necropsy, severe congestion of the enteric tract was observed. Liver damage was present in all animals that died from administration of the chemical (Machle _et al._, 1940).

Inhalation of lethal concentrations of 2-nitropropane (Table 4) gave rise to dyspnea, cyanosis, prostration, convulsions, and coma prior to death in cats, rats, rabbits, and guinea pigs (Treon and Dutra, 1952). Cats also exhibited lacrimation, salivation, and vomiting. Exposure to 328 ppm of 2-nitropropane for several hours induced dyspnea in cats, but no symptoms were observed in any of the other species of animals (Treon and Dutra, 1952).

When rabbits were exposed for 4.5 hours to a concentration of 2341 ppm of 2-nitropropane, a high percentage of erythrocytes contained Heinz bodies (Treon and Dutra, 1952). A concentration as low as 83 ppm induced the appearance of Heinz bodies in the erythrocytes of cats, usually in 5 to 15% of the erythrocytes (Treon and Dutra, 1952).

Table 4. Acute Effects of 2-Nitropropane

Route[a]	Species	Dose (mg/kg)	Response	Reference
oral	rats	725 ± 160	LD50	Martin and Baker, 1967
oral	rats	500	LDLo	Dorigan *et al.*, 1976
oral	mice	400	LD50	Hite and Skeggs, 1979
oral	rabbits	500	LDLo	Machle *et al.*, 1940
i.p.	mice	75	LDLo	Dorigan *et al.*, 1976
inhalation	rats	1513 ppm x 4.5 h[b]	LCLo	Treon and Dutra, 1952
inhalation	rats	3865 ppm x 1 h	LCLo	Treon and Dutra, 1952
inhalation	rats	2773 ppm x 1 h	LCLo	IMC, 1979
inhalation	rats	3712 ppm x 1 h	LC50	IMC, 1979
inhalation	rats	400 ppm x 6 h	LC50	Lewis *et al.*, 1979
inhalation	rats	5098 ppm x 1 h	LC100	IMC, 1979
inhalation	rabbits	2381 ppm x 4.5 h	LCLo	Treon and Dutra, 1952
inhalation	guinea pigs	4622 ppm x 4.5 h	LCLo	Treon and Dutra, 1952
inhalation	cats	714 ppm x 4.5 h	LCLo	Treon and Dutra, 1952

[a] i.p. = intraperitoneal.
[b] h = hour.

Pathologic changes observed in animals exposed to atmospheric concentrations of 2-nitropropane of 2,353 ppm or greater included general vascular endothelial damage in all tissues with associated pulmonary edema and hemorrhage, selective disintegration of the neurons of the brain, and hepatocellular damage (Treon and Dutra, 1952).

IMC (1979) confirmed that toxic vapor concentrations of 2-nitropropane (2773 ppm x 1 hour) caused severe irritation of the nasal and conjunctival membranes in rats. Irritability, ataxia, increased respiration, and eventual respiratory collapse were observed in rats exposed to toxic levels of the chemical. IMC (1979) reported, however, that animals removed from exposure just prior to the terminal stage showed good recovery; animals returned to normal in 24 hours, except for the mucous irritation, which persisted for approximately 4 days.

Application of 2-nitropropane (dose not specified) to the clipped skin of rabbits caused neither skin irritation nor illness (Machle et al., 1940).

(2) Subchronic Exposures

Two guinea pigs, 2 rats, and 1 rabbit survived exposure to 328 ppm 2-nitropropane in air 7 hours/day, 5 days/week, administered over a 199-day period (Treon and Dutra, 1952). Cats, however, did not survive at this concentration; 1 died after the 3rd exposure period, and another died after the 17th exposure period. No pathologic changes were observed in any tissues of any of the animals, except the cats, which exhibited severe liver damage and slight to moderate toxic degeneration of the heart and kidneys (Treon and Dutra, 1952).

Exposure to an air concentration of 83 ppm 2-nitropropane, administered in daily 7-hour exposure periods over a 199-day period was not fatal to 2 cats, 2 guinea pigs, 4 rabbits, 1 rat, and 1 monkey (Treon and

Dutra, 1952). No clinical signs of poisoning were observed in any of the animals. Pathologic changes were restricted to the cats, which had slight diffuse degeneration in the brain, heart, liver, and kidneys (Treon and Dutra, 1952).

(3) Chronic Exposures

In the NIOSH study described in the "Carcinogenicity" section (3.a), all rats and rabbits exposed to either 27 or 207 ppm 2-nitropropane survived the 6-month exposure period and gained weight normally (Lewis et al., 1979). Hematological data were normal for all exposed animals except for decreases in prothrombin times at 1 and 3 months in both species. Biochemical evaluations indicated elevated serum ornithine carbamyl transferase (OCT) levels at 1 and 3 months in rabbits exposed to 207 ppm of 2-nitropropane. In rats, OCT levels were normal, but elevated serum glutamic-pyruvic transaminase levels at 10 days, 1 month, and 6 months indicated possible liver cellular damage. A mild incidence of lung edema after 1, 3, and 6 months exposure to 207 ppm was observed in rats. No signs of brain edema in rats and lung or brain edema in rabbits were noted.

In the most recent study on the toxic effects of 2-nitropropane (Griffen et al., 1980; described in Section 3.a (Carcinogenicity)), exposure to 25 ppm 2-nitropropane for 22 months caused a slight increase in liver weight. Relative liver weights (liver weight/body weight) were significantly higher than controls only in exposed males after 6 and 22 months of exposure (Griffen et al., 1980). No effects were observed on serum chemistry (glutamic-pyruvic transaminase, ornithine carbamyl transferase, thyroxine, and triiodothyronine uptake) or hematology (erythrocyte count, leukocyte count, packed cell volume, hemoglobin concentration, methemoglobin concentration, and prothrombin time).

(4) Carcinogenicity

In a NIOSH Current Intelligence Bulletin on 2-nitropropane, it was reported that all 10 Sprague-Dawley rats exposed by inhalation to 207 ppm 2-nitropropane for 6 months developed hepatocellular carcinoma or hepatic adenoma (Finklea, 1977). Since the publication of that bulletin, there has been great controversy over the methodology of the study, and the suggestion that 2-nitropropane may be a carcinogen in laboratory rats.

The study referred to by Finklea was conducted by Huntingdon Research Center under a NIOSH contract and has been reported in detail by Lewis et al. (1979). The purpose of the study was to determine the subchronic inhalation toxicity of 2-nitropropane in order to recommend acceptable exposure levels in the workplace. In the original protocol, 50 male Sprague-Dawley rats and 15 male New Zealand rabbits were to be exposed 7 hours/day, 5 days/week, for periods up to 24 weeks to air containing nominal concentrations of either 25 or 400 ppm 2-nitropropane. The 25 ppm concentration was chosen because it was the current permissible occupational exposure limit (OSHA, 1976). Interim sacrifices of 10 rats each were to be made after 2 days, 10 days, and 1, 3, and 6 months of exposure; 5 rabbits each were to be sacrificed after 1, 3, and 6 months of exposure. A similar group of untreated controls was also included. During the first 3 days of the experiment, however, excessive mortality occurred among the male rats exposed to 400 ppm 2-nitropropane (which is the LC50 concentration determined by Lewis et al. (1979)). Therefore, it was deemed necessary to restart the experiment with a new group of rats and rabbits exposed to a nominal concentration of 200 ppm (207 ppm actual concentration) of 2-nitropropane. The replacement rats were obtained as weanlings and were used immediately.

All rats and rabbits survived exposure to 2-nitropropane at actual concentrations of 27 and 207 ppm (Lewis et al., 1979). No exposure-related gross pathologic alterations were observed in any tissues of rats exposed to 27 ppm or in rabbits exposed to 27 or 207 ppm. In rats exposed to 207 ppm 2-nitropropane, however, an increased incidence of pulmonary abnormalities consisting of dark hemorrhagic foci scattered over all lobes of the lung was observed after 1, 3, and 6 months. The livers of rats in the 207 ppm group sacrificed at 3 months showed areas of necrosis, were pale in color, and had surface lesions. In rats that had been exposed for 6 months to 207 ppm 2-nitropropane, livers were enlarged and pale with numerous masses and lesions (Lewis et al., 1979).

Histologic studies revealed no compound-related changes in any tissues of rats exposed to 27 ppm 2-nitropropane or in rabbits exposed to either 27 or 207 ppm for 6 months (Lewis et al., 1979). Liver tissue of rats exposed to 207 ppm for 3 months contained focal areas of hepatocellular hypertrophy and hyperplasia. In all 10 rats that had received 6 months of exposure to 207 ppm 2-nitropropane, multiple hepatocellular carcinomas were present (Lewis et al., 1979). These carcinomas reportedly appeared to be highly malignant. In addition, numerous neoplastic nodules were observed in the livers of these rats. No metastases were seen in any other tissues from these rats.

Because histological interpretation of possible malignant processes in tissues can be highly subjective, International Minerals and Chemical Corporation (IMC) requested additional interpretation of the slides for the rats exposed for 3 and 6 months to 2-nitropropane. These slides were examined by Dr. Fredrick Coulston and Dr. Karl Benity of the Institute of Comparative and Human Toxicology of Albany Medical College. In their report, parts of which were presented verbatim in an IMC bulletin (IMC, 1979), they stated that the microscopic changes in the liver sections from the 10 rats exposed to 207 ppm 2-nitropropane for 3 months consisted of a slight to moderate degree of hepatocellular hypertrophy. These hypertrophic areas were present in all zones of the liver lobule. In rats exposed for 3 months, some of the hypertrophic cell complexes showed a slight tendency to nodular formation, but no distinct hepatic nodules were seen. The rats exposed for 6 months had large nodular livers. Drs. Coulston and Benity further reported that the abnormal microscopic changes in the livers of these animals consisted predominantly of large hypertrophic nodules, composed mainly of enlarged hepatocellular plates. In most nodules, various states of coagulation necroses were seen. Cell death consisted of three types: hemorrhagic necroses; massive, relatively fresh coagulation necrosis limited to hepatocytes (with liver cells still visible); and individual liver cell necroses. In several areas of a few nodules, enlarged hepatocellular nuclei that contained large, optically-empty vacuoles surrounded by an extremely thin rim of condensed chromatin were seen. These nuclei were found in areas where the mitotic activity was increased (IMC, 1979).

In their description of the Huntingdon study, Lewis et al. (1979) noted certain shortcomings in the performance of the experiment. These shortcomings included (1) the possibility of ingestion of food and water contaminated with 2-nitropropane because the food and water were not removed from the cages during exposure, (2) the use of replacement rats that were weanlings when the exposure (207 ppm) was restarted and, consequently, may have been more susceptible to the toxic effects of 2-nitropropane, and (3) the failure to include a set of weanling rats as matched controls when the experiment was restarted.

Because of these shortcomings, the experiment was repeated by the Institute of Comparative and Human Toxicology of Albany Medical College under contract by IMC. The experimental protocol was identical to that described for the Huntingdon study, but with its flaws corrected, and, in this experiment, both male and female Sprague-Dawley rats were used. The results of this study were analyzed by Dr. Fredrick Coulston, Director of the research project, and were reported by IMC (1979). Six months of exposure to 200 ppm 2-nitropropane resulted in significant toxic effects on the liver, particularly of males. The effects were characterized by single and multiple cell necroses and concomitant general structural changes. According to Dr. Coulston, "at the time of the 6-month sacrifice of these animals, very little, if any cancer *per se* could be diagnosed although several of the rats had what could be characterized as precancerous lesions. However, when some of these rats were removed from the inhalation exposure and kept for 3 and 6 more months (a recovery period), hepatocellular cancer was diagnosed in most of the rats examined at the end of the 6-month recovery period." In this study, damage to the parenchyma was extensive, and, in the recovery phase, regeneration of the liver parenchyma cells was very active. Based on their observations, the authors of this study concluded that the morphologic and pathologic changes observed did not indicate that 2-nitropropane was a primary carcinogen (IMC, 1979).

In another study conducted by Albany Medical College (reported by IMC, 1979), a group of male and female Sprague-Dawley rats were exposed to 100 ppm 2-nitropropane 7 hours/day, 5 days/week, for 18 months. At the end of the experiment, liver nodules were observed in 22 of 23 males, 1 of 63 male controls, 4 of 30 females, and 2 of 67 female controls (IMC, 1979). Details of histopathologic examinations of liver tissues were not reported in the IMC publication.

The latest series of experiments designed to test for the possible carcinogenic effects of 2-nitropropane has only recently been completed. The final report of this study, conducted by Griffen *et al*. (1980), was provided by IMC for inclusion in this profile. A group of 125 male and 125 female

Sprague-Dawley rats were exposed to 25 ppm 2-nitropropane 7 hours/day, 5 days/week, for periods up to 22 months. A similar group of rats served as matched controls. Ten male and 10 female rats from both the exposed and control groups were sacrificed after 1, 3, 6, and 12 months. Additionally, 10 males and 10 females were removed at 3 and 12 months and subsequently maintained under non-exposure conditions. At the end of the exposure period, no malignancies or any significant pathologic changes attributable to 2-nitropropane exposure had been observed in any tissues of either sex. Focal areas of hepatocellular nodules were observed in 2 of 125 control males, 10 of 125 exposed males, 1 of 125 control females, and 3 of 124 exposed females. Other microscopic observations included focal cytoplasmic vacuolization of hepatocytes and liver congestion (Griffen _et al_., 1980).

(5) Mutagenicity

In the Ames _Salmonella typhimurium_ mutation test, 2-nitropropane caused a dose-related increase in revertants to histidine prototrophy in strains TA1537, TA92, TA98, and TA100, when tested both with and without mammalian microsome activation (Hite and Skeegs, 1979). The mutagenic effect was enhanced in the presence of mammalian microsomes (S-9 preparations). Positive mutagenic responses were also reported in _Salmonella typhimurium_ strains TA98, TA100, TA1535, and TA1537, with and without metabolic activation by rat and hamster liver S-9 fractions, by the NTP (NTP, 1980). IMC (1979) noted that tests by Litton Bionetics employing assays with _Salmonella_ and _Saccharomyces_ (indicator strains not stated) indicated that 2-nitropropane had only slight toxicity for the test organisms. The results of their assays, with and without microsomal activation, suggested a weak mutagenic response with _S. typhimurium_ strain TA98 at the highest concentration used (20 µl/plate). In subsequent tests with higher concentrations, the mutagenic effect of 2-nitropropane was confirmed.

2-Nitropropane was not mutagenic in the micronucleus test performed with mice given oral doses of 100, 200, or 300 mg/kg 2-nitropropane on 2 consecutive days (Hite and Skeggs, 1979).

(6) Teratogenicity

Retarded heart development was observed in pups from 9 of 10 litters from female Sprague-Dawley rats injected intraperitoneally with 170 mg/kg 2-nitropropane on days 1-15 of gestation (Harris *et al.*, 1979). Thirty to 86% of the pups in each litter were affected.

(7) Reproductive Effects

No information was found in the literature searched.

(8) Other Relevant Information

2-Nitropropane is oxidatively degraded by bacteria to yield acetone and nitrite (Kido and Soda, 1976).

Because of the potential for formation of large concentrations of nitrite and methemoglobin in animals exposed to 2-nitropropane, Dequidt *et al.* (1972) measured nitrite, methemoglobin, and 2-nitropropane concentrations in the blood and tissues of exposed Wistar rats. Thirty-six hours after the last of 15 daily intraperitoneal injections of 110 mg/kg 2-nitropropane, the 2-nitropropane content of the liver was 18.7 mg/100 g and of the lungs was 360 mg/100 g. Nitrite was detected in the heart, lungs, kidney, and spleen, but not in the liver. Urinary excretion of nitrite amounted to 10-35 µg/animal in the 24 hours following the first injection. No methemoglobin formation occurred under this exposure regime, but levels as high as 89% were detected in the blood of rats given a single intraperitoneal injection of 1700 mg/kg (Dequidt *et al.*, 1972).

Following a 4-hour exposure to an atmosphere containing 14,700 ppm of 2-nitropropane, the methemoglobin level in the experimental animals was 84%, nitrite was detected in all organs but the liver, and 2-nitropropane was detected only in the liver (23 mg/100 g) (Dequidt et al., 1972). At a concentration of 80 ppm, however, no methemoglobin formation was noted after 5 daily 8-hour exposure periods, despite the presence of nitrite in all organs except the liver. 2-Nitropropane was not detected in any organs.

Based on their studies, Dequidt et al. (1972) concluded that 2-nitropropane was a methemoglobin poison. The chemical was rapidly degraded at the hepatic cell level, as indicated by the presence of nitrite in most of the body organs after intoxication and by the presence of unmetabolized 2-nitropropane in the liver only.

Treon and Dutra (1952) also found that inhalation of 2-nitropropane resulted in formation of methemoglobin in the blood of rabbits and cats. The extent of formation was related to the severity of the exposure.

2-Nitropropane can be eliminated from the body of exposed rats by pulmonary excretion (Dequidt et al., 1972); in rats given single intraperitoneal injections of 2-nitropropane, about 76% of the injected dose was excreted via this route.

b. Human Studies

(1) Pharmacokinetics

No information was found in the literature searched.

(2) Health Effects

Symptoms in humans exposed to 2-nitropropane vapors include anorexia, nausea, vomiting, diarrhea, severe occipital headaches, cyanosis, and irritation of the lungs (U.S. EPA, 1980). Large doses may produce methemoglobinemia, liver and kidney damage, and central nervous system effects.

Skinner (1947) reported that 2 men exposed to atmospheric concentrations of 2-nitropropane between 10 and 30 ppm for periods not exceeding 4 hours/day, 3 days/week, for 1 year showed no ill effects. At another plant where workers were exposed to 20 to 45 ppm 2-nitropropane in the air, 2 workers complained of nausea, vomiting, diarrhea, and anorexia and 3 other workers suffered severe occipital headaches (Skinner, 1947).

High-level exposure to a solvent system containing 2-nitropropane during the application of an epoxy resin as a surface coating within a tank was blamed for the death of one worker and liver damage in a second worker (Gaultier _et_ _al_., 1964, cited in Hine _et_ _al_., 1978).

Hine _et_ _al_. (1978) reported 4 cases in which they believed mortality could be attributed to 2-nitropropane exposure. In all 4 cases, exposure was to a solvent system containing a number of components, but 2-nitropropane was the only compound common to all and the only compound considered to be hepatotoxic. In all 4 cases, liver failure was the primary cause of death. Evidence of liver changes was documented in post-mortem examinations.

Other unpublished studies reported by ACGIH (1979) indicated no ill effects at concentrations below 9 ppm. Workers exposed for not more than 2 hours a day to concentrations between 165 and 445 ppm of a mixture of 1- and 2-nitropropane experienced nausea, dizziness, headaches, and, in one case, diarrhea (ACGIH, 1979).

IMC (1979) reported that it was not aware of any toxicity attributed to exposure to 2-nitropropane at levels of 25 ppm or less. According to IMC (1979), the method used by Skinner (1947) to assay 2-nitropropane in air was in error and the actual concentration was 40 to 90 ppm.

Mild skin irritation following frequent contact with nitroparaffins has been reported by workers (IMC, 1977), but no allergies or other adverse physiological effects have been reported as a result of skin exposure (Martin and Baker, 1969).

(3) Target Organ Toxicity

The most common route of exposure in the workplace is by inhalation of vapors (IMC, 1977). Inhalation of high concentrations will cause damage to the respiratory tract and to other internal organs, primarily the liver (IMC, 1977). Animal studies indicate that, regardless of the route of exposure, the liver is the organ that suffers the most severe damage from 2-nitropropane poisoning.

(4) Epidemiology

The International Minerals and Chemical Corporation (IMC) plant at Sterlington, LA, is the sole commercial manufacturer of 2-nitropropane. Nitromethane, nitroethane, 1-nitropropane, and 2-nitropropane are all made simultaneously in this plant; hence, worker exposure is to all four compounds. Because it has been suggested that 2-nitropropane may be a human carcinogen (Finklea, 1977), IMC initiated a retrospective mortality study to determine if there were any unusual disease mortality patterns among the workers of this plant. The study included 1815 employees who had worked at the plant during the period from January 1, 1946 through June 30, 1977 (Miller and Temple, 1979). Death certificates of 180 employees were examined. Eleven past employees could not be accounted for, but 7 of those had terminated prior to 1955, the year that nitroparaffin production began. Employee exposure was categorized on the basis of the department in which the employee worked. The cohorts were (1) "direct exposure," consisting of 372 employees from laboratories, research, production, derivatives, and warehouses, (2) "indirect exposure," consisting of 366 employees from the machine shop, electric shop, maintenance, and related services, and (3) "no exposure," consisting of 743 employees from all non-nitro paraffin departments such as plant offices and other processes. IMC provided the original data on 1481 individuals employed after January 1, 1955 and 334 employees terminated prior to that date to Drs. Monson and McMahon at the Harvard School of Public Health for analysis and interpretation.

A review of the deaths caused by cancer revealed that no deaths had resulted from cancer of the liver, including hepatocellular carcinoma (Miller and Temple, 1979). No cases were reported indicating benign neoplasms of the liver. The analysis of the data did not suggest any unusual cancer or other disease mortality patterns among the workers at the Sterlington plant, either before or after the start of nitroparaffin production in 1955. Monson and McMahon noted, however, that because the cohort is small and because the period of latency is, in most cases, relatively short, one cannot conclude from these data that 2-nitropropane is noncarcinogenic in humans (Miller and Temple, 1979). Although 2-nitropropane was not specifically addressed in this study, the results and limitations of this study are applicable to 2-nitropropane since simultaneous exposure to all four nitroparaffins occurs in this plant.

The statements of Drs. Monson and McMahon regarding the limitations of this study are in agreement with the conclusions of a study by Brown and Dobbin (1977). Following an industrial survey at the Sterlington plant which was conducted to determine the feasibility of a health effects study on nitroparaffin workers, Brown and Dobbin (1977) concluded that the population exposed was too small and the length of time since onset of exposure was too short to conduct a retrospective cohort mortality study, pregnancy outcome study, or cross-sectional medical study.

15. Ongoing Studies

The long-term tumorigenicity of 2-nitropropane administered via the inhalation route is being evaluated at one dose level in rats. The study is being conducted by T. Lewis at the Division of Biomedical and Behavorial Science, National Institute for Occupational Safety and Health, U.S. Dept. of Health, Education, and Welfare, Cincinnati, OH (SSIE, 1980).

2-Nitropropane has been scheduled for mutagenicity testing in Salmonella (additional tests) and Drosophila during fiscal year 1981 by the National Toxicology Program (NTP, 1980). Tier II mutagenicity testing of 2-nitropropane (rat bone marrow cytology assays, mouse sperm head morphology assays, rat dominant lethal assays, and unscheduled DNA synthesis testing in human fibroblasts) is scheduled to be completed in fiscal year 1981 (NTP, 1980). Reproductive and development toxicity assays are also in progress during fiscal year 1981 (NTP, 1981b).

The mutagenic potential of 2-nitropropane administered by the inhalation route of exposure will be tested at levels of 25 and 200 ppm in mice and rats by D. McGregor at Inveresk Research International, Ltd., Inveresk Gate, Edinburgh EH217UB, Scotland, United Kingdom (SSIE, 1980).

In one phase of a study on the "toxic mechanisms" of industrial compounds, H. Plotnick at the Division of Biomedical and Behavorial Science, National Institute for Occupational Safety and Health, U.S. Dept. of Health, Education, and Welfare, Cincinnati, OH, will study the tissue distribution and excretion pattern of 2-nitropropane in male and female rats. This study is funded by the U.S. Dept. of Health, Education, and Welfare under contract number V00-G24-284 (SSIE, 1980).

16. Exposure Standards

The current occupational exposure standard recommended by the ACGIH (1981) for 2-nitropropane is a Threshold Limit Value-Time Weighted Average (TLV-TWA) of 25 ppm (90 mg/m^3). 2-Nitropropane has been designated as a substance suspect of carcinogenic potential for man by the ACGIH. OSHA (1976) has adopted a similar standard for 2-nitropropane.

17. Sources of Additional Relevant Information

No sources of additional relevant information were identified.

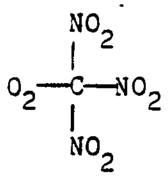
18. Other Pertinent Data

Odor detection thresholds of 24.9 ppm (Amoore, 1976) and 83 ppm (Sutton, 1963) have been reported for 2-nitropropane in humans.

E. TETRANITROMETHANE

1. Chemical Name: Tetranitromethane

2. Chemical Structure:



$$O_2N-C(NO_2)_3$$

3. Synonyms: Methane, tetranitro-

4. Chemical Abstract Service (CAS) Number: 509-14-8

5. Registry of Toxic Effects of Chemical Substances (RTECS) Number: PB4025000

6. Chemical and Physical Properties:

Description:	colorless to pale yellow liquid
Molecular Weight:	196.04
Boiling Point:	125.7°C
Melting Point:	13.8°C
Vapor Pressure:	8 mm Hg (20°C)
Solubility:	insoluble in water; miscible in alcohol and ether
Specific Gravity:	1.6229^{25}_{4}
Stability:	powerful oxidizing agent; attacks iron, copper, brass, zinc, and rubber; dangerous fire and explosion risk

7. Production

Data available from the U.S. EPA (1980) regarding producers of tetranitromethane and production volumes are presented below:

Hummel Chemical Co. (South Plainfield, NJ)
Manufacturer - Small Manufacturer
1977 Production of 1 to 11 thousand lbs

8. Use

Tetranitromethane is used as an oxidant or monopropellant in rocket fuels and also in a qualitative test for unsaturated compounds (Martin and Baker, 1969; Hawley, 1977). Other uses include use to increase the octane number of diesel fuels (*The Merck Index*, 1976) and as a reagent for modification of tyrosine residues (Aldrich, 1980).

9. Manufacturers and Distributors

Tetranitromethane is manufacturerd by Hummel Chemical Co. in South Plainfield, NJ (U.S. EPA, 1980; SRI International, 1980).

Distributors include (*Chem Sources--USA*, 1980):

Accurate Chem.
Aldrich Chem.
Biochemical Lab.
Bio-Clinical Lab.
Chem. Procurement Lab.
Chem. Services
ICN/K and K
Lachat Chem.
Monomer-Polymer and Dajac Lab.
Pfaltz and Bauer
Polysciences
Sigma Chem.
Tridom Chem.
U.S. Biochemical

10. Manufacturing Processes

Tetranitromethane has been commercially prepared by the reaction of nitric acid with acetic anhydride in an agitated, cooled vessel. It can also be prepared in a two-step sequence starting with acetylene, which is reacted with 98% nitric acid to form trinitromethane; the trinitromethane is nitrated in the second step to tetranitromethane (Martin and Baker, 1969).

Tetranitromethane is a normal by-product of TNT manufacture but is seldom recovered from this process (Martin and Baker, 1969).

11. Impurities or Additives

Commercial grade tetranitromethane is 98% pure (Aldrich, 1980).

12. Occupational Exposure

The National Occupational Hazard Survey does not provide an estimate of the number of workers who are potentially exposed to tetranitromethane.

13. Control Technology and Work Practices

Specific factors that may contribute to or prevent employee exposure to tetranitromethane were not found in the literature searched.

14. Biological Effects

a. Animal Studies

(1) Acute Exposures

The acute toxicity of tetranitromethane is summarized in Table 5.

Inhalation of tetranitromethane by rats (20 animals in each group) at three levels of concentration, 1230 ppm, 300 ppm, and 33 ppm, caused death in 50% of the animals in 36.3 minutes, 60 minutes, and 5.8 hours, respectively (Horn, 1954). Successive signs of toxicity observed were considerable preening, increased respiration which was deeper, closed eyes and gasping respiration, lacrimation and rhinorrhea, and salivation. Animals appeared cyanotic and short tonic convulsions and coma appeared prior to death. Mayer *et al*. (1920) reported that in mammals (species unspecified) inhalation of nitro derivatives of methanes caused death due to pulmonary edema.

Intraperitoneal injection of a dose of 0.5 g/kg produced death attributed to methemoglobin formation within one hour in mammals (species unspecified). At the moment of death methemoglobin content in blood measured spectrophotometrically was in the order of 80% (Mayer *et al*., 1920).

The outstanding signs of toxicity in dogs following i.v. injection of 25-30 mg/kg tetranitromethane were pulmonary edema and edema of the liver. Central nervous system effects and slight damage to the kidney were also observed. Methemoglobinemia and Heinz bodies were seen in the blood. Rapid injection was fatal and the compound produced necrosis at the site of injection (Kiese, 1949).

Injection of 65 to 300 mg/kg tetranitromethane intramuscularly into cats produced toxic signs similar to those found in dogs with the exception of pulmonary edema (Kiese, 1949).

Table 5. Acute Effects of Tetranitromethane

Route	Species	Dose (mg/kg)	Response	Reference
Oral	rats, male	130 mg/kg (83-210)	LD_{50}	Vernot *et al.*, 1977
Oral	mice	380 mg/kg (260-510)	LD_{50}	Vernot *et al.*, 1977
Inhalation	rats, male	18 ppm/for 4 hours (16-19)	LC_{50}	Vernot *et al.*, 1977
Inhalation	mice	54 ppm/for 1 hour (48-62)	LC_{50}	Vernot *et al.*, 1977
Inhalation	mammal	500 mg/kg	LD_{Lo}	Mayer *et al.*, 1920

(2) Subchronic Exposures

Horn (1954) reported that inhalation of 6.35 ppm tetranitromethane by 2 dogs and 19 rats (with equal numbers of control animals) for 6 months on a 6 hours per day, 5 day per week basis produced 11 deaths (57.9%) in the rats and no deaths among the dogs. Only one death occurred in the control group of rats. Temporary symptoms in the dogs after the first two days of exposure included occasional coughing, lethargy, unthrifty appearance, and refusal to eat at the termination of each exposure. A yellowish discoloration of the fur persisted in all animals. There was occasional blood-tinged exudate on the nares of the rats. No significant change in body weight between experimental and control animals of either species occurred. Biochemical studies, which included blood urea nitrogen levels, blood sugar, plasma chloride, plasma CO_2 combining power, icteric index, sodium excretion and blood volume determinations, revealed values within normal limits in the dogs (Horn, 1954). The subchronic exposure produced bronchial constriction, mucosal degeneration, purulent bronchitis, interstitial hemorrhage and severe congestion in the lungs of the rats, and slight degenerative changes occurred in the liver and kidney. Histological examination of tissues from the dogs was unremarkable (Horn, 1954).

In an abstract of a study made by Korbakova and Fedorova (1962), it was reported that inhalation of 0.002 mg tetranitromethane for 20 days by rats caused manifestations of disturbances of conditioned reflexes beginning on the seventh day. Serious lesions of all internal organs, particularly the liver and kidneys, were observed.

(3) Chronic Exposures

No information was found in the literature searched.

(4) Carcinogenicity

No information was found in the literature searched.

(5) Mutagenicity

No information was found in the literature searched.

(6) Teratogenicity

Gross development in a litter of five puppies, which were exposed to tetranitromethane in utero and for one and one-half days after birth (length of exposure in utero and dosage unspecified), did not appear to be adversely affected (Horn, 1954).

(7) Reproductive Effects

No information was found in the literature searched.

(8) Other Relevant Information

Tetranitromethane was reported (in an abstract) to inactivate thrombin by a first-order reaction (Astrup, 1948). Nitration of tyrosyl residues in hormones (e.g., human chorionic gonadotropin and growth hormone) and enzymes (e.g., trypsin and 1-malate dehydrogenase) modified the activity of the hormones and enzymes (Arnon and Neurath, 1970; Maddaiah et al., 1972, Sairam et al., 1972; Siegel and Ellison, 1971).

b. Human Studies

(1) Pharmacokinetics

No information was found in the literature searched.

(2) Health Effects

Hager (1949) reported that workers who handled tetranitromethane exhibited variable symptoms. Locally, transient irritation to the eyes, nose and respiratory tract were noted. Initial toxic signs were salivation followed successively by inflammation of the nose and upper respiratory tract, headache, and dyspnea. Subchronic exposure elicited symptoms of headache, weariness, sleepiness, bradycadia, methemoglobinemia and disturbances of respiration.

The death of seven people who handled TNT in the munitions industry was attributed to the tetranitromethane contaminant (Fischer, 1917; cited in Horn, 1954).

(3) Target Organ Toxicity

The central nervous system and heart were affected by prolonged exposure to inhalation of tetranitromethane (Hager, 1949).

(4) Epidemiology

No information was found in the literature searched.

15. Ongoing Studies

Tetranitromethane has been selected for carcinogenicity testing by the National Toxicology Program in rats and mice exposed by inhalation (NTP, 1981a); prechronic testing is currently in progress. Microbial mutagenesis and genetic toxicity testing of tetranitromethane were scheduled to be completed by the NIEHS in fiscal year 1981 (NTP, 1981b).

16. Exposure Standards

The current occupational exposure standard recommended by the ACGIH (1981) for tetranitromethane is a Threshold Limit Value-Time Weighted Average (TLV-TWA) of 1 ppm (8 mg/m^3). A similar standard has been adopted by OSHA (1976).

17. Sources of Additional Information

No sources of additional relevant information were identified.

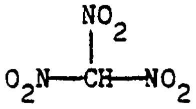
18. Other Pertinent Data

No other information that would aid in the assessment of tetranitromethane as an occupatioal hazard was found in the literature searched.

F. TRINITROMETHANE

1. Chemical Name: Trinitromethane

2. Chemical Structure:



$$O_2N\text{—}\overset{\overset{\displaystyle NO_2}{|}}{CH}\text{—}NO_2$$

3. Synonyms: Methane, trinitro-
Nitroform

4. Chemical Abstract Service (CAS) Number: 517-25-9

5. Registry of Toxic Effects of Chemical Substances (RTECS) Number:

Not listed

6. Chemical and Physical Properties:

Description:	colorless oil or white crystals
Molecular Weight:	151.04
Boiling Poing:	45-47°C (22 mm Hg); explodes at 760 mm Hg
Melting Point:	14.3°C (decomposes)
Vapor Pressure:	---
Solubility:	16.7 g/100 ml water (0°C) 193.8 g/100 ml water (60°C 5.29 g/liter ethanol
Specific Gravity:	1.479_4^{20}
Stability:	explodes when heated rapidly

7. Production

Data available from the U.S. EPA (1980) regarding producers of trinitromethane and production volumes are presented below:

Plant Site Not on File
    Manufacturer, Small Manufacturer
    1977 Production of 1 to 10 thousand lbs

8. Use

Trinitromethane is used in explosives and propellants (The Merck Index, 1976).

9. Manufacturers and Distributors

Trinitromethane is manufactured by Hummel Chemical Co. in South Plainfield, NJ (SRI International, 1980).

10. Manufacturing Processes

Trinitromethane (nitroform) is made by the reaction of acetylene with nitric acid (Martin and Baker, 1969).

11. Impurities or Additives

No information was found in the literature searched.

12. Occupational Exposure

The National Occupational Hazard Survey does not provide an estimate of the number of workers who are potentially exposed to trinitromethane.

13. Control Technology and Work Practices

Specific factors that may contribute to or prevent employee exposure to trinitromethane were not found in the literature searched.

14. Biological Effects

a. Animal Studies

(1) Acute Exposures

The results of exposure of mice to inhalation of trinitromethane for 2 hours were reported in an abstract of a study made by Timofievalaya (1964). In this study, an LDLo of 0.7 mg/l (≈113 ppm), an LC50 of 0.8 mg/l (≈130 ppm), and an LD100 of 1.0 mg/l (≈162 ppm) trinitromethane were found. Symptoms observed prior to death included irritation of mucous membranes of the eyes and respiratory tract, dyspnea, excitability, motor incoordination, convulsions, and narcosis. Levels of 29% methemoglobin were found in the blood. Threshold concentrations of 0.04-0.05 mg/l (≈8 ppm) were noted in cats and rats where changes in conditioned reflexes and neuromuscular activity were observed.

An oral LDLo of 150 mg/kg trinitromethane and an oral LD50 of 300 mg/kg were observed in mice by Timofievskaya (1964). Tonic-clonic convulsions were the main symptoms occurring prior to death.

(2) Subchronic Exposures

In an abstract of a study by Timofievskaya (1964), it was reported that daily inhalation of 0.12 mg/l (≈19 ppm) trinitromethane for 2 hours over a period of 2 months altered excitability of the nervous system, increased reticulocytes in the blood, produced 6 to 9% methemoglobinemia, and death to 46% of the rats. Inhalation of 0.002-0.01 mg/l (≈0.3-1.6 ppm) trinitromethane 4 hours/day for 7 months altered the threshold of nervous excitability. In the blood there was a decreased number of erythrocytes, an increased level of reticulocytes (to 4.6%), lymphocytopenia, and neutrophilia. Hippuric acid formation in the liver was decreased, and proteinuria was increased.

(3) Chronic Exposures

No information was found in the literature searched.

(4) Carcinogenicity

No information was found in the literature searched.

(5) Mutagenicity

No information was found in the literature searched.

(6) Teratogenicity

No information was found in the literature searched.

(7) Reproductive Effects

No information was found in the literature searched.

(8) Other Relevant Information

No information was found in the literature searched.

b. Human Studies

(1) Pharmacokinetics

No information was found in the literature searched.

(2) Health Effects

No information was found in the literature searched.

(3) Target Organ Toxicity

No information was found in the literature searched.

(4) Epidemiology

No information was found in the literature searched.

15. Ongoing Studies

No current toxicological or environmental studies of trinitromethane were found.

16. Exposure Standards

No recommended or promulgated occupational exposure standards for trinitromethane were found.

17. Sources of Additional Relevant Information

No sources of additional relevant information were identified.

18. Other Pertinent Data

No other information that would aid in the assessment of trinitromethane as an occupational hazard was found in the literature searched.

APPENDIX A - NITROPARAFFINS

The following list includes all of the nitroparaffins considered under the class definition. The compounds in the list were identified primarily from the following sources: U.S. EPA TSCA list and U.S. EPA (1980), USITC (1980), SRI International (1980), Chem Sources--USA (1980), 1980-81 OPD Chemical Buyers Directory (1980), Kirk-Othmer's Encyclopedia of Chemical Technology, The Merck Index (1976), and Hawley (1977).

CAS numbers are given, where available, to aid in identification as organic compounds may be recognized by a variety of synonyms.

	CAS No.
1,1-Dinitrocyclohexane	4028-15-3
1,1-Dinitroethane	600-40-8
1,2-Dinitroethane	7570-26-5
Dinitromethane	625-76-3
2,2-Dinitropropane	595-49-3
1-Nitrobutane	627-05-4
2-Nitrobutane	600-24-8
Nitrocyclohexane	1122-60-7
Nitroethane	79-24-3
1-Nitrohexane	646-14-0
Nitromethane	75-52-5
1-Nitro-2-methylpropane	625-74-1
2-Nitro-2-methylpropane	594-70-7
1-Nitropentane	628-05-7
1-Nitropropane	108-03-2
2-Nitropropane	79-46-9
Tetranitromethane	509-14-8
1,1,1-Trinitroethane	595-86-8
Trinitromethane	517-25-9

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