IPCS

INTERNATIONAL PROGRAMME ON CHEMICAL SAFETY

Environmental Health Criteria 138

2-Nitropropane

under the joint sponsorship of the United Nations Environment Programme, International Labour Organisation, and the World Health Organization

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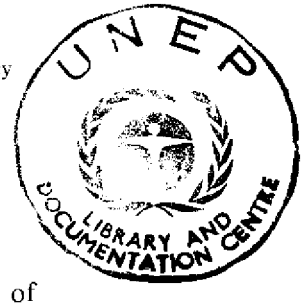
Environmental Health Criteria 138

2-NITROPROPANE

First draft prepared by Dr R.B. Williams,
United States Environmental Protection Agency



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The **International Programme on Chemical Safety (IPCS)** is a joint venture of the United Nations Environment Programme, the International Labour Organisation, and the World Health Organization. The main objective of the IPCS is to carry out and disseminate evaluations of the effects of chemicals on human health and the quality of the environment. Supporting activities include the development of epidemiological, experimental laboratory, and risk-assessment methods that could produce internationally comparable results, and the development of manpower in the field of toxicology. Other activities carried out by the IPCS include the development of know-how for coping with chemical accidents, coordination of laboratory testing and epidemiological studies, and promotion of research on the mechanisms of the biological action of chemicals.

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NOTE TO READERS OF THE CRITERIA DOCUMENTS

Every effort has been made to present information in the criteria documents as accurately as possible without unduly delaying their publication. In the interest of all users of the Environmental Health Criteria documents, readers are kindly requested to communicate any errors that may have occurred to the Director of the International Programme on Chemical Safety, World Health Organization, Geneva, Switzerland, in order that they may be included in corrigenda.

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A detailed data profile and a legal file can be obtained from the International Register of Potentially Toxic Chemicals, Palais des Nations, 1211 Geneva 10, Switzerland (Telephone No. 7988400 or 7985850).

ENVIRONMENTAL HEALTH CRITERIA FOR 2-NITROPROPANE

A WHO Task Group on Environmental Health Criteria for 2-Nitropropane met in Geneva from 4 to 8 November 1991. Dr B.H. Chen, IPCS, welcomed the participants on behalf of the Director, IPCS, and the three IPCS cooperating organizations (UNEP/ILO/WHO). The Task Group reviewed and revised the draft criteria document and made an evaluation of the risks for human health and the environment from exposure to 2-nitropropane.

The first draft of this monograph was prepared by Dr R.B. Williams of the US Environmental Protection Agency. The second draft was also prepared by Dr R.B. Williams incorporating comments received following the circulation of the first draft to the IPCS Contact Points for Environmental Health Criteria documents.

Dr B.H. Chen and Dr P.G. Jenkins, both members of the IPCS Central Unit, were responsible for the overall scientific content and technical editing, respectively.

The efforts of all who helped in the preparation and finalization of the document are gratefully acknowledged.

ABBREVIATIONS

DDT	dichlorodiphenyltrichloroethane
DMSO	dimethyl sulfoxide
SCE	sister chromatid exchange
SGPT	serum glutamic pyruvic transaminase
STEL	short-term exposure limit
TWA	time-weighted average

SUMMARY

1.1 Properties and analytical methods

2-Nitropropane (2-NP) is a colourless, oily liquid with a mild odour. It is flammable, only moderately volatile, and stable under ordinary conditions. It is only slightly soluble in water but miscible with many organic liquids, and it is an excellent solvent for many types of organic compounds. Adequate analytical methods exist for the identification and measurement of 2-NP at environmental concentrations. Current methods use gas chromatography and a flame ionization or electron capture detector or, alternatively, high-performance liquid chromatography with an ultraviolet detector. For measurement in air, 2-NP must first be trapped and concentrated in a solid sorbent.

1.2 Uses and sources of exposure

1.2.1 Production

Current world production figures are not available. In 1977 production in the USA was approximately 13 600 tonnes. 2-NP is currently manufactured by two USA companies and one French company. It is produced naturally in trace amounts in the combustion of tobacco and other nitrate-rich organic matter, but there is no evidence that it is produced by any biological processes.

1.2.2 Uses and loss to the environment

2-NP is used as a solvent, principally in blends, and has many industrial applications as a solvent for printing inks, paints, varnishes, adhesives and other coatings such as beverage container linings. It has also been used as a solvent to separate closely related substances such as fatty acids, as an intermediate in chemical syntheses, and as a fuel additive. Losses to the environment are mainly to the air and are due principally to solvent evaporation from coated surfaces.

1.3 Environmental transport and distribution

2-NP appears to be highly mobile in the natural environment. Since it is slightly water soluble, slightly adsorbed by sediment,

slightly bioaccumulated, and evaporates readily into the atmosphere, it will be distributed in both air and water and not accumulated in any individual environmental compartment. Ultraviolet photoabsorption by 2-NP is within the range of wavelengths occurring naturally in the environment, and it is thus likely that 2-NP undergoes slow photolysis in the atmosphere. Slow biological conversion of 2-NP to less toxic compounds also appears likely in both aquatic and terrestrial environments.

1.4 Environmental levels and human exposure

General population exposure to 2-NP appears to be very low and is derived from cigarette smoke (1.1 to 1.2 μg/cigarette), from residues in coatings such as beverage can coatings, adhesives and print, and from vegetable oils fractionated with 2-NP. Industrial exposure worldwide is unknown, but in the USA appears to be limited to 0.02–0.19% of the workforce. Significant exposure (exposure to 9.1 mg/m^3 (2.5 ppm) or more) in the USA may be limited to about 4000 workers (approximately 0.005% of the workforce). Occupational exposure limits in the air vary among different countries and range from 3.6 mg/m^3 (1 ppm) (TWA) to 146 mg/m^3 (40 ppm) (STEL). Manufacture of 2-NP is an enclosed process and usually involves little employee exposure, but some workers in industries such as painting, printing, and solvent extraction have in the past been exposed to levels much greater than occupational exposure limits. Concentrations as high as 6 g/m^3 (1640 ppm) in air were recorded in a drum-filling operation.

1.5 Kinetics and metabolism

Human uptake of 2-NP occurs mainly through the lungs. In experimental animals, 2-NP has been shown to be rapidly absorbed not only via the lungs but also from the peritoneal cavity and the gastrointestinal tract. There is no satisfactory information on absorption via the skin. Information on distribution in rats is somewhat contradictory. 2-NP is rapidly metabolized, mainly to acetone and nitrite. Some isopropyl alcohol may also be formed. Following intraperitoneal injection, 2-NP and its carbon-containing metabolites are concentrated initially in fat and subsequently in bone marrow as well as in the adrenal glands and other internal organs. Following inhalation, 2-NP and its carbon-containing metabolites are concentrated in the liver and kidney, with relatively little in fat. Several different enzyme systems may

be involved and there are species differences concerning rates and pathways. 2-NP and its carbon-containing metabolites are rapidly lost from the body by metabolic transformation, exhalation, and excretion in the urine and faeces. Satisfactory information on the distribution and excretion of nitro moiety metabolites is lacking.

1.6 Effects on laboratory mammals and *in vitro* systems

2-NP has moderate acute toxicity for mammals. Males are more sensitive than females, at least among rats, and sensitivity differs widely among the species that have been tested. The LC_{50} (concentration causing 50% mortality within 14 days) for rats following a 6-h exposure was 1.5 g/m^3 (400 ppm) for males and 2.6 g/m^3 (720 ppm) for females. Lethality appeared to be associated mainly with the narcotic effects, but mammals exposed to concentrations of at least 8.4 g/m^3 (2300 ppm) for one hour or longer displayed severe pathological changes including hepatocellular damage, pulmonary oedema, and haemorrhage.

There is clear evidence that 2-NP is carcinogenic in rats. Long-term inhalation exposure of rats to 0.36 g/m^3 (100 ppm) for 18 months (7 h/day, 5 days/week) induced destructive changes in the liver, including hepatocellular carcinomas in some males. A concentration of 0.75 g/m^3 (207 ppm) induced more severe damage, including a high incidence of hepatocellular carcinomas, more quickly. Moderate-chronic oral dosage also induced excess hepatocellular carcinomas in rats. However, long-term inhalation exposure of rats to 91 or 98.3 mg/m^3 (25 or 27 ppm) produced no detectable injury. Exposure of mice and rabbits to concentrations of 2-NP that induced hepatocellular carcinomas in rats had little or no effect, but these studies were too limited to completely rule out 2-NP carcinogenicity in these two species. 2-NP slightly retarded fetal development of rats, but there is a paucity of data on embryotoxicity, teratogenicity, and reproductive toxicity. 2-NP was found to be strongly genotoxic in rat hepatocytes both *in vitro* and *in vivo*, but no significant genotoxicity was observed in other organs of the rat or in cell lines of extrahepatic origin without exogenous metabolic activation. 2NP has been shown to be mutagenic in bacteria both in the presence and absence of exogenous metabolic activation.

1.7 Effects on humans

Human exposure to high concentrations of 2-NP is largely or entirely occupationally related. High concentrations (actual values

are unknown but in one case they were estimated to be 2184 mg/m^3 (600 ppm)) are acutely toxic and have produced industrial fatalities. Initial symptoms included headache, nausea, drowsiness, vomiting, diarrhoea, and pain. Victims often showed temporary improvement, but in some cases death occurred 4 to 26 days after exposure. Hepatic failure was the primary cause of death, and lung oedema, gastrointestinal bleeding, and respiratory and kidney failure were contributing factors. Occupational exposure to estimated levels of 73 to 164 mg/m^3 (20 to 45 ppm) induced nausea and loss of appetite, which persisted for several hours after leaving the workplace, whereas occupational exposure to estimated levels of 36.4 to 109 mg/m^3 (10 to 30 ppm) (< 4 h/day for ≤ 3 days/week) produced no noticeable ill effects.

Although available data are inadequate, there is no indication that chronic occupational exposure to 2-NP at concentrations usually encountered in the workplace induces hepatic or other neoplasms, or other long-term adverse effects.

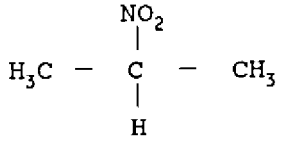
1.8 Effects on other organisms in the laboratory and field

The few studies performed on microorganisms, invertebrates, and fish indicate low toxicity of 2-NP for non-mammalian organisms.

2. IDENTITY, PHYSICAL AND CHEMICAL PROPERTIES, AND ANALYTICAL METHODS

2.1 Identity

Chemical structure:



Empirical formula: $C_3H_7NO_2$

Synonyms: Dimethylnitromethane, isonitropropane, nitroisopropane, 2-NP

Trade names: NiPar S-20 (solvent), NiPar S-30 (solvent, a mixture of 1- and 2-nitropropane)

CAS registry number: 79-46-9

RTECS number: TZ 5250000

Relative molecular mass: 89.09

2.2 Physical and chemical properties

2-Nitropropane (2-NP) is an important synthetic organic chemical. Its physical properties have been described by Angus Chemical Co. (1985), Baker & Bollmeier, (1981), Woo et al. (1985), and Weast (1986) and are summarized in Table 1. It is a colourless, oily liquid with a mild odour and remains liquid over a relatively broad temperature range, i.e. -93 to 120 °C. 2-NP is flammable, and although only moderately volatile, its vapour forms flammable or explosive mixtures with air. It is stable under ordinary circumstances, but may undergo explosive decomposition under conditions of extreme shock combined with heavy confinement and elevated temperature. 2-NP is only slightly soluble in water (17 ml/litre at 20 °C) and water is even less

Table 1. Physical properties of 2-nitropropane

		Reference
Appearance	colourless, oily liquid	Stokinger (1982)
Relative molecular mass	89.09	Stokinger (1982) Weast (1986) Windholz (1983)
Specific gravity (liquid density) (at 20 °/4 °C)	0.988	Baker & Bollmeier (1981) Stokinger (1982)
Vapour density (air = 1.00)	3.06	Stokinger (1982)
Vapour pressure (20 °C)	1.72 MPa (12.9 torr)	Stokinger (1982)
Boiling point	120.3 °C	Baker & Bollmeier (1981) Stokinger (1982) Windholz (1983)
Melting point	-93 °C	Weast (1986)
Water solubility (20 °C)	17 ml/l	Baker & Bollmeier (1981) Stokinger (1982) Windholz (1983)
Refractive index (20 °C)	1.3944	Baker & Bollmeier (1981) Weast (1986)
Flash point (open cup)	38 °C	Stokinger (1982)
Lower inflammability limit	2.6 volume % in air	National Fire Protection Association (1968)
Partition coefficients		
water/air	128	Filser & Baumann (1988)
olive oil/air	710	Filser & Baumann (1988)
in vivo whole body (rat)/air	175	Filser & Baumann (1988)

soluble in 2-NP (5 ml/l at 20 °C). With increasing temperature, solubility of both 2-NP in water and water in 2-NP increases, and an azeotrope containing 29.4% water ultimately is formed. Its boiling point is 88.6 °C. 2-NP is, however, miscible with many organic compounds including chloroform, aromatic hydrocarbons, alcohols, esters, ketones, ethers, and higher aliphatic carboxylic

acids. Alkanes and cycloalkanes have more limited solubility in 2-NP (Baker & Bollmeier, 1981). Azeotropes are formed with some organic liquids.

2-NP, like other nitroparaffins, undergoes a variety of chemical reactions. The chemistry of nitroparaffins has been the subject of a number of reviews and symposia and has been summarized by Baker & Bollmeier (1981), Goldwhite (1965), Stokinger (1982), Woo et al. (1985), and others. 2-NP is an acidic substance. The nitro form, which is mildly acidic, exists in equilibrium with its more strongly acidic "aci" tautomer and with the anionic form (nitronate) of the latter (Fig. 1). The aci tautomer is referred to as a nitronic acid and forms metal salts. It can be dissolved and neutralized by strong bases and gives a characteristic colour reaction with ferric chloride. Prolonged action of bases leads to decomposition. Aqueous acids hydrolyse 2-NP first to a hydroxamic acid and ultimately to carboxylic acids and hydroxylammonium salts. 2-NP reacts with nitrous acid to form a pseudonitrole which is colourless in crystalline form but blue when melted or in solution. The carbon atom bearing the nitro group is easily halogenated in the presence of a base. Photochemical chlorination, however, yields reaction products in which chlorine atoms are attached to the terminal carbons. In the presence of a base, 2-NP condenses with carbonyl compounds to yield a β-nitroalcohol, which may dehydrate spontaneously to a nitro-olefin. Nitro-olefins thus formed, and a variety of other unsaturated compounds, undergo Michael addition reactions with 2-NP in the presence of a catalytic amount of base. 2-NP will condense with formaldehyde and a secondary amine (the Mannich reaction). Mild reduction of 2-NP yields isopropylhydroxylamine, and strong reduction produces isopropylamine. Auto-oxidation catalysed by cuprous chloride yields 2-hydroperoxy-2-nitropropane (Fieser & Fieser, 1972, 1974).

Taste and odour are subjective biological properties derived from chemical and physical properties. The odour has been described as "sweet-solventy, rubbery, and alcohol-like" (letter from S.E. Ellis of Arthur D. Little, Inc. to G. Crawford of Occusafe Inc., 1982). There also is some uncertainty concerning odour threshold. Treon & Dutra (1952) stated that the odour of 2-NP was detectable at 1070 mg/m^3 (294 ppm) but not at 302 mg/m^3 (83 ppm), without describing the methodology by which these values were determined; their values have nevertheless been incorporated into various guidelines (Crawford et al., 1984). Two

Fig. 1. The various forms of 2–NP in solution (from Porter and Bright, 1983)

recent studies redetermined the odour threshold for 2-NP. In one the ED_{50} (minimum concentration detected by 50% of the population) was estimated to be 18.2 mg/m^3 (5.0 ppm) with 95% confidence limits from 11.3 mg/m^3 (3.1 ppm) to 28.76 mg/m^3 (7.9 ppm), and, in the other, all of a four-member test panel detected 2-NP at 11.3 mg/m^3 (Crawford et al., 1984). There was no consensus as to the taste of a 6.4 g/litre (0.072 mol/litre) solution of 2-NP in water (Marcstrom, 1967). The most frequent response was bitter, but other tasters found it (1) sweet, (2) bitter and sour, (3) bitter, cool, and anaesthetizing, (4) burning, (5) burning and cool, or (6) burning, sweet, bitter, and sour. Wilks & Gilbert (1972a) reported a taste detection threshold for 2-NP in water of 12.5 mg/litre.

2.3 Conversion factors

1 ppm 2-NP in air = 3.64 mg/m^3
1 mg/m^3 = 0.27 ppm 2-NP in air

2.4 Analytical methods

Analytical methods for 2-NP appear limited to the analysis of air, water, blood plasma, coatings, and cigarette smoke (Table 2). Since the colorimetric methods are less sensitive or are cumbersome, the method of choice is probably gas chromatography with either a flame ionization or an election capture detection. Charcoal is not a satisfactory adsorbent for 2-NP since recovery is poor (Andersson et al., 1983) and there may be decomposition (Glaser & Woodfin, 1981). In addition to Chromosorb 106, Amberlite XAD-7 appears satisfactory as a solid sorbent for quantitatively collecting 2-NP from the air (Andersson et al., 1983), although its collection efficiency is markedly reduced in humid air (Andersson et al., 1984). Use of a collection tube with two sections, however, can compensate for the reduced efficiency (Andersson et al., 1984). The high-performance liquid chromatography method developed for blood (Derks et al., 1988) could probably be adapted to other biological materials.

Table 2. Analytical techniques for determining 2-nitropropane[a]

Methods	Detection limit	Comments	Reference
Air			
Trapping in ethanol; concentration determined spectrophotometrically at 277.5 nm	0.1 mg/ml ethanol	absorption is linear between 0.1 and 2.0 mg/ml; ethanol was especially purified and redistilled	Treon & Dutra (1952)
Trapping in concentrated sulfuric acid; resulting nitrous acid combined with resorcinol to form a red-blue colour; measured spectro-photometrically at 560 nm	ca. 1 µg/ml sulfuric acid	absorption is linear between 1 and 5 µg/ml sulfuric acid; no interference from primary nitroparaffins, but all other secondary, some tertiary and some halogenated nitro-paraffins interfere	Jones & Riddick (1952); Jones (1963)
Trapping in solid sorbent tube (Chromosorb 106, 60/80 mesh); desorption: ethyl acetate; separation-detection: GC-FID	3.6 mg/m^3	working range is 3.6 to 36 mg/m^3; 2-NP stable on absorbent for at least 28 days	Glaser & Woodfin (1981)
Methodology similar to above	3.1 mg/m^3	Method is a modification of that proposed by Glaser & Woodfin (1981); range: 3.1 to 28.3 mg/m^3; no interference from methyl butyl ketone, heptane, 1-nitropropane, toluene, and xylene	US NIOSH (1987a)
Water			
Sample (40 µl) collected with a syringe and injected directly into GC; detection: FID	ca. 0.5 mg/m^3	water elutes quickly extinguishing flame in FID; flame can be reignited before 2-NP emerges	Wilks & Gilbert (1972a)

Table 2 (contd).

Methods	Detection limit	Comments	Reference
Blood			
Blood collected in chilled, screw-capped vial with heparin; centrifuged; deproteinized with acetonitrile; Tris buffer added; separation: HPLC; detection: UV at 224 nm	1 ng	UV absorption linear from 0 to 250 ng; uses 0.3 ml blood sample; samples are unstable and must be analysed promptly	Derks et al. (1988)
Coating (beverage can)			
Redissolve coating in solvent suitably distinct from 2-NP; acetone suitable for vinyl co-polymer coatings; separation: GC	not given	reference provides few details on methodology	Wilks & Gilbert (1972b)
Can (empty) simultaneously perforated and fitted with a diaphragm; hypodermic needle inserted through diaphragm and fitted with stopcock; can heated (150 °C, 15 min); headspace sampled with heated syringe; separation: GC	not given	method captures about 90% of residual 2-NP	Wilks & Gilbert (1972b)

Table 2 (contd).

Methods	Detection limit	Comments	Reference
Cigarette smoke			
Steam distillation of smoke condensate on filters, extraction in ethyl ether, re-extraction in NaOH, neutralization with H_2SO_4 and re-extraction in ethyl ether, concentration of extract and injection in GC equipped with FID or ECD detectors	0.8 µg/cigarette	may be adapted for air and water analysis	Hoffmann & Rathkamp (1968)

[a] Abbreviations: ECD = electron capture detector; FID = flame ionization detector; GC = gas chromatograph; HPLC = high-performance liquid chromatograph; UV = ultraviolet

3. SOURCES OF HUMAN AND ENVIRONMENTAL EXPOSURE

3.1 Natural occurrence

There is no evidence that 2-NP and other nitroaliphatic compounds are produced by biological processes, although a related organic compound, β-nitropropionic acid, has been isolated from plants and microorganisms (Goldwhite, 1965). However, nitroaliphatic compounds are produced in low concentrations by combustion of organic matter and have been detected in tobacco smoke. Hoffmann & Rathkamp (1968) reported 1.1-1.2 μg 2-NP in the smoke from single 85-mm USA blended non-filter cigarettes, and ascribed the production of this and other nitroaliphatics to interactions in the combustion zone between hydrocarbons and nitrogen dioxide generated by decomposition of nitrates.

3.2 Anthropogenic sources

3.2.1 Production levels and processes

Although 2-NP is an important industrial chemical, current world production figures are not available. In 1977 production by the sole USA manufacturer was estimated to be 13 600 tonnes, of which 5400 tonnes were sold in the USA and 8200 tonnes were either exported or used internally (Finklea, 1977). 2-NP currently is produced by two USA manufacturers, Angus Chemical Co., Sterlington, Louisiana, and W. R. Grace Co., Deer Park, Texas (SRI International, 1988, 1990; USITC, 1990), and by one European manufacturer, Société Chimique de la Grande Paroisse, France (Anon., 1976, 1982; IARC, 1982). In the USA, 2-NP, together with nitromethane, nitroethane and 1-nitropropane, is manufactured by a vapour phase reaction of nitric acid with an excess of propane at high temperature and pressure (370-450 °C, 0.8-1.2 MPa (8-12 atm.)) (Baker & Bollmeier, 1981). The proportions of the four nitroaliphatic compounds in the reaction product are a function of the reaction temperature. In Europe, propane is reacted with nitrogen peroxide (N_2O_4) and an excess of oxygen at 150-330 °C and 0.9-1.2 MPa (9-12 atm.), yielding the same nitroaliphatic compounds in slightly different proportions as produced by the USA process (Anon., 1976). Reaction products are condensed, washed, and separated by fractional distillation. There is no evidence that 2-NP is produced through human

activities except by combustion and deliberate manufacture, although nitromethane has been detected in vehicle exhaust (Seizinger & Dimitrades, 1972).

3.2.2 Uses

The importance of 2-NP as an industrial chemical stems mainly from its desirable and occasionally unique characteristics as a solvent (Purcell, 1967; Anon., 1976; Fishbein, 1981; Baker & Bollmeier, 1981; IARC, 1982; ACGIH, 1986). It is an excellent solvent or cosolvent for a variety of fats, waxes, gums, resins, dyes and other organic compounds, including vinyl, acrylic, polyamide and epoxy resins, chlorinated rubbers, and organic cellulose esters. The ability of 2-NP to form an azeotrope with water and the associated large heat of absorption permit it to displace monomolecular layers of water molecules and secure a better bond between pigments and the surfaces to which they are applied. Its major use is as a solvent for inks, paints, varnishes, adhesives and other coatings such as beverage container linings. It is used principally in blends with other solvents to impart desirable characteristics, such as greater solvency, better flow characteristics and film integrity, greater pigment dispersion, increased wetting ability, improved electrostatic spraying properties, or reduced drying time. 2-NP is also used industrially as a processing solvent for separating closely related substances in natural products or reaction mixtures. These have included, for example, separation of oleic acid from polyunsaturated fatty acids and cetyl from oleyl alcohols.

In addition to the above, 2-NP has a number of minor uses (Anon., 1976; Baker & Bollmeier, 1981). These include a medium for chemical reactions, an intermediate for the manufacture of 2-nitro-2-methyl-1-propanol, 2,2-dinitropropane, 2-amino-2-methyl-1-propanol and other propane derivatives, and a component of explosives, propellants, and fuels for internal combustion engines. The latter usage appears limited to model engines used by hobbyists and to racing cars. Although the addition of 2-NP to fuel improves diesel engine performance, it is not used commercially as a diesel fuel additive since superior alternatives are available (Banes, 1989)[a]. In the USA, mixed isomers of nitropropane are used to denature ethanol (US FDA, 1987). The addition of 2-NP to hydrocarbon mixtures has been

[a] Personal communication from the US Environmental Protection Agency, Ann Arbor, Minneapolis

shown to inhibit corrosion of tin-plated steel aerosol cans (Flanner, 1972).

3.3 Release into the environment

There is some quantitative data on releases of 2-NP into the environment. The US Environmental Protection Agency has supported a thorough, though largely speculative, analysis of the problem (US EPA, 1980). Releases of 2-NP occur mainly into the atmosphere and can result from spillage, from venting of gases and fugitive emissions during manufacture, transfer and use, and from solvent evaporation from coated surfaces. The US EPA document estimated that of the 14 000 tonnes of 2-NP produced in the USA in 1979, 5714 tonnes (41%) was released into the air, and 1 tonne into water. Only 230 tonnes (1.6%) was destroyed by incineration or waste treatment. The major contributor to this release estimate was evaporation of 2-NP used as a solvent in printing ink and surface coatings (4450 tonnes, 78% of releases). Manufacture of 2-NP is a largely enclosed process and in 1979 it accounted for only 21 tonnes (0.3%) of the amount released into the environment. A more recent examination of this problem (National Library of Medicine, 1989) reported a similar situation concerning environmental releases of 2-NP in the USA. Out of a yearly total of 299 tonnes, 205 tonnes (69%) was released into the air with 123 tonnes coming from point (large, easily identified) sources and 82 tonnes from non-point (small, not easily identified) sources. Only 2 tonnes (< 1%) was released directly into water, and 1 tonne into municipal sewage treatment plants. The remainder was buried in closed containers (76 tonnes, 25%) or was disposed of in unspecified ways (15 tonnes, 5%).

4. ENVIRONMENTAL TRANSPORT, DISTRIBUTION, AND TRANSFORMATION

4.1 Transport in the environment

2-NP appears to be highly mobile in the natural environment. Cupitt (1980) considered physical removal of 2-NP from the atmosphere unlikely because it was not soluble enough to be rapidly washed out and had a vapour pressure too great for strong adsorption on particles. The partition of 2-NP between air and water at equilibrium was estimated by the method of Swann et al. (1983) to be about 0.5% in air and 99.5% in water (US EPA, 1985). These values indicate rapid and easy exchange between air and water. The soil sorption coefficient (ratio of soil concentration to water concentration) and the bioconcentration factor were estimated by the methods of Kenaga (1980) to be 20 and 2.5, respectively (US EPA, 1985). Measured values for absorption and bioaccumulation were somewhat greater than these estimates. Freitag et al. (1982, 1985) obtained concentration factors over water for activated sludge, unicellular algae (*Chlorella fusca*), and fish (golden ide) of 70, 20, and < 10, respectively. These values indicate that 2-NP is not strongly bioaccumulated and is readily desorbed from sediment particles and leached from soil. Thus, in summary, since 2-NP is slightly water soluble, slightly adsorbed by sediment, slightly bioaccumulated, and evaporates readily into the atmosphere, it will be distributed in both air and water and not accumulated in any individual environmental compartment.

4.2 Biotic and abiotic transformation

Data concerning the destruction of 2-NP by biotic and abiotic processes are limited. 2-NP has significant photoabsorption in the environmentally relevant range of > 290 nm (Sadtler, 1961) and is likely to undergo photolysis (Cupitt, 1980; US EPA, 1985). On the basis of physical and chemical properties Cupitt (1980) hypothesized that it would be rapidly removed from the atmosphere by photolysis and estimated a reduction in concentration of 1/e (0.369) in 0.2 days. This is equivalent to a half-life of 0.14 days (3.36 h). However, measurements of photochemical reactivity do not support such a rapid destruction of 2-NP. Studies aimed at defining the relationship between organic solvents and photochemical smog production ranked 2-NP as low to moderate in terms of its interactions with oxidants and

its ability to produce formaldehyde and other lachrymators (Levy, 1973). Laboratory measurements also suggested slow decomposition (Freitag et al., 1985). The methodology employed (Korte et al., 1978; Lotz et al., 1979; Freitag et al., 1982), i.e. irradiation of the solvent adsorbed on silica gel by light from a high pressure mercury lamp filtered through pyrex, was too different from natural conditions to permit quantitative extrapolation from laboratory results to rates of photolysis in the atmosphere. The study provided comparative photodecomposition rates for a large number of solvents. The rate of photodecomposition for 2-NP was roughly half that of dichlorodiphenyltrichloroethane (DDT), similar to the rates for dodecane and 2,4-dichlorobenzoic acid, and roughly twice those for kepone and dieldrin. Paszyc (1971) reported that the major decomposition products for both gaseous and liquid 2-NP under laboratory conditions were nitrogen dioxide, acetone, isopropyl nitrite, isopropanol, methylcyanide, water, and propane, regardless of whether irradiation was monochromatic 253.7 nm light or the full spectrum of light produced by a high pressure mercury lamp. Cupitt (1980) speculated that the major products of photodecomposition in nature would be formaldehyde and acetaldehyde.

Biological decomposition of 2-NP appears likely, but is probably rather slow in nature. Enzymes capable of oxidizing or initiating non-enzymatic oxidation of 2-NP have been identified in horseradish (De Rycker & Halliwell, 1978; Porter & Bright, 1983; Indig & Cilento, 1987), pea seedlings (Little, 1957), and a variety of microorganisms including bacteria, yeasts, and fungi (Little, 1951; Kido et al., 1975; Soda et al., 1977; Dhawale & Hornemann, 1979; Patel et al., 1982). In *in vitro* preparations of horseradish (Dhawale & Hornemann, 1979), pea seedlings (Little, 1957), a fungus (*Streptomyces achromogenes*) (Dhawale & Hornemann, 1979), and a yeast (*Hansenula mrakii*) (Kido et al., 1975), 2-NP was converted to a less toxic compound, acetone, and a moderately toxic compound, nitrite. In addition to nitrite, some nitrate may also be formed (Indig & Cilento, 1987). In the yeast, nitrite was subsequently reduced to ammonia. The importance of these processes in nature is unknown. Kido et al. (1975), however, reported that only 4 out of 14 species of microorganisms tested would grow in a medium containing 5 g 2-NP/litre. The only study of 2-NP decomposition by a population of microorganisms (Freitag et al., 1985) utilized activated sludge grown at 25 °C. Solvent concentrations in these experiments were low (50 μg/litre) to prevent adaptation to the substances tested (Korte et al., 1978).

In 5 days only 0.4% of the 2-NP was converted to carbon dioxide. In summary, these data suggest that in both terrestrial and aquatic communities 2-NP is biologically decomposed and that the rate may be slow, but they offer no definite information on the problem.

5. ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE

5.1 Environmental levels and general population exposure

General population exposure to 2-NP appears to be very low. There seem to be no records of its occurrence in water or in outdoor air away from areas of manufacture and use. The only information on intake exists in the form of a memorandum from Modderman (1983)*. The daily intake per person in the USA was estimated to be 50 to 100 mg. The residuum from its use as a solvent for beverage can coatings, film laminating adhesives and printing inks for flexible food packaging may account for as much as 37 ng/day and from vegetable oils fractionated with 2-NP, 30 ng/day. 2-NP residues of 0.077 mg/litre (77 ppb) to 0.24 mg/litre (204 ppb) have been found in such oils. In a further report on the evaluation of 2-nitropropane as a food processing solvent, it was assumed that residues of less than 10 μg/kg would occur in oils, giving rise to estimated daily intakes of 10 ng/day. The use of 2-NP as a food processing solvent was not recommended (FAO/WHO, 1990a,b). As mentioned in section 3.1, smokers are exposed regularly to low concentrations of 2-NP. Hoffmann & Rathkamp (1968) reported 1.1 to 1.2 μg in the smoke of a single cigarette. 2-NP was reported to occur in the expired air of 11.1% (5 of 54 individuals) of a sample of healthy adult urban dwellers (Krotoszynski et al., 1979). The geometric mean was 0.406 ng/litre with one-sigma limits of 0.119 ng/litre and 1.38 ng/litre, (at 25 °C, 98 MPa (760 mmHg)). The sample was entirely of non-smokers who had avoided medication and prolonged exposure to perfume, paint, glue, aerosols, dust, tobacco smoke and areas polluted with industrial wastes during, and for at least 7 days prior to, the sampling period, and also avoided cosmetics, spices, seasonings, and alcoholic beverages during and immediately prior to sampling. The origin of the exhaled 2-NP is unclear. Exposure to 2-NP may be further reduced in the future since a number of regulations have been enacted and recommendations made to declare it a harmful, carcinogenic substance and a toxic waste, and to discourage its use (IARC, 1982; IRPTC, 1986; US FDA, 1987; US NIOSH, 1988).

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* Memorandum from Modderman, J.P. to Shibko, S., Associate Director for Regulatory Evaluation, Department of Health & Human Services, USA, 8 pp. "Exposure estimates for chemicals to be included in the NTP annual report on carcinogens".

5.2 Potential occupational exposure

The number of workers in the USA who handle 2-NP or mixtures containing 2-NP has been variously estimated as 15 000 (US EPA, 1977), 38 600 (Occupational Health Services, Inc., 1982), 100 000 (Finklea, 1977), and 185 000 (Beall et al., 1980). Based on employment values of the US Bureau of the Census (1987) these estimates of exposed workers represent from 0.02% to 0.19% of the civilian workforce in the USA. The low estimate of 15 000, although quoted in a US Environmental Protection Agency report, originated with a manufacturer of 2-NP. The estimate generated by Occupational Health Services, Inc., carried out under contract with a manufacturer of 2-NP, was based on a detailed survey of distributors, manufacturers, and users, and thus may represent a reasonable approximation. This report considered 38 600 to be the best estimate of the total number of exposed workers in the USA and set 126 600 workers as an upper boundary. It further estimated that significant exposure (defined as exposure to at least 10% of the US OSHA exposure limit or 9.1 mg/m^3 (2.5 ppm)) ranged from 4000 (best estimate) to 10 600 (upper boundary) workers. Sources of worker exposure identified in a survey conducted in the USA by the National Institute for Occupational Safety and Health (Finklea, 1977) included rotogravure and flexographic inks used in printing, and coatings and adhesives used in industrial construction and maintenance, highway marking, ship building and maintenance, furniture manufacture, and food packaging. A US NIOSH survey estimated that 9815 workers in the USA were exposed to 2-NP or to trade-name products containing 2-NP (US NIOSH, 1983).

Occupational exposure limits are summarized in Table 3.

There is little data on actual occupational exposure, although the limited information on conditions in the USA summarized in Table 4 suggests that it is highly variable. Manufacture of 2-NP, an enclosed process, appears to involve little employee exposure much of the time, but spills and operations such as filling drums can briefly expose a few workers to high concentrations. In general, low exposures may be typical in some painting operations and in the manufacture of tyres, but other painting and manufacturing operations appear, at least in the past, to have exposed workers to dangerously high concentrations. Workers were exposed to concentrations of 2-NP up to at least 2744 mg/m^3 (754 pm) in a pigment production facility and up to at least

Table 3. Occupational exposure limits for 2-nitropropane in air[a]

Country	Exposure limit mg/m^3	ppm	Category of limit
Australia	36	10	TWA
Belgium	36	10	TWA
Brazil	70	20	AL
Canada	90	25	CLV
Denmark	36	10	TWA
Finland	18	5	TWA
	150	40	STEL
Germany	18	5	1-year TWA(TRK)
Hungary	10	3	CLV
Netherlands	3.6	1	8-h TWA
	7.3	2	STEL
Poland	30	8	TWA
	70	20	STEL
Romania	47	13	TWA
	70	20	STEL
Sweden	18	5	TWA
	36	10	CLV
Switzerland	18	5	TWA
United Kingdom	90	25	8-h TWA
USA	90	25	8-h TWA (OSHA)
	36	10	8-h TWA (ACGIH)
Yugoslavia	90	25	TWA

[a] From: IRPTC (1986)

ACGIH = American Conference of Governmental Industrial Hygienists
AL = Acceptable or tolerable limit
CLV = Ceiling value
MAK = Maximum worksite concentration
OSHA = Occupational Safety and Health Administration
STEL = Short-term exposure limit
TLV = Threshold limit value
TWA = Time-weighted average (MAK in Switzerland)
TRK = Technical guiding concentration

265 mg/m^3 (73 ppm) in a solvent extraction plant. Evidence exists that concentrations of 2-NP at the solvent extraction plant prior to the investigation were at times substantially greater than the values measured during the investigation (Crawford et al., 1985). Exposure levels mentioned in the report by Occupational Health Services, Inc. (1982) were mainly in the vicinity of 3.6 mg/m^3 (1 ppm), although one printing plant (Table 4) reported a peak concentration of 237 mg/m^3 (65 ppm) which lasted 30 min, and a time-weighted average of 36-44 mg/m^3 (10-12 ppm). In addition to inhalation, it is likely that workers using 2-NP as a solvent will have at least occasional contact with the liquid. 2-NP also has been reported to be a minor component of both fresh and used machine cutting fluid emulsion (Yasuhara et al., 1986). The importance of exposure to 2-NP as a contaminant of 1-nitropropane is unknown. In an investigation involving 1-nitropropane-sensitized ammonium nitrate blasting agents (Cocalis, 1982), 2-NP was below the detectable limit. Occupational exposure may be reduced in the future since strong recommendations have been issued on minimizing all worker contact with 2-NP and its fumes and on substituting other less toxic solvents where possible due to the carcinogenicity of 2-NP (IRPTC, 1986; US EPA, 1986; US NIOSH 1988).

Table 4. Air concentration of 2-NP in the work place

Activity	Concentration		Reference
	mg/m^3	ppm	
Manufacture of 2-NP	3.64	~ 1	Brown & Dobbin (1977)
Manufacture of 2-NP	0.7-364; 98% of samples were < 36.4	0.2-100; 98% of samples were < 10	Miller & Temple (1979)
Vulcanizing tyres	0-0.18	< 0.05	Hollett & Schloemer (1978)
Painting (bus maintenance)	0.11	< 0.03[a]	Love & Kern (1981)
Painting (railway cars)	1.46	< 0.4	Hartle (1980)
Solvent extraction	167.4	0-100 (average 46)	Crawford et al. (1985)
Laboratory (1958)	14.6	0-21 (average 4)	Angus Chemical Co. & Occusafe, Inc. (1986)
2-NP storage & transfer area (1962); drum filling operation	2111-6000	580-1640	Angus Chemical Co. & Occusafe, Inc. (1986)
Pigment production facility (1970)	109-2745	30-754	Angus Chemical Co. & Occusafe, Inc. (1986)
Painting (battery cases)	36.4-109	10-30	Skinner (1947)
Manufacturing (coating forms)	72.8-164	20-45	Skinner (1947)
Printing	~ 40	1-65 (~ 11)	Occupational Health Services, Inc. (1982)

[a] below limit of detection

6. KINETICS AND METABOLISM

6.1 Absorption

2-NP is absorbed via the lungs, the peritoneal cavity, the gastrointestinal tract, and possibly, to a lesser extent, via the skin. Absorption via the lungs, peritoneal cavity, and gastrointestinal tract have been used in experimental studies and have been investigated using rats and ^{14}C-labelled 2-NP. Pulmonary absorption was examined by Nolan et al. (1982), Müller et al. (1983), and Filser & Baumann (1988). Nolan et al. (1982) considered, on the basis of respiratory rate and tidal volume of the rat and the accumulation of 2-NP during the 6-h period of exposure, that a minimum of 40% of the inhaled 2-NP was absorbed. This value is minimal since it does not include 2-NP metabolized and eliminated during exposure. The data of Müller et al. (1983) suggested that immediately following exposure to 728 mg/m^3 (200 ppm) for 3 h, plasma contained approximately 0.4% as 2-NP and 7.2% as metabolites of the 2-NP inhaled. The metabolites were mainly acetone but also included a small amount of isopropanol. These percentages were estimated from the results of Müller et al. (1983) and normative data for the laboratory rat (Baker et al., 1979), and support rapid pulmonary uptake of 2-NP since 2-NP and its metabolites sequestered elsewhere in the body and loss of metabolized 2-NP during exposure were not considered. Filser & Baumann (1988) reported that uptake of gaseous 2-NP was rapid, the clearance rate being equal to the ventilation rate. The value they cite for the latter, 32 litres.h^{-1}.kg^{-1}), seems large in comparison with normative data for the laboratory rat (Baker et al., 1979).

The rate of 2-NP uptake by rats from intraperitoneal injection was examined by Müller et al. (1983). Ten minutes after an injection of 25 mg/kg, the blood plasma contained 3.3% of the dose as 2-NP and 1.9% as metabolites, acetone, and isopropanol, indicating an uptake of greater than 5.2% since presumably some of the dose was already lost from the body and to other tissues in the body during this initial period. These percentages were estimated from the data of Müller et al. (1983) and normative data for the laboratory rat (Baker et al., 1979). A dose of 50 mg/kg yielded partially dissimilar results. The 10-min average value was low and also had a very large standard deviation. This may have reflected large differences among the rats in their initial uptake

rates for 2-NP or an experimental problem such as injection into the gastrointestinal tract rather than the peritoneal cavity. Blood plasma contained, 10 min after injection, only 1.4% of the dose as 2-NP and 1.3% as acetone and isopropanol. These data indicate that uptake from the peritoneal cavity is fairly rapid, and suggest that the relatively slower uptake of the 50-mg/kg dose may have reflected saturation of the uptake mechanisms, since initial concentrations in the plasma did not exceed those following the 25-mg/kg dose. Intraperitoneal injections were used by Andrae et al. (1988), Guo et al. (1990), Hussain et al. (1990), and Conaway et al. (1991) to demonstrate that 2-NP induced nucleic acid damage in the livers of Wistar, F-344 and Sprague-Dawley rats.

Absorption of 2-NP via the gastrointestinal tract was investigated with male Wistar rats by Derks et al. (1989). They found that the systemic availability of orally administered 2-NP from a water solution was very high (90%) and absorption was rapid, maximum plasma values being reached within 15 min after dosage. Absorption of 2-NP given in olive oil was much slower and availability was only 34% during the initial 3 h following dosage. The authors suggested that absorption from oil was incomplete at 3 h and might ultimately be much higher, since the olive oil was absorbed and the 2-NP redistributed between the oil and aqueous phases.

Although workers are cautioned against dermal contact with 2-NP (Beall et al., 1980; US EPA, 1986), there appear to be no quantitative data on dermal absorption. The solubility of 2-NP in both polar and non-polar solvents, together with its small molecular size, suggests that it should be absorbed readily through the skin (Malkinson & Gehlmann, 1977). Dermal application of 2 g 2-NP/kg to rabbits produced no obvious symptoms (Wilbur & Parekh, 1982); however, as noted below, the rabbit is relatively resistant to the toxicity of 2-NP.

6.2 Distribution

The distribution of 2-NP and its carbon-containing metabolites among the organs and tissues in Sprague-Dawley rats was examined by Nolan et al. (1982) via inhalation, and by Müller et al. (1983) via intraperitoneal injection. Both utilized ^{14}C-labelled 2-NP and thus their data do not reveal the distribution of nitrite and other nitrogen-containing metabolites generated from the nitro portion of the 2-NP molecule. One hour after

intraperitoneal injection, radioactivity was concentrated in fat; there were intermediate amounts in the blood, liver, and kidney, and lower amounts in other organs and tissues (Müller et al., 1983). By 40 h, the highest concentrations were in bone marrow and adrenal tissue, intermediate amounts being found in the kidney, liver, spleen, lungs, and omental fat, and by 8 days only the concentration of ^{14}C in adrenal tissue was noticeably greater than elsewhere in the body. However, Nolan et al. (1982), found, both immediately and 48 h after a 6-h period of 2-NP inhalation, that highest concentrations of carbon from 2-NP were in the liver and kidney and relatively little in the fat.

Differences in methodology limit intercomparison of these studies. Their major consistency is the presence of high concentrations of 2-NP and its labelled carbon in the liver and kidney, organs (as discussed below) actively involved in the metabolism of 2-NP and excretion of its metabolites.

The relevance of these studies on tissue distribution of 2-NP and its carbon-containing metabolites to the toxicity of 2-NP is unclear, since (as discussed below) most of the dose is rapidly metabolized initially to acetone and nitrite. The ^{14}C label used in these studies thus traced mainly the distribution of acetone and its metabolites in measurements made more than a few hours after dosing.

Dequidt et al. (1972) provided limited data on the distribution of nitrite among body organs of the rat following inhalation and intraperitoneal injection of 2-NP. The data suggest a fairly uniform distribution among the heart, lungs, kidney, spleen, and, sometimes, the liver. In the majority of experiments, however, no nitrite was detected in the liver. No explanation is offered for the latter observation, and data in the paper are so erratic as to suggest the possibility of analytical problems.

6.3 Metabolic transformation

Starting with a report by Scott (1943), there have been numerous studies on the metabolic transformation of 2-NP by mammals, mammalian cells, microorganisms, and isolated enzymes. These studies have shown that the major pathway for metabolic transformation of 2-NP involves oxidation to nitrite and acetone. Evidence for the formation both of nitrite and acetone was reported from studies on liver microsomes from rats pretreated

with phenobarbital or 3-methylcholanthrene (Ullrich et al., 1978), cultured hepatocytes from untreated rats (Haas-Jobelius et al., 1991), liver microsomes from untreated mice (Marker & Kulkarni 1986a,b; Dayal et al., 1991), V79 Chinese hamster cells (Haas-Jobelius et al., 1991), and a yeast (Kido et al., 1975). Nitrite was reported to be a major metabolite of 2-NP in rabbits (Scott, 1943), rats (Dequidt et al., 1972), and liver microsomes from rats (Sakurai et al., 1980) and mice (Marker & Kulkarni, 1985). Acetone was identified as a major metabolite of 2-NP in rats and chimpanzees (Muller et al., 1983).

Enzymatic oxidation of the nitronate form of 2-NP to nitrite and acetone by horseradish peroxidase (Porter & Bright, 1983), a dioxygenase from the yeast *Hansenula mrakii* (Kido et al., 1984), and mouse liver microsomes (Dayal et al., 1991) was several times more rapid than that of 2-NP under identical conditions. In addition to acetone, a smaller amount of isopropanol is produced at least in rats and chimpanzees (Muller et al., 1983). The source of the isopropanol was not specified in this study, but since reduction of acetone in the body is negligible (De Bruin, 1976), isopropanol may be formed directly by oxidation of 2-NP. The formation of a hydroxyisopropyl radical during the oxidation of 2-NP was suggested by Kuo & Fridovich (1986).

The metabolic fates of these metabolites of 2-NP are well known. Acetone is produced by a minor metabolic pathway in the mammalian body (Smith et al., 1983) and has been detected in small amounts in the blood, urine, and expired air of normal humans (Mabuchi, 1979; Conkle et al., 1975). It may be excreted directly via expired air, urine, and loss through the skin, or may enter into the general metabolism either via cleavage to a 2-carbon acetyl fragment and a 1-carbon formyl fragment or via oxidation to pyruvic acid (De Bruin, 1976). The proportion excreted unchanged increases with increasing dosage, suggesting an easily saturable metabolic pathway. Isopropanol is oxidized to acetone (De Bruin, 1976).

Nitrite may exist as a minor constituent of the mammalian body. It is constantly replenished by ingestion and synthesis, and constantly removed by oxidation to nitrate. Nitrite and nitrate in the blood stream are rapidly and homogeneously distributed throughout the body (Parks et al., 1981). Nitrite rapidly oxidizes divalent ferrous haemoglobin to trivalent ferric methaemoglobin (Burrows, 1979). Little is transported to the tissues or excreted, at

least in dogs, sheep, and ponies (Schneider & Yeary, 1975). Dequidt et al. (1972), however, reported substantial urinary excretion of nitrite by rats following inhalation or intravenous injection of 2-NP. Methaemoglobin is incapable of transporting oxygen and, during enzymatic repair of this defect, nitrite is reoxidized to nitrate. Parks et al. (1981) reported that 10 min after intratracheal instillation of labelled nitrite into mice, 70% of the label in plasma was in nitrate, 3% in nonionic compounds, and only 27% remained as nitrite. Similar results were obtained with rabbits. Nitrate is slowly excreted through the kidneys (Schneider & Yeary, 1975) and also into saliva where it is reduced back to nitrite by bacteria and reabsorbed into the body via the gastrointestinal tract (Friedman et al., 1972). Small amounts of nitrite in the stomach may react with secondary amines and other amino substrates to form N-nitroso compounds which might be absorbed (Sander & Schweinsberg, 1972; Fine et al., 1982).

The enzymatic system oxidizing 2-NP to acetone and nitrite was identified through *in vitro* experiments using microsomes isolated from mammalian liver. Ullrich & Schnabel (1973) determined that cytochrome P-450, in liver microsomes from phenobarbital-pretreated rats, bound 2-NP. Ullrich et al. (1978) subsequently reported that liver microsomes from rats pretreated with phenobarbital or 3-methylcholanthrene rapidly catalysed the oxidation of 2-NP to acetone and nitrite. The latter were produced in roughly equal quantities. Surprisingly, however, the rate of this reaction was not diminished under conditions of reduced oxygen pressure. The activity of preparations from untreated control rats was generally very low. Sakurai et al. (1980) demonstrated that this enzyme system in rats was active in metabolizing other aliphatic nitro compounds. Marker & Kulkarni (1985, 1986a, 1986b), working with mice, obtained somewhat different results. They reported rapid denitrification of 2-NP to nitrite and acetone by liver microsomes from untreated mice, and an acetone production at least twice the nitrite release. These authors suggested that multiple forms of cytochrome P-450 are involved, and claimed that nitrite is sequestered in the reaction mixture and that denitrification of 2-NP may involve a reductive or at least non-oxidative pathway as well as an oxidative pathway. They also noted large differences in the rates of hepatic microsomal enzymatic nitrite release among the five strains of mice tested. Jonsson et al. (1977) demonstrated that hepatic microsomes from uninduced rabbits could denitrify a compound related to 2-NP, 2-nitro-1-phenylpropane.

In addition to oxidative denitrification, a reductive pathway has been shown to occur in cultured hepatocytes from Wistar rats and in V79 Chinese hamster cells. Nitroreduction was indicated by the fact that the cells formed acetone oxime, the tautomeric form of nitrosopropane (Haas-Jobelius et al., 1991).

Evidence for the involvement of more than one pathway for the metabolism of 2-NP in the rat was also obtained by Denk et al. (1989). Their experiments on the pharmacokinetics of 2-NP in rats exposed by inhalation suggested that there are two different pathways both in male and female animals, a saturable one of low capacity and high affinity according to Michaelis-Menten kinetics and a non-saturable one following first-order kinetics. First-order kinetics was similar in the two sexes, but striking differences between sexes were observed in the kinetics of the saturable pathway. The authors showed that in females more 2-NP was metabolized by the non-saturable pathway at concentrations above 655 mg/m^3 (180 ppm), and in males at concentrations above 218 mg/m^3 (60 ppm), and linked their observations to the reported higher susceptibility to liver damage of males as compared to females (Griffin & Coulston, 1983). Denk et al. (1989) suggested that it is the first-order metabolic process which results in the formation of toxic products whereas the saturable pathway was suggested to lead to less toxic metabolites.

These observations on the hepatic metabolism of 2-NP and related compounds by rats, mice, and rabbits indicate differences among species and even strains. It is probable that more than one enzyme system is involved. In mice as well as rats hepatic cytochrome P-450 may be important in the metabolism of this xenobiotic.

Observations by Ivanetich et al. (1978) suggested an additional detoxifying role for hepatic microsomal cytochrome P-450. They demonstrated that under aerobic conditions *in vitro* 2-NP could degrade the haem moiety of cytochrome P-450 in phenobarbital-induced rats and speculated that this provided an additional mechanism for trapping reactive metabolites before these could damage essential cellular constituents.

In addition to the hepatic enzymatic systems examined in rats and mice, Mochizuki et al. (1988), as mentioned above, described a 2-NP denitrifying system in adrenal microsomes of uninduced guinea-pigs. They identified this cytochrome-P-450-dependent monooxygenase as benzo[*a*]pyrene hydroxylase.

6.4 Elimination and excretion

Elimination of 2-NP and its metabolites has been examined mainly in rats and, to a much lesser extent, in chimpanzees in studies which utilized measurements of radioactivity from ^{14}C-labelled 2-NP as well as measurements of 2-NP and its metabolites. Dosage by inhalation, intravenous injection, and intraperitoneal injection all yielded fairly similar results. During a 48-h period after a 6-h exposure of rats to 73 mg/m^3 (20 ppm) and to 560.6 mg/m^3 (154 ppm) of ^{14}C-labelled 2-NP, about 50% of the radioactivity in the absorbed dose was excreted via the lungs as carbon dioxide (Nolan et al., 1982). The proportion of the absorbed dose excreted via the lungs as unchanged 2-NP was 4% at the low dose level and 22% at the high level. Still less of the labelled carbon was eliminated via faeces and urine, i.e. 11% and 8%, respectively, at the low dose level, and 5% and 11%, respectively, at the high level. Disappearance of 2-NP from the blood after exposure at the high dose level followed a first-order relationship and yielded a half-life of 48 min. Limited data in Müller et al. (1983) yielded a half-life for rats of approximately 80 min for 2-NP in plasma following a 3-h exposure to a concentration of 728 mg/m^3 (200 ppm). Nolan et al. (1982), however, found that disappearance of the ^{14}C label of the 2-NP from the plasma was markedly slower and biphasic. During the first 12 h following exposure to 560.6 mg/m^3 (154 ppm), the half-life for plasma radioactivity was 172 min and, following exposure to 73 mg/m^3 (20 ppm), 354 min. After 12 h, loss of radioactivity from plasma was much slower, the half-life being approximtely 35-36 h for both doses. These data on loss of 2-NP and its ^{14}C label indicate that 2-NP is rapidly eliminated from the body mainly by metabolic transformation and to a lesser degree by pulmonary excretion of the unchanged compound. The major carbon-containing metabolites of 2-NP, acetone and isopropanol, presumably enter into the general metabolism of the body and are eliminated via the intermediary metabolism as part of a much larger carbon pool.

Pulmonary excretion of 2-NP, like loss of the ^{14}C label from plasma, is dose dependent, biphasic, and follows first-order kinetics (Nolan et al., 1982). Fifty times more 2-NP was exhaled during the first hour following exposure to 560.6 mg/m^3 (154 ppm) than during the first hour following exposure to 73 mg/m^3 (20 ppm). Following exposure to 73 mg/m^3, 2-NP was excreted for the first 7 h at a rate which decreased by one half every 64 min, and subsequently decreased by one half every 16 h,

whereas following exposure to 560.6 mg/m^3, the half-times of excretion were 71 min for the first 12 h, and 16 h for the subsequent period. Changes in the rates of pulmonary excretion of ^{14}C-labelled carbon dioxide were similar for 48 h following exposure to 73 and 560.6 mg/m^3. Eighty seven per cent of the total was eliminated during the first 12 h after exposure; loss was somewhat less rapid thereafter. The dose-dependent nature of pulmonary excretion of 2-NP suggests that greater concentrations of 2-NP in the blood markedly increase exhalation of the unchanged compound and reduce the percentage metabolized. Thus exposure of the tissues to 2-NP and its metabolites may not be a linear function of the inhaled dose.

Derks et al. (1989) found that the plasma half-life of intravenous doses of 0.01-0.05 g/kg in rats was 45 min during the first 4 h. Loss was linear over this dose range and could be described by an open single-compartment model. They suggested that the measured loss from plasma may be due in part to spontaneous conversion of 2-NP to its anionic form, 2-NP nitronate.

Elimination of 2-NP by Sprague-Dawley rats following intraperitoneal injection of ^{14}C-labelled 2-NP was studied by Müller et al. (1983) and was generally similar to the elimination of 2-NP following inhalation. The concentration of 2-NP in plasma declined exponentially with time, with half-lives of 70 and 125 min during at least the initial 6 h following injections of 25 and 50 mg/kg, respectively. Metabolites of 2-NP, acetone and isopropanol, reached maxima 2-4 h after injection of 25 mg/kg, and at least 4-6 h after injection of 50 mg/kg. The concentration of isopropanol ranged from 1/16 to 1/34 the concentration of acetone. During the initial 40 h after injection of 50 mg/kg, 4.5% of the dose was exhaled as 2-NP, 10.4% as acetone, and 38.1% as carbon dioxide. Losses via urine (5.9%) and faeces (0.7%) were small in comparison with the 53% loss via exhalation. Müller et al. (1983), however, reported that only 12% of the dose was recovered from the carcasses, leaving a large amount (28.4%) unaccounted for and thus casting some doubt on their values.

With one exception, results similar to the above were obtained following intravenous injection of ^{14}C-labelled 2-NP (10 mg/kg) into male chimpanzees (Müller et al., 1983). The concentration of 2-NP in plasma declined exponentially with time, the half-life being 92 min. The concentration of acetone reached a maximum 6 h after injection and remained high for at least 48 h. The

concentration of isopropanol peaked 3 h after injection when it approached that of acetone, but otherwise was a third to a quarter that of acetone. The concentration of 2-NP and its carbon-containing metabolites (i.e. the concentration of ^{14}C) in plasma declined exponentially with a half-life of 5.5 h for the initial 10 h, and a half-life of 48 h thereafter. As in rats, exhalation was the major means of elimination of 2-NP and its carbon-containing metabolites. During the first 3 days after injection, only 5-6% of the ^{14}C in the dose was recovered in urine and only 0.4-0.5% in faeces. Acetone, isopropanol, and 2-NP were mainly eliminated via renal excretion; urine collected during 6 to 24 h after injection contained 3.1 mg acetone/litre, 7.2 mg isopropanol/litre, and 1.8 mg 2-NP/litre. Isopropanol may thus be maintained at low concentrations in the plasma both by oxidation to acetone and by rapid excretion. In addition to acetone, isopropanol, and 2-NP, ^{14}C was excreted as an unidentified polar metabolite which by 24 h after injection contained 90% of the radioactivity in the urine. The one striking difference between results with rats and with chimpanzees, i.e. the relatively much higher plasma concentrations of isopropanol in comparison to acetone, might indicate interspecific variation in the excretion of 2-NP and its metabolites.

Dequidt et al. (1972) provided limited information on the excretion of nitrite following inhalation and intraperitoneal injection of 2-NP. Rats weighing approximately 250 g each were given a daily injection of 0.11 g/kg. Urinary excretion of nitrite was 10 to 35 μg/animal during the first day following the initial injection, and reached a daily rate of 11 mg/animal by the fourth injection. The latter rate of excretion represents three quarters of the nitrogen injected daily as 2-NP, and stands in sharp contrast to the results of Schneider & Yeary (1975), who reported that little intravenously injected nitrite was excreted by dogs, sheep or ponies. Following exposure of rats to a 2-NP concentration of 2766 mg/m^3 (760 ppm) for 8 h on each of two successive days, daily elimination of nitrite was approximately 30 mg/animal. This was equivalent to about 20% of the 2-NP inhaled daily and possibly as much as 50% of the absorbed daily dose. The amount of 2-NP inhaled was estimated from normative data for the rat (Baker et al., 1979), and absorption was assumed to be 40% of the amount inhaled (Müller et al., 1983). No nitrite was detected in urine during exposure of rats to 291 mg/m^3 (80 ppm) for 8 h per day on 5 successive days.

6.5 Retention and turnover

There is no evidence that 2-NP is retained for more than a few hours in the body. It is rapidly lost by exhalation and metabolic transformation. The known carbon-containing metabolites, acetone and isopropanol, are excreted rapidly and are also transformed into compounds which are normal to the body and enter into its general intermediary metabolism. There is less information on nitrite, the major metabolite of the nitro moiety. In rats much of the nitrite is excreted as such in the urine. There is no evidence for excessive accumulation of 2-NP or its metabolites in any organ or tissue. Information is also lacking on possible *N*-nitroso and other toxic compounds synthesized from nitrite or the nitro moiety.

7. EFFECTS ON LABORATORY MAMMALS AND *IN VITRO* TEST SYSTEMS

7.1 Single exposure

Data on single exposures to experimental animals, summarized in Table 5, indicate substantial differences in sensitivity among the species tested. The route of administration was mainly via inhalation, but other routes were also used. A quantitative comparison of the results from these studies is difficult due to a lack of information on both strain and sex of the animals used, to differences in the route of administration, and to large variations in dosage. The LC_{50} for mortality within 14 days following a 6-h exposure was estimated to be 1456 mg/m^3 (400 ppm) for male rats and 2621 mg/m^3 (720 ppm) for females (Baldwin & Williams, 1977). Exposure of rats (of unspecified sex) via inhalation to 14 058 mg/m^3 (3862 ppm) for 1 h or to 9584 mg/m^3 (2633 ppm) for 2.25 h killed some of the animals within days. Exposure of rats to a much higher concentration of 2-NP, i.e. 53 508 mg/m^3 (14 700 ppm), killed all animals within 4 h. An inhalation exposure of 4994 mg/m^3 (1372 ppm) or less for 2.25 h was not lethal to rats. Unlike rats, LC_{50} values were similar, i.e. 2031 and 2038 mg/m^3 (558 and 560 ppm), respectively, for male and female mice following a 6-h exposure (Baldwin & Williams, 1977). Cats appeared more sensitive to acute exposure to 2-NP than rats. Exposure to 8565 mg/m^3 (2353 ppm) for 1 h (or lower concentrations for proportionately longer) was lethal to some cats. Rabbits and guinea-pigs, on the other hand, appeared far less sensitive to 2-NP than rats. Rabbits survived a 2.25-h exposure to 9584 mg/m^3 (2633 ppm) and guinea-pigs a 2.25-h exposure to 15 699 mg/m^3 (4313 ppm). The sequence in acute sensitivity of animals to inhaled 2-NP (from most to least) was cat, rat and mouse, rabbit, and guinea-pig. The cat was almost an order of magnitude more sensitive than the guinea-pig.

There are limited data on lethality via routes of administration other than inhalation. Large intraperitoneal doses were found to be promptly lethal to rats; 1.7 and 1.1 g/kg killed animals within 2 h and 4 h, respectively (Dequidt et al., 1972). The 14-day oral LD_{50} for mice was 0.40 g/kg. The minimal oral lethal dose for the rabbit, 0.50–0.75 g/kg, was much larger than the estimated minimum lethal dose via inhalation, 0.24 g/kg. Dermal application of 2 g/kg to rabbits produced no obvious local or systemic effects.

Table 5. Effects of single exposure to 2-nitropropane in mammals[a]
a) Lethality

Species	Sex	Concentration		Estimated total dose[b] (g/kg)	Effects/results	Reference
		g/m^3	ppm			
Oral administration						
Rabbit[cd]					lethal dose estimated as 0.50-0.75 g/kg	Machle et al. (1940)
Mouse	M/F				14-day LD_{50}: 0.40 g/kg	Hite & Skeggs (1979)
Inhalation						
Rat[c] (Wistar)		53.5	14 700	1.51	all animals died within 4 h	Dequidt et al (1972)
Rat[cd]		5.5-14.1	1513-3865	0.10-0.17	death of some animals[c]	Treon & Dutra (1952)
		2.6-8-57[d]	714-2353	0.06-0.08	no deaths[d]	Treon & Dutra (1952)
Rat[cd] (Wistar)		2.77	760	0.16	death within 48 h;	Dequidt et al. (1972)
Rat[e] (CD)	M	2.93	805	0.16	8/10 died within 14 days	Baldwin & Williams (1977)[f]
	F	2.19	602	0.13	no deaths within 14 days[e]	Baldwin & Williams (1977)[f]
	M	2.10	574	0.14	8/8 died within 14 days	Baldwin & Williams (1977)[f]
	M	1.68	461	0.10	7/8 died within 14 days	Baldwin & Williams (1977)[f]

Table 5 (contd).

Species	Sex	Concentration		Estimated total dose[b] (g/kg)	Effects/results	Reference
		g/m^3	ppm			
Inhalation (contd)						
Rat[e] (CD)	M	1.47	405	0.08	5/8 died within 14 days	Baldwin & Williams (1977)[f]
		1.34	367	0.08	no deaths within 14 days	Baldwin & Williams (1977)[f]
Mouse[e] (ICR)	F	2.70	740	0.47	14/14 died within 14 days	Baldwin & Williams (1977)[f]
		2.33	640	0.41	11/14 died within 14 days	Baldwin & Williams (1977)[f]
		1.8	495	0.32	2/14 died within 14 days	Baldwin & Williams (1977)[f]
Mouse (ICR)	M	2.69	738	0.41	9/14 died within 14 days	Baldwin & Williams (1977)[f]
		2.08	558	0.28	7/14 died within 14 days	Baldwin & Williams (1977)[f]
		1.65	454	0.23	no deaths within 14 days	Baldwin & Williams (1977)[f]
Cat[cd]		2.6-8.56	714-2353	0.07-0.19	death of some animals	Treon & Dutra (1952)
		1.19-2.87	328-787	0.02	no deaths	Treon & Dutra (1952)
Guinea-pig[cd]		16.8-35.0	4622-9607	0.53-0.63	death of some animals	Treon & Dutra (1952)
		8.67-34.7	2381-9523	0.23-0.32	no deaths	Treon & Dutra (1952)

Table 5 (contd).

Species	Sex	Concentration		Estimated total dose[b] (g/kg)	Effects/results	Reference
		g/m^3	ppm			
Inhalation (contd)						
Rabbit[c]		8.67-34.7	2381-9523	0.24-0.27	death of some animals	Treon & Dutra (1952)
		5.1-14.1	1401-3865	0.10-0.16	no deaths	Treon & Dutra (1952)
Intraperitoneal administration						
Rat[c,f]				1.7	death within 2 h	Dequidt et al. (1972)
				1.1	death within 4 h	Dequidt et al. (1972)
Mouse[c] (Swiss ICR/HQ)	M			0.80	LD_{50}	Friedman et al. (1976)

[a] Values recalculated as necessary to ppm and g/kg

[b] Estimated dose calculated by the formula: tidal volume x respiration frequency x exposure time x 2-NP conc. x alveolar retention/animal weight. Tidal volume and respiration frequency from Kaplan et al. (1983) for mice (0.15 ml, 163/min); from Baker et al. (1979) for rats (0.86 ml, 85.5/min); from Hoar (1976) for guinea-pigs (1.68 ml, 84/min); from Kozma et al. 81974) for rabbits (15.8 ml, 45/min); from Reece (1984) and Breazile (1971) for cats (42 ml, 31/min); alveolar retention in rat (0.40) from Nolan et al. (1982), used for all species; where not stated animal weights assumed to be average values, 20 g for mice, 250 g for rats, 500 g for guinea-pigs, 2.5 kg for rabbits, and 4.0 kg for cats

[c] Sex not specified

[d] Exposure time varied from 1 to 7 h

[e] Exposure time was 6 h

[f] Baldwin & Williams (1977) also exposed female rats for 6 h to concentrations of 2-NP lower than 2.2 g/m^3 (602 ppm); these concentrations, i.e. 1.15, 1.35 and 1.69 g/m^3 (316, 370 and 464 ppm), like 2.2 g/m^3, produced no deaths within 14 days

Table 5. Effects of single exposure to 2-nitropropane
b) other effects

Route of administration	Species	Sex	Estimated total dose[b] g/kg)	Effects/results	Reference
Intraperitoneal	rat (Sprague-Dawley)	M	0.15	maximum hepatic injury achieved with this dose	Filser & Daumann (1988)
Intraperitoneal	rat (Wistar)	M	0.05	lipid accumulation, centrilobular necrosis, mitochondrial abnormalities, and changes in endoplasmic reticulum and glutathione content in liver within 24 h, as well as changes in enzyme activity in liver and brain	Zitting et al. (1981)
Dermal	rabbit	M & F	2	no toxic effects observed	Wilbur & Parekh (1982)

[b] See footnote *b* in Table 5a.

The effects of acute exposure to 2-NP, in addition to lethality, are characterized primarily by hepatotoxicity and, at high exposure levels, methaemoglobin formation and depression of the central nervous system. Machle et al. (1940), in a description of symptoms resulting from exposure of laboratory animals to simple nitroparaffins, listed the following progression for guinea-pigs and rabbits after a latent period of 20 to 40 min: progressive weakness, unsteadiness, and incoordination ending in complete ataxia. The rate of respiration at first slowed and later became increasingly rapid. Most of these symptoms appear to reflect the narcotic effects normally associated with inhalation of volatile hydrocarbons, but the more rapid breathing may reflect an attempt by the body to compensate for the formation of methaemoglobin and loss of oxygen-carrying capacity of the red blood cells. Treon & Dutra (1952) noted similar progression from exposure to high concentrations of 2-NP vapour, i.e. lethargy and weakness, dyspnoea, cyanosis, prostration, and ultimately coma and death, but did not report more rapid breathing following a depression in rate of respiration. They also noted lacrimation, salivation, and gastric regurgitation in cats. In addition, the authors observed that, even with animals which died promptly (within 9.5 h) following a single exposure, there was a loss in body weight averaging 2.8%. Animals exposed to 8.56 g/m^3 (2353 ppm) or higher concentrations of 2-NP displayed pathological changes including hepatocellular damage, pulmonary oedema and haemorrhage, some disintegration of neurones in the brain, and widespread damage to the endothelium.

Methaemoglobin and Heinz bodies (masses of denatured haemoglobin within erythrocytes) were found in the blood of animals following single exposures to high concentrations of 2-NP. In the case of cats, 60 to 80% of the haemoglobin was converted to methaemoglobin by exposure to 15.9 to 33.6 g/m^3 (4360 to 9230 ppm) for 1 to 2 h, whereas much longer exposure of rabbits to these concentrations converted only 4 to 8% of the haemoglobin (Treon & Dutra, 1952). Dequidt et al. (1972) reported high levels of methaemoglobin in rats, i.e. 84% and 89%, following 1-h inhalation exposure to 53.5 g/m^3 (14 700 ppm) and intraperitoneal injection of 1.7 g/kg, respectively. Much lower methaemoglobin concentrations, 0.2 to 8.6%, resulted from a 1-h exposure to 2.8 g/m^3 (760 ppm). One day after exposure to 15.4 g/m^3 (4230 ppm) for 4.5 h or 8.5 g/m^3 (2335 ppm) for 2.25 h, rabbits had Heinz bodies in 45 to 80% of their red cells. These bodies disappeared gradually over 9 to 16 days (Treon & Dutra, 1952).

Exposure of rabbits to 13.8 g/m^3 (3790 ppm) for 1 h or 9.4 g/m^3 (2580 ppm) for 2.25 h resulted in the formation of Heinz bodies in only 0 to 2% of the red cells. Formation of Heinz bodies in the cat may have reflected its high sensitivity to 2-NP. A 1-h exposure to 13.8 g/m^3 (3790 ppm) and a 20 min exposure to 16.4 g/m^3 (4505 ppm) resulted in the appearance of Heinz bodies in 27% and 16% of the erythrocytes, respectively.

Observations by Zitting et al. (1981) indicated that a single intraperitoneal injection of 0.05 g 2-NP/kg to rats can produce significant changes in the fine structure of the liver and in the physiology of both liver and brain. 2-NP produced a visible accumulation of lipid in hepatocytes, especially in periportal areas after 4 h, and the lipid level continued to increase for the next 20 h. Within 4 h after injection there was also degranulation of the rough endoplasmic reticulum in hepatocytes and proliferation of the smooth endoplasmic reticulum. Within 24 h the former had almost disappeared and the latter was vacuolated or compacted. In addition, some hepatocytes had abnormal mitochondria and there was necrosis of hepatocytes around the central vein. The latter was reflected in a concurrent fourfold increase of serum alanine aminotransferase. Other enzymatic parameters in the liver were also markedly affected within 24 h. Cytochrome P-450 was markedly depressed, 7-ethoxycoumarin *O*-deethylase and 7-ethoxyresorufin *O*-deethylase were diminished in activity, and microsomal epoxide hydratase, UDP-glucuronosyltransferase and glutathione peroxidase were increased in activity. In addition, the liver concentration of glutathione nearly doubled.

The major observed neurochemical effect was a significant increase in acetylcholine esterase activity in the cerebrum and in isolated synaptosomes. There was little or no change in RNA, 2',3'-cyclic nucleotide 3'-phosphohydrolase, or acid proteinase in the brain.

Zitting et al. (1981) noted that these histopathological and enzymatic changes induced by 2-NP are nearly identical to the effects of carbon tetrachloride on the rat and are thus indicative of lipid peroxidation.

Hepatotoxicity following exposure to 2-NP has also been observed in mice (Dayal et al., 1989). Intraperitoneal doses of 0.8 g/kg (9 mmol/kg) in male mice and 0.6 g/kg (6.7 mmol/kg) in female mice significantly increased plasma activities of enzymes

indicative of hepatic damage (sorbitol dehydrogenase, alanine aminotransferase, and aspartate aminotransferase) 48, 72, and 96 h after injection. These enzyme activities were not elevated 24 h after this dosage nor after small doses of 2-NP.

7.2 Short-term and long-term repeated exposure

Data for repeated exposure, like that for single exposure, indicate that the cat is more sensitive to 2-NP than the other species tested (Table 6). Rats, rabbits, guinea-pigs, and monkeys survived 1.2 g/m^3 (328 ppm) (7 h/day, 5 days/week) throughout approximately 6 months of exposure (Treon & Dutra, 1952). However, cats exposed to the same concentrations of 2-NP began dying after the third day of exposure and were all dead by the end of the 17th day (Treon & Dutra, 1952). Rats and guinea-pigs survived 5 days of exposure (7 h/day) to 2.46 g/m^3 (672 ppm), but death occurred in rats exposed for 2 days (8 h/day) to 2.77 g/m^3 (760 ppm). Rats were reported to survive 15 days of daily intraperitoneal injections of 0.11 g/kg (Dequidt et al., 1972). The doses used in these repeated exposures were found to produce no more than trace levels of methaemoglobin (maximum = 4.3%) and low concentrations (0 to 11 mg/kg) of nitrite in the tissues.

Non-lethal chronic doses of 2-NP have been shown to produce a number of harmful effects in rats (Table 6). Exposure of rats to 0.75 g/kg (207 ppm) for up to 24 weeks (7 h/day, 5 days/week) initially induced pulmonary lesions and oedema, hepatocellular hypertrophy, hyperplasia, and necrosis of the liver (Lewis et al., 1979). By the end of 24 weeks all the rats developed rapidly growing hepatocellular carcinomas. A similar exposure to a slightly lower concentration of 2-NP, 0.73 g/m^3 (200 ppm), induced hepatic nodules and other destructive changes in the liver, especially in male rats (Griffin & Coulston, 1983). These changes included fatty degeneration, nodules consisting mainly of hyperplastic areas, distortion of lobular architecture, necrosis and peripheral compression. Male rats also had an elevated serum alanine aminotransferase level (an indicator of liver damage) and slightly reduced growth. Chronic exposure of rats to 0.36 g/m^3 (100 ppm) for up to 18 months produced similar, although slightly less severe, damage than that resulting from exposure to 0.73 g/m^3 (200 ppm) (Griffin & Coulston, 1983; Coulston et al., 1985). Only male rats developed hepatocellular carcinoma; female rats had increased renal calcification and occasional hepatic masses and

Table 6. Short-term and long-term toxicity of 2-nitropropane in mammals[a]

Species	Sex	Dose and/or concentration[b]	Effects/results	Reference
Oral studies				
Rat (Wistar)	M & F	0.25 g/kg, 5/week for 4 weeks	mortality of males (4/10); decreased growth in first week; increased urine, ALAT, ASAT, and gamma-GT (males only), anaemia, thrombocyte and leucocyte count, liver, spleen and heart weight, and haemosiderin content of spleen; cellular and nuclear polymorphism, single cell necrosis, and proliferation of oval cells and/or bile ducts in liver	Wester et al. (1989)
Rat (Sprague-Dawley)	M	0.089 g/kg (1 mmol), 3/week for 16 weeks, maintained but not dosed for next 61 weeks	some deaths by 16 week; throughout study body weights significantly lower than controls; all rats exposed 16 weeks or longer developed massive hepatocellular carcinomas; metastases to the lungs in 4 animals	Fiala et al. (1987b)
Rat (Wistar)	M & F	0.05 g/kg, 5/week for 4 weeks	increased anaemia, thrombocyte conc., and heart weight	Wester et al (1989)
Rat (Wistar)	M & F	0.002 and 0.01 g/kg, 5 week for 4 weeks	increased water intake by males dosed with 0.002 g/kg	Wester et al. (1989)

Table 6 (contd).

Species	Sex	Dose and/or concentration[b]	Effects/results	Reference
Inhalation studies				
Rat[d] (Wistar)		2.77 g/m^3 (760 ppm), 8 h/day for 2 days; estimated dose over 8 h, 0.16 g/kg	animals dead within 2 h after end of second inhalation session; 2-NP conc. in liver = 180 ppm; methaemoglobin = 2.4%	Dequidt et al. (1972)
Rat[e]		2.45 g/m^3 (672 ppm), 7 h/day for 5 days; estimated dose over 7 h, 0.12 g/kg	no deaths	Treon & Dutra (1952)
		1.20 g/m^3 (328 ppm), 7 h/day, 5 days/week for 130 days over 199 days; estimated dose over 7 h, 0.06 g/kg	no deaths	Treon & Dutra (1952)
Rat (Sprague-Dawley)	M	0.75 g/m^3 (207 ppm), 7 h/day, 5 days/week for up to 24 weeks; estimated dose over 7 h, 0.04 g/kg	body weight and haematological parameters unaffected; some pulmonary oedema and some pulmonary lesions within 3 months; liver weight elevated; hepatocellular hypertrophy, hyperplasia and liver necrosis in all rats within 3 months; liver neoplasms in all rats within 6 months; these hepatocellular carcinomas appeared to be growing rapidly and deforming surrounding tissues	Lewis et al. (1979)

Table 6 (contd).

Species	Sex	Dose and/or concentration[b]	Effects/results	Reference
Inhalation studies (contd)				
Rat[e]		0.73 g/m^3 (200 ppm), 7 h/day, 5 days/week for 6 months; estimated dose over 7 h, 0.03 g/kg	growth slightly reduced and SGPT elevated in male rats; liver weight increased in both sexes; morphological changes in liver more pronounced in males; these included fatty metamorphosis and hepatic nodules consisting mainly of hyperplastic areas with distortion of lobular architecture, necrosis and peripheral compression	Griffin et al. (1978)
Rat[d] (Sprague-Dawley)		0.73 g/m^3 (200 ppm), 7 h/day for 5 days	no effect on body or organ weight to end of experiment (94 week) aside from a brief decrease in weight gain immediately following exposure; no significant effects on mortality or pathology	Griffin et al. (1986)
Rat[c]	M	0.73 g/m^3 (200 ppm), 7 h/day, 5 days/week for up to 7 months	severe liver damage with vacolar degeneration in exposed rats after 3 months	Coulston (1982)

Table 6 (contd).

Species	Sex	Dose and/or concentration[b]	Effects/results	Reference
Inhalation studies (contd)				
Rat[e]		0.36 g/m^3 (100 ppm), 7 h/day, 5 days/week for up to 18 months; estimated dose over 7 h, 0.013 g/kg	male rats had lower body weight, increased renal calcification, elevated SGPT, and enlarged livers with necrosis, vacuolar degeneration and probable hepatocellular carcinomas; female rats had increased renal calcification and occasional hepatic masses and nodules showing hyperplasia and vacuolar degeneration	Griffin & Coulston (1983); Coulston et al. (1985)
Rat[e]		0.29 g/m^3 (80 ppm), 8 h/day for 5 days; estimated dose over 8 h, 0.016 g/kg	no deaths; no trace of 2-NP in organs at end of experiment; methaemoglobin = 0; nitrite = 0-10 ppm in tissues, but no nitrite in urine	Dequidt et al. (1972)
Rat (Sprague-Dawley)	M	0.1 g/m^3 (27 ppm), 7 h/day, 5 days/week for up to 24 weeks; estimated dose over 7 h, 0.005 g/kg	no gross or microscopic alteration of any tissue, haematological parameter or serum biochemistry	Lewis et al. (1979)
Rat[e]		91 mg/m^3 (25 ppm), 7 h/day, 5 days/week for up to 22 months; estimated dose over 7 h, 0.003 g/kg	no changes in behaviour, appearance, rate of weight gain, final weight, serum chemistry or haematology; no significant increase in tumours and lesions associated with exposure; no evidence of methaemoglobinaemia	Griffin et al. (1980, 1981)

Table 6 (contd).

Species	Sex	Dose and/or concentration[b]	Effects/results	Reference
Inhalation studies (contd)				
Mouse[d] (ICR)		0.73 g/m^3 (200 ppm), 7 h/day, 5 days/week for 48 weeks	depression in body weight during first 3 months in females and throughout experiment in males; increased liver weight and elevation of liver transaminases in females; toxic hyperplasia of liver predominantly in females	Griffin et al. (1984)
Mouse[e]		0.36 g/m^3 (100 ppm), 7 h/day, 5 days/week for 18 months	slight depression of body weight during first 8 months in males; no effects on organ weight; no evidence of hepatocellular carcinoma; some indications of liver toxicity (nodular hyperplasia in females)	Coulston et al. (1986); Griffin et al. (1987)
Cat[e]		2.6 g/m^3 (714 ppm), 4.5 h/day for 4 days; estimated dose over 7 h, 0.10 g/kg	deaths starting with first exposure, but some animals survived 4 exposures	Treon & Dutra (1952)
		1.2 g/m^3 (328 ppm), 7 h/day, 5 days/week for 17 exposures; estimated dose over 7 h, 0.07 g/kg	deaths starting with third exposure; all animals dead by end of 17th exposure	Treon & Dutra (1952)
		1.15 g/m^3 (317 ppm), 7 h/day for 2 days; estimated dose over 7 h, 0.07 g/kg	no deaths	Treon & Dutra (1952)

Table 6 (contd).

Species	Sex	Dose and/or concentration[b]	Effects/results	Reference
Inhalation studies (contd)				
Cat[e]		0.3 g/m^3 (83 ppm), 7 h/day, for 130 out of 191 days; estimated dose over 7 h, 0.02 g/kg	no deaths	Treon & Dutra (1952)
Rabbit[e]		1.2 g/m^3 (328 ppm), 7 h/day, ca. 5 days/wk for up to 130 out of 199 days; estimated dose over 7 h, 0.06 g/kg	no deaths	Treon & Dutra (1952)
Rabbit (white, NZ)	M	0.75 g/m^3 (207 ppm), 7 h/day, 5 days/week for 24 weeks; estimated dose over 7 h, 0.03 g/kg	no gross or microscopic alterations to tissues	Lewis et al. (1979)
Rabbit[e]		0.3 g/m^3 (83 ppm), 7 h/day for 130 out of 191 days; estimated dose over 7 h, 0.014 g/kg	no deaths	Treon & Dutra (1952)
Rabbit[e]		0.1 mg/m^3 (27 ppm), 7 h/day, 5 days/week for 6 months; estimated dose over 7 h, 0.005 g/kg	no gross or microscopic alterations to tissues	Lewis et al (1979)

Table 6 (contd).

Species	Sex	Dose and/or concentration[b]	Effects/results	Reference
Inhalation studies (contd)				
Guinea-pig[e]		2.45 g/m^3 (672 ppm), 7 h/day for 5 days; estimated dose over 7 h, 0.12 g/kg	no deaths	Treon & Dutra (1952)
Guinea-pig[e]		1.2 g/m^3 (328 ppm), 7 h/day, ca. 5 days/week for 95-130 days out of up to 199 days; estimated dose over 7 h, 0.06 g/kg	no deaths	Treon & Dutra (1952)
Monkey[e]		1.2 g/m^3 (328 ppm), 7 h/day, ca. 5 days/week for 100 days exposure	no deaths	Treon & Dutra (1952)
		0.3 g/m^3 (83 ppm), 7 h/day for 130 out of 191 days	no deaths	Treon & Dutra (1952)
Intraperitoneal studies				
Rat[d] (Wistar)		0.11 g/kg, 1/day for 7 days	apparently no deaths prior to sacrifice 3 days after the last injection; methaemoglobin = 4.3%; nitrite = 0.29-1.15 ppm in organs (heart, lungs, kidneys, spleen)	Dequidt et al. (1972)

Table 6 (contd).

Species	Sex	Dose and/or concentration[b]	Effects/results	Reference
Intraperitoneal studies (contd)				
Rat[d] (Wistar)		0.11 g/kg, 1/day for 15 days	apparently no deaths prior to sacrifice 36 h after the last injection; methaemoglobin = 0; nitrite = 0-10.8 ppm in organs (heart, lungs, kidneys, spleen)	
Rat (Sprague-Dawley)	F	0.001 g/kg, 5/week for 2 weeks	no significant effects on kidney function	Bernard et al. (1989)
Dermal study				
Rabbit[e]		1 application/day on clipped anterior abdomen for 5 days; dose not stated	no skin irritation, illness, systemic effects or deaths	Machle et al. (1940)

[a] values from the literature recalculated as necessary to ppm or g/kg

[b] estimated dose calculated by the formula: tidal volume x respiration frequency x 2-NP conc. x alveolar retention/animal weight. Tidal volume and respiration frequency from Baker et al. (1979) for rats (0.086 ml, 85.5 /min); from Hoar (1976) for guinea-pigs (1.68 ml, 84/min); from Kozma et al. (1974) for rabbits (15.8 ml, 45/min); from Reece (1984) and Breazile (1971) for cats (42 ml, 31/min); alveolar retention in rat (0.40) from Nolan et al. (1982), used for all species; where not stated in reference, animal weights assumed to be average values, 250 g for rats, 500 g for guinea-pigs, 2.5 kg for rabbits, and 4.0 kg for cats

[c] strain not specified

[d] sex not specified

[e] neither strain nor sex specified

nodules showing hyperplasia and vacuolar degeneration. No toxic effects were reported after chronic exposure of rats to 90 mg/m^3 (25 ppm) or 100 mg/m^3 (27 ppm) (Lewis et al., 1979; Griffin et al., 1980, 1981). Daily intraperitoneal injections of 1 mg/kg (5/week for 2 weeks) had no significant effect on kidney function (Bernard et al., 1989).

Chronic oral dosage of 2-NP by gavage for 16 weeks produced tumours in rats (Fiala et al., 1987b). The dose was 0.089 g/kg (1 mmol/kg), given 3 times per week, and this yielded a weekly dosage of 0.27 g/kg, an amount similar to the highest sustained estimated inhalation dosage. The body weights of rats treated with 2-NP were significantly lower than those of controls, and all treated rats surviving 16 weeks or longer developed both benign tumours and massive hepatocellular carcinomas. Metastases to the lungs were observed in four of the 22 surviving animals (Fiala et al., 1987b). Wester et al. (1989) treated rats with oral doses of 0.002, 0.01, 0.05, and 0.25 g/kg, 5 times per week for 4 weeks by gavage. With a dose of 0.25 g/kg there was some mortality among male rats, and in both sexes there was decreased growth, anaemia, increased liver and heart weights, and severe damage to the liver. At a dose of 0.05 g/kg the major harmful effect appeared to be anaemia. Lower concentrations (0.01 and 0.002 g/kg) did not produce obvious harm over the period of the experiment.

Rabbits and mice appear more resistant to the sublethal effects of 2-NP than rats (Table 6). Chronic inhalation exposure of five rabbits to 0.75 g/m^3 (207 ppm) (7 h/day, 5 days/week) for 24 weeks, a treatment which induced hepatocellular carcinomas and severe liver damage in rats, had no detectable effect (Lewis et al., 1979). Rabbits also were unaffected by repeated dermal application of 2-NP (Machle et al., 1940). Liver damage was found in mice, especially females, during chronic exposure to 0.72 g/m^3 (200 ppm) (7 h/day, 5 days/week) for 48 weeks, but hepatocellular or other carcinomas were not detected (Griffin et al., 1984). Exposure of mice to 0.36 g/m^3 (100 ppm) (7 h/day, 5 days/week) for 18 months produced some liver damage, especially in females, as shown by nodular hyperplasia (Coulston et al., 1986, Griffin et al., 1987).

7.3 Reproduction, embryotoxicity, and teratogenicity

There is limited information on the embryotoxicity and teratogenicity of 2-NP. Hardin et al. (1981) gave intraperitoneal injections of 0.17 g/kg (1.91 mmol/kg) of 2-NP in corn oil to pregnant rats on days 1-5 of gestation. The dosage was a previously determined maximum tolerated dose which produced no mortality, no marked signs of toxicity, and less than a 10% reduction in body weight gain during dosing or within 2 weeks following 15 daily intraperitoneal injections to non-pregnant rats. In pregnant rats, this dose was reported to give no evidence of maternal toxicity or teratogenicity, but produced a significant incidence of delayed fetal development. Harris et al. (1979) reported that 2-NP at a dose of 0.17 g/kg retarded fetal heart development by 1 to 2 days in pups from 9 out of 10 litters produced by female rats treated with 2-NP. In the affected litters, 30% to 86% of the pups had retarded heart development.

There appear to be no studies that have examined specifically the effects of 2-NP on reproductive function. No effects on reproductive organs, however, were noted in the above two studies nor in any of those studies on the effects of single exposures or short-term or long-term administration of 2-NP (Tables 5 and 6). There also was no evidence of an increase in dominant lethality or in sperm abnormality in genetic studies relating to reproduction (McGregor, 1981).

7.4 Mutagenicity and related end-points

7.4.1 Prokaryotes and yeast

2-NP has been found to be mutagenic in a variety of test systems. All investigators reported mutagenicity in several strains of *Salmonella typhimurium* used with the Ames test, both with and without an exogenous activating system (S9) (Table 7). In addition, Kawai et al. (1987) reported mutagenicity with a strain of *Escherichia coli*, but Litton Bionetics, Inc. (1977) did not find mutagenicity with a strain of *Saccharomyces cerevisiae*. Most investigators found greater mutagenicity with activation by S9 than without. With the strain that was generally most sensitive to 2-NP, i.e. TA100, most investigators providing detailed results observed an approximate doubling in the number of mutants at a concentration of 3 mg 2-NP/plate. Göggelmann et al. (1988), however, observed a 10- to 12-fold increase in mutant numbers at

Table 7. Genotoxicity of 2-nitropropane

Test system	Result[a]	References[b]
Prokaryotes and yeast[c]		
Salmonella typhimurium		
strain TA92	+	1
strain TA92 with S9	+	1
strain TA98	+	1,2,5,7,8,9
	-	6,16,19
strain TA98 with S9	+	1,2,3,5,8,9,17
strain TA98NR	+	2,9
strain TA98NR with S9	+	2,9
strain TA100	+	1,2,4,5,6,7,8,9,19
	-	17
strain TA100 with S9	+	1,2,3,4,5,6,8,9,17,19
strain TA100NR	+	2,9
strain TA100NR with S9	+	2,9
strain TA102	+	4,8,19
strain TA102 with S9	+	4,8,19
strain TA1535	?	5
	-	17
strain TA1535 with S9	+	3
	?	5
	-	17
strain TA1537	-	17
strain TA1537 with S9	-	3,17
strain TA1538	-	17
strain TA1538 with S9	-	17
Escherichia coli		
strain WP2 uvrA/pKM101	+	7
strain WP2 uvrA/pKM101	+	7

Table 7 (contd).

Test system	Result[a]	References[b]
Saccharomyces cerevisiae		
strain D4	-	17
strain D4 with S9	-	17
Eukaryotes[f]		
In vivo		
Drosophila		
Sex-linked recessive lethal	-	10,11
Mouse		
erythrocytes		
(micronuclei) m, f	-	1,16,23
sperm (abnormality)	?	11
Rat		
Liver (DNA repair synthesis) m, f	+	12,13,23
(micronuclei)	+	23
(DNA and RNA base modifications) m, f	+	18,20,21,22
(DNA strand breakage) m	+	24
Kidney (DNA strand breakage) m	-	24
(DNA and RNA base modifications) m, f	-	22
Brain (DNA strand breakage) m	-	24
Lung (DNA strand breakage) m	-	24
Bone marrow (chromosome aberrations) m, f	-	11
(micronuclei) m	-	23
Testes		
(dominant lethal test) m	-	11

Table 7 (contd).

Test system	Result[a]	References[b]
In Vitro		
Mouse		
3T3-NIH fibroblasts (DNA repair synthesis)	-	13
Rat		
hepatocytes (DNA repair synthesis) m, f	+	12,13,26
hepatoma cells, 2sFou (DNA repair synthesis and micronuclei)[g]	+	25
hepatoma cells, C2Rev7 (DNA repair synthesis and micronuclei)[g]	+	25
hepatoma cells, H4IIEC3/G$^-$ (DNA repair synthesis, micronuclei and gene mutations)[g]	+	25
208F - embryonic fibroblasts (DNA repair synthesis)	-	13
LLC WRC 256 carcinoma Walker rat (DNA repair synthesis)	-	13
Hamster		
CHO cells (chromosome aberrations and sister chromatid exchanges)	-	14
CHO cells (DNA repair synthesis)	-	13
V79 cells (DNA repair synthesis)	-	12,13,25,26
V79 cells (mutations)	+	25
V79 cells (micrnuclei)	-	25,26
Human		
Lymphocytes (chromosome aberrations and sister chromatid exchanges)	-[d]	9,15
Lymphocytes (chromosome aberrations and sister chromatid exchanges) with S9	-[e]	9,15
Fibroblasts (DNA repair synthesis)	-	11

Table 7 (contd).

Test system	Result[a]	References[b]
Human (contd)		
W138 embryonic lung fibroblasts NC1-H322 adenocarcinoma lung cells A549 adenocarcinoma lung cells HEp2 epidermal carcinoma larynx cells (DNA repair synthesis)	-	13

[a] + = positive response; - = negative response; ? = inconclusive result

[b] (1) Hite & Skeggs (1979) (2) Speck et al. (1982)
(3) Haworth et al. (1983) (4) Simmons et al. (1986)
(5) Löfroth et al. (1986) (6) Hughes et al. (1987)
(7) Kawai et al. (1987) (8) Fiala et al. (1987a)
(9) Göggelmann et al. (1988) (10) Zimmering et al. (1985)
(11) McGregor (1981) (12) Ziegler-Skylakakis et al. (1987)
(13) Andrae et al. (1988) (14) Galloway et al. (1987)
(15) Bauchinger et al. (1987) (16) Kliesch & Adler (1987)
(17) Litton Bionetics, Inc. (1977) (18) Conaway et al. (1991a)
(19) Conaway et al. (1991b) (20) Fiala et al. (1989)
(21) Hussain et al. (1990) (22) Guo et al. (1990)
(23) George et al. (1989) (24) Robbiano et al. (1991)
(25) Roscher et al. (1990) (26) Haas-Jobelius et al. (1991)

[c] Liver S9 fractions are prepared by treating rats, mice or hamsters with Aroclor 1254 or another microsomal enzyme inducer, and, after several days, removing the livers, homogenizing them, and centrifuging. The supernatant, the S9 fraction, contains liver microsomal enzymes.

[d] Bauchiner et al. (1987) (ref. 15) reported a weak but significantly positive result on one test, but considered results overall to be negative

[e] Göggelmann et al. (1988) (ref. 9) reported a very weak positive result

[f] m = male; f = female

[g] pretreated with dexamethasone

2.45 mg/plate, with or without activation by S9. Fiala et al. (1987a) reported that non-ionic 2-NP yielded only a doubling of mutant numbers at 4.9 mg/plate with S9 activation and no increase without activation, whereas 2-NP nitronate at this concentration yielded a threefold increase in mutant numbers with activation. Without activation 2-NP nitronate at 2.5 mg/plate yielded a nearly 6-fold increase in mutant numbers; nitronate at 4.9 mg/plate was toxic to this test organism. Fiala et al. (1987a) concluded that the mutagenicity of 2-NP is produced mainly or entirely by the nitronate anion and suggested that the low level of mutagenicity observed with non-ionic 2-NP may have resulted from its conversion to the nitronate form within the microorganisms. A

similar conclusion was drawn by Dayal et al. (1989) from their comparison of 2-NP, nitromethane, nitroethane, and their nitronates for mutagenicity in *Salmonella*. Some of the variability in results obtained by others may stem from varying proportions of non-ionic 2-NP and 2-NP nitronate in the stock 2-NP used in their tests. Fiala et al. (1987a) further observed that dimethyl sulfoxide (DMSO), a solvent used to solubilize 2-NP in these tests, modified the mutagenicity of 2-NP nitronate in a variable manner.

Several of the studies discussed above examined the question of how 2-NP induces mutations in the test systems. In addition to 2-NP, 1- and 2-aminopropane and a number of mononitroalkanes (nitromethane, nitroethane, 1-nitropropane, 1- and 2-nitrobutane, and 1- and 2-nitropentane) were tested for mutagenicity with bacterial systems, mainly strains of *Salmonella typhimurium* (Hite & Skeggs, 1979; Speck et al., 1982; Löfroth et al., 1986; Kawai et al., 1987; Göggelmann et al., 1988; Dayal et al., 1989). Only 2-NP proved to be significantly mutagenic. Some investigators observed weak mutagenicity with nitroethane, 1-nitropropane, 2-nitrobutane, and 2-nitropentane, which, at least in the case of nitromethane and nitroethane, may have been produced by the 2-NP present in these solvents as a contaminant.

Löfroth et al. (1986) and Fiala et al. (1987a) speculated that the relative mutagenicity of 2-NP and other nitroalkanes correlated with the concentrations of their nitronate anions. The more highly mutagenic compounds, such as 2-NP and 1,1-dinitroethane, had high concentrations of nitronate at cellular pH. A thorough comparison of 2-NP, other secondary nitroalkanes, and their nitronates (Conaway et al., 1991) showed greater mutagenicity of the nitronates and confirmed these speculations.

These studies do not support the hypothesis that mutagenicity of 2-NP is produced largely or entirely by nitrite resulting from its metabolic breakdown, since the response of tester strains to sodium nitrite was quite different from their response to 2-NP (Löfroth et al, 1986). Unlike nitroarenes and nitroheterocyclics, 2-NP probably does not derive its mutagenicity exclusively from enzymatic reduction to a hydroxylamine. Strains of *S. typhimurium*, i.e. TA98NR and TA100NR, lacking the "classical" nitroreductase demonstrated either a very slightly (Speck et al., 1982) or markedly (Göggelmann et al., 1988) reduced, but still significant, level of mutagenicity. Göggelmann et al. (1988)

suggested that some of this mutagenicity may be due to some residual nitroreductase activity still present in these strains.

The increased mutagenicity generally observed with S9 activation of 2-NP and the reduced mutagenicity in tester strains deficient in nitroreductase activity suggest an involvement of metabolism in the mutagenicity of 2-NP in *S. typhimurium*. Fiala et al. (1987a) presented evidence that metabolic oxidation of the 2-NP anion can result in the formation of reactive species such as hydroxyl radicals, which are capable of damaging DNA bases. Incubation of 2-NP nitronate under roughly physiological conditions with thymidine and a 1-electron oxidation system, horseradish peroxidase and hydrogen peroxide, yielded 2-NP free radicals (which in part condensed into 2,3-dimethyl-2,3-dinitrobutane) and oxidation products of thymidine of the type produced by hydroxyl radical attack. A common source of hydroxyl radicals is superoxide, which is known to be produced during oxidation of 2-NP nitronate by horseradish peroxidase and hydrogen peroxide (Porter & Bright, 1983). The extent to which such reactions may occur in the *Salmonella* tester strains or *in vivo* is unknown. There is, however, evidence from the literature for microbial oxidation of 2-NP and 2-NP nitronate (Kido et al., 1984; Fiala et al., 1987a). The existence of this proposed mechanism for inducing mutations through the production of DNA-damaging hydroxyl radicals is further supported by the reduction in 2-NP mutagenicity in TA102 by DMSO, a known scavenger of such radicals (Fiala et al., 1987a). The fact that DMSO had little effect on the mutagenicity of 2-NP in TA100 indicated that formation of hydroxyl radicals cannot be the only mechanism inducing mutations. Fiala et al. (1987a) hypothesized that the 2-NP radical may act directly by forming adducts with DNA bases. This would provide an additional mechanism for inducing mutations that would not require hydroxyl radicals.

7.4.2 Eukaryotes

The genotoxic effects of 2-NP in eukaryotic organisms are summarized in Table 7. Results were negative in two sex-linked recessive lethal tests using *Drosophila* despite exposure to high concentrations of 2-NP. Zimmering et al. (1985) dosed the flies by injection and by feeding with concentrations that induced an approximately 30% mortality, whereas McGregor (1981) exposed the flies to 2-NP vapour at a concentration of 2.55 g/m^3 (700 ppm) for 4.5 h. Sex-linked recessive lethal mutation frequency was not

increased except in mature spermatozoa in one stock of flies. Since this increase was not reproducible, its significance is doubtful.

Results were variable but mainly negative in a variety of *in vivo* mammalian test systems. In the dominant lethal test and the bone marrow chromosomal aberration test using rats and in the sperm abnormality test using mice, animals were exposed to 91 or 728 mg/m^3 (25 or 200 ppm) for 7 h/day on 5 consecutive days. Neither exposure level produced a positive response in any of the test systems used (McGregor, 1981). Negative results were obtained with the mouse micronucleus test even with an almost lethal oral dose of 0.3 g/kg on 2 consecutive days (Hite & Skeggs, 1979), and with a single intraperitoneal dose of 0.3 g/kg (Kliesch & Adler, 1987).

One set of genotoxicity tests using rats, however, yielded strongly positive results (Andrae et al., 1988; Ziegler-Skylakakis et al., 1987). In both *in vivo* and *in vitro* tests, 2-NP induced DNA repair synthesis in rat liver cells. In the *in vitro* experiments, cultures of rat hepatocytes were incubated with 2-NP, while in the *in vivo* experiments rats were injected intraperitoneally with 2-NP, sacrificed 4 h later, and cultures of their hepatocytes were examined for DNA repair synthesis. Exposure of hepatocyte cultures for 18 to 20 h to concentrations of 2-NP as low as 2.7 mg/litre (30 μmol/litre) induced a detectable (approximately 2-fold above the control level) increase in repair synthesis. The highest concentration tested, i.e. 89 mg/litre (10 mmol/litre), induced a 12- to 15-fold increase above control levels in hepatocytes from male rats and a 25- to 30-fold increase in hepatocytes from female rats. The *in vivo* experiments also demonstrated the existence of a sexual difference in susceptibility to 2-NP. In males, the lowest dose (20 mg/kg) induced a doubling in repair synthesis and the highest dose (80 mg/kg) a 3.6-fold increase, whereas in females these doses induced a very small increase and a doubling, respectively. In contrast to 2-NP, 1-NP given *in vivo* had no effect on DNA repair synthesis and did not increase *in vitro* repair synthesis above that expected from its contamination with 2-NP. Andrae et al. (1988) considered that their results from the *in vivo* experiments were in agreement with the observed greater hepatocarcinogenicity of 2-NP in male rats than in females. Their observation that 2-NP did not induce any increase in repair synthesis in any of nine non-hepatic cell lines derived from human, mouse, hamster, and rat tissues led the

authors to suggest that 2-NP is not a direct-acting genotoxic agent but rather requires metabolic activation by liver-specific metabolism.

Several papers have confirmed and expanded these initial observations on the genotoxicity of 2-NP to rat liver cells. George et al. (1989) showed that oral dosage similarly induced unscheduled DNA synthesis and also resulted in the formation of micronuclei in rat liver. 2-NP did not, however, significantly increase the frequency of micronuclei in mouse bone marrow. Intraperitoneal injection of 0.1 g/kg produced in 6 h a significant increase in 8-hydroxydeoxyguanosine and 8-hydroxyguanosine, products respectively of DNA and RNA damage caused by hydroxyl or other oxygen-radical-forming agents (Fiala et al., 1989; Hussain et al., 1990). This treatment produced significantly lower levels of 8-hydroxydeoxyguanosine, 8-hydroxyguanosine, and other presumed modified nucleosides in female rats than in males, and had little effect on the nucleic acids of the kidney, findings that are in agreement with the known carcinogenicity of 2-NP (Guo et al., 1990). The organ specificity of the genotoxicity of 2-NP in the rat was confirmed by Robbiano et al. (1991) who reported that oral doses of 45-713 mg/kg produced maximum numbers of single strand breaks in the liver 6 h after administration and did not induce DNA fragmentation in lung, kidney, bone marrow or brain. Damage to rat liver nucleic acids was also caused by intraperitoneal injection of other secondary nitroalkanes and a ketoxime capable of being converted to a secondary nitroalkane, but not with a primary or a tertiary nitroalkane (Conaway et al., 1991). These authors suggest that the greater genotoxicity of the secondary nitroalkanes may stem from the greater stability of their nitronate forms at physiological pH values.

Observations by Roscher et al. (1990) and Robbiano et al. (1991) suggest that cytochrome P-450-dependent monooxygenases are important in the activation of 2-NP in liver. Robbiano et al. (1991) found an increase in damage to liver DNA in rats pretreated with phenobarbital or β-naphthoflavone, inducers of cytochrome P-450-dependent monooxygenases, and a reduction in liver DNA damage in rats pretreated with methoxsalen, an inhibitor of cytochrome P-450. Roscher et al. (1990) examined the effect of 2-NP on rat hepatoma cell lines that express various forms of cytochrome P-450-dependent monooxygenases and V79 Chinese hamster cells that lack these enzyme activities. 2-NP

increased DNA repair synthesis, micronuclei formation, and the frequency of mutants resistant to 6-thioguanine in hepatoma cells pretreated with dexamethasone, an inducer of various liver-specific cytochrome P-450 forms. Genotoxicity was reduced or absent in hepatoma cells not treated with the inducer. In the V79 cells, 2-NP produced only mutations to 6-thioguanine resistance.

2-NP demonstrated only a very limited level of genotoxicity in other cell lines. Results were negative in a DNA repair synthesis assay with human diploid fibroblasts exposed for 3 h to 2-NP concentrations up to 5 g/litre (56 mmol/litre) (McGregor, 1981), as well as with various cell lines of extrahepatic origin (Andrae et al., 1988). 2-NP did not cause chromosomal aberrations or SCEs in Chinese hamster ovary (CHO) cells either with or without S9 (Galloway et al., 1987). In these experiments the maximum concentrations used, i.e. 1.6 and 5.0 g/litre (18 and 56 mmol/litre) were estimated to reduce cell growth by 50%. Weakly positive results, however, were obtained in cytogenetic tests using human lymphocytes (Bauchinger et al., 1987; Göggelmann et al., 1988). Exposure of cells to high concentrations of 2-NP (commercial grade, at least 94% 2-NP) for 1 h induced a significant increase in chromosomal aberrations (open breaks accompanied by gaps) at a concentration of 5.3 g/litre (60 mmol/litre) with S9 activation and at 7.1 g/litre (80 mmol/litre) without S9 activation (Bauchinger et al., 1987). In addition, the frequency of sister chromatid exchange was significantly increased at all concentrations of 2-NP (0.7 to 7.1 g/litre; 7.5 to 80 mmol/litre), but only with S9 activation. Repetition of the experiment with 2-NP of greater than 99% purity yielded similar results (Göggelmann et al., 1988). There was no significant increase in chromosomal changes without S9 activation, but there was a small but significant increase at the highest treatment levels, i.e. 7.1 and 10 g/litre (80 and 111 mmol/litre), with S9 activation. 1-NP of 97% purity produced no significant mutagenic or cytogenetic effects on this test system with or without S9 activation. The authors concluded that 2-NP can exert a clastogenic effect on human lymphocytes only with metabolic activation, and hypothesized that it acted via a different metabolic pathway in the lymphocytes than it did in the bacterial *S. typhimurium* system, where it induced mutations without exogenous activation.

7.5 Carcinogenicity

That 2-NP is unquestionably a potent carcinogen in rats was demonstrated by Lewis et al. (1979). Inhalation exposure of male Sprague-Dawley rats to 0.75 g/m^3 (207 ppm) for 7 h/day, 5 days/week, over a 24-week period induced hepatocellular neoplasms in all surviving animals. Inhalation exposure of rats to 0.36 g/m^3 (100 ppm) similarly administered over 18 months was associated with hepatocellular carcinomas in male rats and produced changes in the livers of female rats (nodules showing hyperplasia and vacuolar degeneration) which may have been precursors to carcinoma (Griffin & Coulston, 1983; Coulston et al., 1985). Oral dosing of male rats with 89 mg/kg (1 mmol/kg), three times a week for 16 weeks, induced massive hepatocellular carcinomas in all rats, observed when they were sacrificed 40 weeks later (Fiala et al., 1987a). Metastases to the lungs were present in 4 out of 22 surviving animals, suggesting a high degree of malignancy. Long-term inhalation exposure of rats to low concentrations (100 mg/m^3; 27 ppm) did not produce any evidence of increased hepatocellular carcinoma or precursor tumour lesions of any sort (Lewis et al., 1979; Griffin et al., 1980, 1981). Evidence that inhalation exposure to low doses of 2-NP can cause DNA damage in rats was presented by Denk et al. (1990). Male and female Sprague-Dawley rats, 4-6 days old at the beginning of treatment, were exposed to 0, 91, 146, 182, 291, and 455 mg/m^3 (0, 25, 40, 50, 80 and 125 ppm) for 6 h/day, 5 days/week for 3 weeks, and this was followed by promotion with polychlorinated biphenyls (Clophen A50) for 8 weeks. This treatment produced a dose-dependent increase in the numbers of preneoplastic liver foci deficient in adenosine-5'-triphosphatase. Cunningham & Matthews (1991) showed that 2-NP can also induce cell proliferation in rat liver. Rats were exposed to daily oral doses of 20, 40 or 80 mg/kg by gavage for 10 days, and cell proliferation during exposure was quantified by measuring the incorporation of bromodeoxyuridine into newly synthesized DNA. Exposure to 40 and 80 mg/kg resulted in statistically significant increases in the frequency of S-phase cells from 1.9% in the vehicle-treated animals to 6.3% and 11%, respectively. Exposure to 20 mg/kg had no effect on the labelling index. The non-carcinogenic isomer of 2-NP, 1-NP, did not affect DNA synthesis at doses of 20, 40 and 80 mg/kg.

There is no substantial evidence that 2-NP induces cancer in species other than the rat (Table 6). Inhalation exposure of rabbits

to 750 mg/m^3 (207 ppm) for 1 h/day, 5 days/week for 24 weeks, initially produced some evidence of liver damage. At the end of 6 months of exposure, the five rabbits examined displayed no more than minor changes in the liver and no evidence of carcinoma (Lewis et al., 1979). Exposure of mice to 728 mg/m^3 (200 ppm), similarly administered for 48 weeks, produced damage to the liver, especially in females, but no carcinoma (Griffin et al., 1984). It is possible that degenerative changes observed in the livers of exposed females may have been precursors to subsequent tumour development. A lower concentration of 2-NP, 360 mg/m^3 (100 ppm), similarly administered to ICR mice for 18 months, induced liver damage in the form of nodular hyperplasia in females but no increase in hepatocellular carcinoma (Coulston et al., 1986; Griffin et al., 1987). The latter study is the only inhalation study in a species other than the rat that was of sufficient duration to allow for latency in tumour development. No studies of carcinogenicity using oral dosing in any species except the rat have been reported. Thus, despite the absence of clear evidence, the possibility of carcinogenicity in species other than the rat cannot be discounted.

There appear to be no laboratory studies on species other than rats, mice and rabbits suitable for assessing the potential carcinogenicity of 2-NP. As discussed in section 8.2.2, there is no evidence from limited epidemiological studies that 2-NP is carcinogenic in humans.

Griffin & Coulston (1983) argued that 2-NP does not act as an initiating carcinogen in the rat, but rather induces cancer as a response to extensive liver damage (Angus Chemical Co., 1985). They offered as evidence the results of an experiment demonstrating the absence of long-term effects from short-term exposure to 2-NP (Griffin et al., 1986). Exposure of rats of both sexes to 730 g/m^3 (200 ppm), 7 h/day for 5 days, did not produce any effect on longevity or on the development of hepatocellular or other carcinomas up to the end of the experiment, which lasted for 94 weeks. This argument is markedly weakened by the observation of Andrae et al. (1988) and others (Fiala et al., 1989; George et al., 1989; Guo et al., 1990; Conaway et al., 1991) that 2-NP is an active genotoxic agent in rat hepatocytes both *in vitro* and *in vivo*.

7.6 Pharmacological effects

In vivo pharmacological studies have not been performed. However *in vitro* studies with guinea-pig tissues suggest that 2-NP may have several pharmacological effects. A 0.1 μM (8.9 μg/litre) solution inhibited oxygen consumption of polymorphonuclear leucocytes by 50% (Estes & Gast, 1960). These authors further reported that, with increasing concentrations of 2-NP, respiration of heart homogenate was initially depressed and subsequently stimulated.

2-NP also produces two opposite neural effects on smooth muscle preparations (Bergman et al., 1962). Contraction is induced partly by ganglionic stimulation and partly by direct liberation of a transmitter from nerve endings, but at the same time 2-NP inhibits the response to acetylcholine and other smooth muscle stimulants. Bergman et al. (1962) found that the action of nitroparaffins on smooth muscle was similar to that of nicotine in that their ability to induce contraction was inhibited by morphine and by high, but not low, concentrations of atropine.

8. EFFECTS ON HUMANS

8.1 General population exposure

As indicated in section 5.1, general population exposure to 2-NP appears to be very low, and there is no information on the effects of this exposure. 2-NP has been used as a component of paints and other consumer products. There is no evidence that exposure to 2-NP from the use of such products has resulted in detectable injury or illness in the general population.

8.2 Occupational exposure

8.2.1 Acute toxicity

Significant human exposure to 2-NP is largely or entirely occupationally related. High concentrations are acutely toxic and seven industrial fatalities have been attributed to inhalation of 2-NP fumes (Gautier et al., 1964; Hine et al., 1978; Rondia, 1979; Harrison et al., 1985, 1987; US NIOSH, 1987b). In all cases, exposure was to a solvent mixture containing 2-NP, was for a total of 5 to 16 h in the course of 1 to 3 days, and occurred while paints or coatings were being applied in confined spaces, such as tank interiors, underground vaults and ship's holds, with little or no ventilation. The actual concentrations of 2-NP that caused deaths were not measured, but were thought to be high and in one case estimated at 2.18 g/m^3 (600 ppm), as determined by GC-FID from the 2-NP content of the victim's blood (0.013 g/litre) (Harrison et al., 1987). Initial symptoms requiring medical treatment appeared during exposure or within a few hours following exposure and included headache, nausea, dizziness, drowsiness, weakness, anorexia, vomiting, diarrhoea, and neck, thoracic, and abdominal pain. Victims were hospitalized and in general initially showed improvement, in some cases to the point of being discharged after a day or less. But improvement, where present, was temporary and in all seven cases was followed within a few days by worsening condition and rehospitalization of those previously discharged. Later symptoms included persistent nausea, vomiting, anorexia, jaundice, reduced urine output, diarrhoea, bloody stools, mental confusion, restlessness, loss of reflexes, and increases in serum aminotransferases and other indicators of hepatic lesions. Death occurred within 4 to 26 days (average, 10 days) following exposure. In all cases the primary cause was acute hepatic failure.

Contributing factors included lung oedema, gastrointestinal bleeding, and respiratory and kidney failure. Postmortem microscopic examination of the liver revealed necrosis of hepatic tissue and in some cases fatty degeneration. None of the victims had a past history of liver disease or drank excessively.

In addition to these fatalities, there have been four additional serious but nonlethal cases attributed to acute exposure to 2-NP (Gautier et al., 1964; Hine et al., 1978; Harrison et al., 1985, 1987; US NIOSH, 1987b). All but one were colleagues of the deceased described above, but may have received lesser doses. Initial symptoms were similar to those of the deceased, but were followed by full recovery rather than decline and death. Serum enzyme levels, however, remained mildly elevated for months following exposure. As in the case of the deceased, the actual concentrations of 2-NP to which these workers were exposed are unknown. One of the survivors had a 2-NP serum concentration of 8.5 mg/litre when hospitalized. Since his coworker hospitalized at the same time with a serum concentration of 13 mg/litre subsequently died, Harrison et al. (1987) speculated that either 2-NP has a very steep dose-response curve or that there are substantial differences in individual susceptibility. Six men (out of a group of approximately 300) developed toxic hepatitis after exposure to an epoxy resin coating containing 2-NP (Williams et al., 1974). The development of toxic hepatitis was ascribed to methylenedianiline in the coating, and the possibility that 2-NP may have been at least a partial cause was not considered.

Exposure to lower concentrations of 2-NP appears to produce some of the symptoms described above. Brief and intermittent exposure to concentrations above 364 mg/m^3 (100 ppm) may produce headache and nausea (Angus Chemical Co. & Occusafe, Inc., 1986). Exposure to vapours (estimated to contain 73 to 164 mg/m^3 (20 to 45 ppm) using colorimetric methods available at the time of the study) of a solvent mixture that polluted the workplace air produced a daily cycle in symptoms (Skinner, 1947). Workers started the day feeling well, but by noon some exhibited nausea and lack of appetite. Later in the working day these symptoms intensified and were accompanied by vomiting and diarrhoea. Vomiting continued after the workers left the workplace, and they were unable to eat supper but were able to sleep. By morning they were feeling well again. Colleagues not experiencing nausea and vomiting had occipital headaches, which appeared and gradually intensified during the working day. All

of the workers were free of symptoms when away from the workplace for a day or more, and the substitution of methyl ethyl ketone for 2-NP brought complete relief. Skinner (1947) noted that in another plant exposure of workers to 36-109 mg/m^3 (10-30 ppm) for less than 4 h/day on not more than 3 days per week produced no noticeable ill effects.

The flaw in all but one (Hine et al., 1978) of these case studies is that exposure was to a solvent mixture containing 2-NP and not to 2-NP alone (Hine et al., 1978). Thus the observed effects cannot be assigned to 2-NP with total confidence. A number of factors, however, point to 2-NP as the main, if not sole, causative agent. It was the only solvent common to all the mixtures, and the only solvent present in the mixtures known to be hepatotoxic. Symptoms and damaging effects on the body from the solvent mixtures were fairly similar to each other despite widely different solvent compositions (apart from the common presence of 2-NP), and were fairly similar to those in the single case resulting from exposure to 2-NP alone. In addition, as described above, substitution of another solvent for 2-NP eliminated all symptoms. The weight of evidence thus supports the view that the symptoms and damage to the human body described above which followed exposure to solvent mixtures containing 2-NP, resulted mainly, if not entirely, from 2-NP.

8.2.2 *Effects of long-term exposure*

Despite the fact that 2-NP has been in use for over 40 years, there are very few data on long-term effects and such information is derived mainly from unpublished reports from manufacturers of 2-NP.

Angus Chemical Co., a major manufacturer of 2-NP, has assembled information on more than 1800 occupationally exposed workers from a variety of plants in the USA, Mexico, Germany, Sweden, and the Netherlands (Table 8). Where information was available, medical records on living employees indicated no problems with liver functions and no obvious symptoms or conditions that could be connected with chronic exposure to 2-NP (Angus Chemical Company and Occusafe, Incorporated, 1986).

A major portion of the above investigation was an earlier mortality study conducted by Miller & Temple (1979) on 1481 workers employed in the manufacture of 2-NP during the period

Table 8. Studies of long-term occupational exposure to 2-nitropropane

Activity[a]	Exposure concentration[b] mg/m^3 (ppm)		Exposure duration (years)	No. of exposed employees	Reference
	TWA	STEL			
Manufacture of 2-NP, 1940-1955	25-91 (7-25)	> 218 (> 60)	< 1-15 average 2.5	55	Angus Chem. Co. & Occusafe, Inc. (1986)
Manufacture of 2-NP, 1946-1982, Sterlington, LA, USA	3.6-36 (1-10)	91-5970 (25-1640)	< 5-> 21 average 8[c]	804	Angus Chem. Co. & Occusafe, Inc. (1986); Miller & Temple (1979); Bolender (1983)
Extraction of triglycerides, USA	3.6-193 (1-53; average 9[c])	109-473 (30-130)	< 5-ca. 25	18-19	Angus Chem. Co. & Occusafe, Inc. (1986); Crawford et al. (1985); Tabershaw Occupational Medicine Assoc. (1980); Life Extension Inst. (1983)
Automobile assembly plant, Germany	unknown		< 5-> 25	456	Angus Chem. Co. & Occusafe, Inc. (1986)
Paint mfg., Germany	unknown		5-10	6	Angus Chem. Co. & Occusafe, Inc. (1986)
Paint mfg., Germany	40-91 (11-25)		11-15	5	Angus Chem. Co. & Occusafe, Inc. (1986)
Chemical mfg., Germany	unknown		5-10	80	Angus Chem. Co. & Occusafe, Inc. (1986)
Chemical mfg., Germany	unknown		< 5	4	Angus Chem. Co. & Occusafe, Inc. (1986)
Extraction plant, Sweden	3.6-18.2 (1-5)	73-364 (20-100)	5-10	15	Angus Chem. Co. & Occusafe, Inc. (1986)

Table 8 (contd).

Activity[a]	Exposure concentration[b] mg/m^3 (ppm)		Exposure duration (years)	No. of exposed employees	Reference
	TWA	STEL			
Paint mfg., Netherlands	unknown		5-10	180	Angus Chem. Co. & Occusafe, Inc. (1986)
Chemical co., USA	3.6-36 (1-10)	65.6-364 (18-100)	< 5-20	41	Angus Chem. Co. & Occusafe, Inc. (1986)
Printing co., USA	1.8-87 (0.5-24)	2.5-124 (0.7-34)	?	140	Angus Chem. Co. & Occusafe, Inc. (1986)
Paint mfg., Mexico	3.6 (1)	< 91 (< 25)	5-10	100	Angus Chem. Co. & Occusafe, Inc. (1986)
Ink mfg., Mexico	11-18 (3-5)	73-80 (20-22)	5-10	8	Angus Chem. Co. & Occusafe, Inc. (1986)
Coatings mfg., Mexico	14.6-91 (4-25)	237-251 (65-69)	< 5-20	30	Angus Chem. Co. & Occusafe, Inc. (1986)
Chemical distillation, Mexico	36-55 (10-15)	> 91 (> 25)	< 5-10	2	Angus Chem. Co. & Occusafe, Inc. (1986)
Paint mfg., USA	unknown		< 20	150	Angus Chem. Co. & Occusafe, Inc. (1986)
Automotive mfg., USA	3.6-36 (1-10)	142 (39)	< 18	10	Angus Chem. Co. & Occusafe, Inc. (1986)

[a] mfg. = manufacturing; co. = company
[b] TWA = time weighted average; STEL = short-term exposure level; values in parentheses are in ppm
[c] This average is an approximation

1955 to 1977. The exposures were defined as direct, indirect or zero exposure. Formal industrial hygiene monitoring was not performed until 1977. Individual exposures were based on job titles rather than actual exposure data. Angus Chemical Company and Occusafe, Incorporated (1986) concluded that analysis of these data did not suggest any unusual cancer or other disease pattern in this group of workers. They noted, however, that because the cohort was small and the duration of exposure and observation was relatively short, it was not possible to conclude from these data that 2-NP is not carcinogenic to humans. In a follow-up report on the same cohort (Bolender, 1983), the findings did not change the earlier conclusion.

It is necessary to emphasize that this cohort had a limited number of workers with long exposure (> 15 years). Since the individual exposure data are not available, it cannot be concluded from available data that 2-NP is non-carcinogenic in humans.

9. EFFECTS ON OTHER ORGANISMS IN THE LABORATORY AND FIELD

The limited data on the effects of 2-NP on organisms other than mammals is summarized below. Kido et al. (1975) reported that 2-NP (5 g/litre) inhibited the growth of 10 of the 14 species of microorganisms tested, although all 14 species contained enzymes capable of oxidizing 2-NP to acetone and nitrite (see section 4.2). Organisms inhibited by 2-NP included bacteria (*Escherichia coli, Pseudomonas iodinum*), yeasts (*Endomyces fibuliger, Hansenula anomala, H. octospora, H. sauveolens, H. matritensis*), and fungi (*Aspergillus niger, Penicillium oxalicum, Fusarium oxysporum*). Organisms capable of growing on the medium containing 2-NP similarly included bacteria (*Sarcina lutea, Brevibacterium protophormiae*), a yeast (*Hansenula mrakii*), and a fungus (*Rhizopus batatas*). Fridman et al. (1976) reported that the minimum concentration of 2-NP inhibiting the growth of *E. coli* and *Staphylococcus aureus* was 1000 mg/litre. Observations on aquatic macroorganisms appear more limited than those on microorganisms. The lowest concentration of 2-NP in sea water inducing narcosis in barnacle larvae at 18-22 °C was approximately 0.7-0.8 g/litre (Crisp et al., 1967). At 22 °C the 96-h LC_{50} for fathead minnows (*Pimephales promelas*) was > 210 mg/litre (Curtis et al., 1980; Curtis & Ward, 1981). Aeration of the holding tanks during the toxicity test produced flawed results because 2-NP was lost continuously by volatilization and a nominal highest concentration of 612.5 mg/litre was reduced to 496 mg/litre at the start of the test and to 210 mg/litre by 96 h. There was no significant mortality at concentrations of 2-NP below 210 mg/litre although at lower concentrations it did produce severe (though undescribed) sublethal effects. Observations on non-mammalian terrestrial organisms are limited to two related species, the oriental fruit fly (*Dacus dorsalis*) and the Mediterranean fruit fly (*Ceratitis capitata*). Burditt et al. (1963) found that 2-NP was not especially effective as a fumigant against eggs and larvae of these species. The 2-h LC_{50} values for eggs and larvae of the oriental fruit fly were > 103 and 75 g/m^3 (> 28 300 and 20 600 ppm), respectively, and for the Mediterranean fruit fly, > 103 and 35 g/m^3 (> 28 300 and 9600 ppm), respectively. These observations, in summary, suggest a fairly low acute toxicity to non-mammalian organisms.

10. EVALUATION OF HUMAN HEALTH RISKS AND EFFECTS ON THE ENVIRONMENT

10.1 Human health risks

Although there are no known biological sources of 2-NP, very low level non-occupational exposure must be almost universal because 2-NP is known to be a minor component of tobacco smoke and probably is present in smoke from other types of nitrate-rich organic matter. Residues in food products containing fatty acids separated with 2-NP and in beverage can linings and other coatings may represent additional sources of exposure to low (μg) amounts of 2-NP. The effects, if any, on human health of low-level exposure are unknown.

Sources of worker exposure include rotogravure and flexographic inks used in printing, and coatings and adhesives used in industrial construction and maintenance, highway markings, ship building and maintenance, furniture manufacture, and food packaging. Based on a survey conducted in the USA in 1980, occupational exposure to 2-NP appeared to be limited to a fraction of 1% of the workforce, and significant occupational exposure (exposure to > 9.1 mg/m^3 (> 2.5 ppm)) to about 0.005% of the workforce. Thus, tens of thousands of workers may have received significant occupational exposure worldwide. The effects of this occupational exposure are unclear.

Very few industrial fatalities have been attributed to 2-NP. All involved acute exposure to high concentrations of vapours from solvent mixtures containing 2-NP during applications of coatings in confined spaces; all deaths resulted primarily from hepatic failure. Exposure to non-lethal concentrations of 2-NP may result in temporary illness or discomfort, but there is no case history or epidemiological evidence that the chemical induces cancer or other long-term harmful effects in humans. On the other hand, the numbers of individuals studied and the periods since first exposure to 2-NP were inadequate to detect possible long-term harmful effects.

Animal data has demonstrated that 2-NP is a strong hepatocarcinogen in rats. Chronic exposure to high but non-lethal concentrations (at least 0.36 g/m^3, 100 ppm) induced a high frequency of hepatic tumours and hepatic cancer in rats but these

observations were not reproduced in limited studies on mice and rabbits. The mechanism by which 2-NP induces cancer in rats has not been elucidated as yet. 2-NP is strongly genotoxic to rat hepatocytes both *in vitro* and *in vivo*. It appears likely that the hepatocarcinogenicity of the compound in rats is a consequence of liver-specific formation of reactive products. The DNA-damaging species has not yet been identified. Since it can induce liver cell proliferation, 2-NP may also have tumour-promoting activity. Similarities or differences between metabolic activation of 2-NP in rats and in humans are largely unknown. At present, any substance shown to be carcinogenic in any mammalian species is considered a potential human carcinogen. Accurate risk assessment from exposure to 2-NP requires further studies.

10.2 Effects on the environment

2-NP does not represent a threat to the environment. It appears highly mobile in the natural environment and is not accumulated in any individual compartment. It is likely that 2-NP will be destroyed by photolysis when exposed in the atmosphere to sunlight, and by biological processes in soil and water. There are, however, insufficient experimental and observational data on the behaviour of 2-NP in the environment to validate these assumptions or to estimate rates of degradation in nature. Limited observations on microorganisms, invertebrates, and fish show a low level of acute toxicity to non-mammalian organisms.

11. RECOMMENDATIONS FOR PROTECTION OF HUMAN HEALTH

There are no indications that 2-NP is carcinogenic in humans. However, in view of its carcinogenicity in rats, it is recommended that occupational exposure and its presence in consumer products such as paints and varnishes be minimized and that it be replaced with a less toxic solvent whenever practical. Monitoring of the workplace should be continued to control actual worker exposure. Although it is not feasible to eliminate non-occupational exposure, such exposure should be minimized. 2-NP should not be used in food processing.

12. FURTHER RESEARCH

12.1 Environment

Although it appears likely that 2-NP is highly mobile in the environment, is not accumulated in any environmental compartment, and is degraded in the environment to less toxic substances by microorganisms and ultraviolet radiation, it would be desirable to confirm experimentally these assumptions and to quantify the speed of degradation in various environmental compartments.

12.2 Epidemiology

Cohorts of workers in production plants as well as cohorts of workers using products containing 2-NP (e.g., inks, paints) should be investigated for incidence of cancer and other ill effects.

12.3 Toxicokinetics

A more detailed examination of the metabolism and distribution in the body of 2-NP and its metabolites is needed to facilitate an understanding of the marked species and sex differences in toxic effects. Studies on distribution and metabolism should include metabolites of both the carbon and the nitrogen moieties. Experimental data should be obtained on dermal uptake. Studies on the metabolism of 2-NP in human cells are needed to facilitate the eventual extrapolation of data obtained with laboratory animals to humans.

12.4 Carcinogenesis

Continued efforts should be made to elucidate the biochemical and molecular mechanisms whereby 2-NP induces genotoxic effects and cancer.

13. PREVIOUS EVALUATIONS BY INTERNATIONAL BODIES

2-NP was evaluated by the Joint FAO/WHO Expert Committee on Food Additives in 1979 and 1981, but no ADI was allocated. The Committee recommended that 2-NP should not be used as a solvent in food processing, but it was temporarily acceptable for use as a fractionating solvent in the production of fats and oils (FAO/WHO, 1984). 2-NP was re-evaluated by JECFA in 1989; it was considered to be a potent liver carcinogen in rats, and the temporary acceptance for use as a fractionating solvent in the production of fats and oils was not extended (FAO/WHO, 1990a, 1990b). The European Economic Community found 2-NP to be flammable and to be harmful by inhalation, ingestion, and dermal contact. It required that member states ensure that it receives proper packaging, labelling, and storage (IRPTC, 1986).

The International Agency for Research on Cancer evaluated 2-NP in 1981 (IARC, 1982) and concluded that there was sufficient evidence for its carcinogenicity in rats but that epidemiological information was inadequate to evaluate its carcinogenicity to humans. 2-NP is classified in Group 2B, i.e. as possibly carcinogenic to humans (IARC, 1987).

REFERENCES

ACGIH (1986) Documentation of the threshold limit values and biological exposure indices, 5th ed. Cincinnati, Ohio, American Conference of Governmental Industrial Hygienists, Inc. pp 441-442.

Andersson K, Levin J-O, & Nilsson C-A (1983) Evaluation of solid sorbents for sampling aliphatic and aromatic nitro compounds. Chemosphere, 12: 377-384.

Andersson K, Levin J-O, Lindahl R, & Nilsson C-A (1984) Influence of air humidity on sampling efficiency of some solid adsorbents used for sampling organics from work-room air. Chemosphere, 13: 437-444.

Andrae U, Homfeld H, Vogl L, Lichtmannegger J, & Summer KH (1988) 2-Nitropropane induces DNA repair synthesis in rat hepatocytes *in vitro* and *in vivo*. Carcinogenesis, 9: 811-815.

Angus Chemical Company (1985) Technical data sheet: NiPar S-20™ nitropropane solvent, TDS 20B. Northbrook, Illinois, Angus Chemical Company, 12 pp.

Angus Chemical Company & Occusafe, Incorporated (1986) Industrial hygiene and occupational health information on 2-nitropropane, December 1982, and updates for December 1983, 1984, 1985. Northbrook, Illinois, Angus Chemical Company, 39 pp and 46 attachments (Unpublished report presented to the ACGIH TLV Committee).

Anon (1976) Grande Paroisse looks for growth in nitroparaffins market. Eur Chem News, 6 August: 23-24, 30.

Anon (1982) International mineral and chemical's nitroparaffins business will be acquired by Alberto Natural Gas (Canada) and Pacific Gas Transmission (US) for up to $ 55 million. Chem Week, 7 April: 24,251.

Baker PJ & Bollmeier AF (1981) Nitroparaffins. In: Grayson M & Eckroth D ed. Kirk-Othmer encyclopedia of chemical technology, 3rd ed. New York, John Wiley and Sons, vol 15, pp 969-987.

Baker HJ, Lindsey JR, & Weisbroth SH (1979) Appendix 1. Selected normative data. In: Baker HJ, Lindsey JR, & Weisbroth SH ed. The laboratory rat. Volume I: Biology and diseases. Orlando, Florida, Academic Press, append 1.

Baldwin RS & Williams R (1977) 2-Nitropropane LC_{50}. Northbrook, Illinois, International Minerals and Chemical Corporation, 6 pp (Unpublished report No. PLR-218/AMR-072).

Bauchinger M, Kulka U, & Schmid E (1987) Analysis of cytogenetic effect in human lymphocytes induced by metabolically activated 2-nitropropane. Mutat Res, 190: 217-219.

Beall LR, Alexander V, Bien CT, Chen C, & Infante P (1980) Health hazard alert - 2-Nitropropane. Cincinnati, Ohio, National Institute for Occupational Safety and Health, 8 pp (Publication No. 80-142).

Bergman F, Chaimovitz M, & Wind E (1962) Dual action of nitroparaffins on the guinea-pig ileum. Brit J Pharmacol, 18: 381-396.

Bernard AM, De Russis R, Normand J-C, & Lauwerys RR (1989) Evaluation of the subacute nephrotoxicity of cyclohexane and other industrial solvents in the female Sprague-Dawley rat. Toxicol Lett, **45**: 271-280.

Bolender FL (1983) 2-NP mortality epidemiology study of the Sterlington, LA employees: An update, 1-1-46 thru 12-31-81. Northbrook, Illinois, International Minerals and Chemical Corporation, 24 pp (Unpublished report).

Breazile JE (1971) Text book of veterinary physiology. Philadelphia, Pennsylvania, Lea and Febiger, p 347.

Brown D & Dobbin R (1977) Industrial hygiene survey report. IMC, Sterlington, Louisiana. Cincinnati, Ohio, National Institute for Occupational Safety and Health, 14 pp.

Burditt AK, Hinman FG, & Balock FG (1963) Screening of fumigants for toxicity to eggs and larvae of the oriental fruit fly and Mediterranean fruit fly. J Econ Entomol, **56**: 261-265.

Burrows GE (1979) Methylene blue or tolonium chloride antagonism of sodium nitrite induced methemoglobinemia. J Vet Pharmacol Ther, **2**: 81-86.

Cocalis JC (1982) Mining target environmental surveillance study. Nitropropane sensitized, ammonium nitrate blasting agents. Morgantown, West Virginia, National Institute for Occupational Safety and Health, Environmental Investigations Branch, Division of Respiratory Diseases Studies, 25 pp.

Conkle JP, Camp BJ, & Welch BE (1975) Trace composition of human respiratory gas. Arch Environ Health, **30**: 290-295.

Conaway CC, Nie G, Hussain NS, & Fiala ES (1991a) Comparison of oxidative damage to rat liver DNA and RNA by primary nitroalkanes, secondary nitroalkanes, cyclopentanone oxime, and related compounds. Cancer Res, **51**: 3143-3147.

Conaway CC, Nie G, Hussain NS, & Fiala ES (1991b) Evaluation of secondary nitroalkanes, their nitronates, primary nitroalkanes, nitrocarbinols, and other aliphatic nitro compounds in the Ames *Salmonella* assay. Mutat Res, **261**: 197-207.

Coulston F (1982) Influence of glutathione or diethyl maleate in the induction of hepatocellular carcinomas in rats exposed to 200 ppm of 2-nitropropane. Alamogordo, New Mexico, Coulston International Corporation, 14 pp (Unpublished report).

Coulston F, Stein AA, & Griffin TB (1985) Pathology final report. Histologic study of selected tissues from rats exposed to 2-nitropropane at 100 ppm. Alamogordo, New Mexico, Coulston International Corporation, 222 pp.

Coulston F, Griffin T, & Eason R (1986) Chronic inhalation exposure of mice to 2-nitropropane (100 ppm). Alamogordo, New Mexico, Coulston International Corporation, 5 pp (Unpublished report).

Crawford GN, Garrison RP, & McFee DR (1984) Odor threshold determination for 2-nitropropane. Am Ind Hyg Assoc J, **45**: B7-B8.

Crawford GN, Garrison RP, & McFee, DR (1985) Health examination and air monitoring evaluation for workers exposed to 2-nitropropane. Am Ind Hyg Assoc J, **46**: 45-47.

Crisp DJ, Christie AO, & Ghobashy AFA (1967) Narcotic and toxic action of organic compounds on barnacle larvae. Comp Biochem Physiol, 22: 629-649.

Cunningham ML & Matthews HB (1991) Relationship of hepatocarcinogenicity and hepatocellular proliferation induced by mutagenic noncarcinogens vs carcinogens. Toxicol Appl Pharmacol, 110: 505-513.

Cupitt LT (1980) Fate of toxic and hazardous materials in the air environment. Research Triangle Park, North Carolina, US Environmental Protection Agency, 28 pp (EPA-600/3-80-084).

Curtis MW & Ward CH (1981) Aquatic toxicity of forty industrial chemicals: Testing in support of hazardous substance spill prevention regulation. J Hydrol, 51: 359-367.

Curtis MW, Curran CM, & Ward CH (1980) Aquatic toxicity testing as fundament for a spill prevention program. In: Proceedings of the 1980 Conference on Control of Hazardous Material Spills. Nashville, Tennessee, Vanderbilt University, pp 284-288.

Dayal R, Gescher A, Harpur ES, Pratt I, & Chipman JK (1989) Comparison of the hepatotoxicity in mice and the mutagenicity of three nitroalkanes. Fundam Appl Toxicol, 13: 341-348.

Dayal R, Goodwin B, Linhart I, Mynett K, & Grescher A (1991) Oxidative denitrification of 2-nitropropane and propane-2-nitronate by mouse liver microsomes: lack of correlation with hepatic potential. Chem Biol Interact, 79(1): 103-114.

De Bruin A (1976) Biochemical toxicology of environmental agents. Amsterdam, Oxford, New York, Elsevier Science Publishers, p 104.

Denk B, Bauman M, & Filser JG (1989) Pharmacokinetics and hepatotoxicity of 2-nitropropane in rats. Arch Toxicol, 13(suppl): 330-332.

Denk B, Filser JG, Demi E, Kessler W, Shen J, & Oesterle D (1990) Dose-dependent emergence of preneoplastic foci in rat livers after exposure to 2-nitropropane. Arch Toxicol, 64: 329-331.

Dequidt J, Vasseur P, & Potencier J (1972) Etude toxicologique expérimentale de quelques nitroparaffines : 1. Etude du 2-nitropropane. Bull Soc Pharm Lille, 1972: 83-89.

Derks HJGM, Van Heiningen A, Klaassen R, & Olling M (1988) High performance liquid chromatographic method for the determination of 2-nitropropane in rat plasma. J Chromatogr, 442: 436-440.

Derks HJGM, Van Heiningen A, Klaassen R, & Olling M (1989) Toxicokinetics of 2-nitropropane in the rat. Bilthoven, The Netherlands, National Institute of Public Health and Environmental Protection, 19 pp (Report No. 328605.003).

De Rycker J & Halliwell B (1978) Oxidation of 2-nitropropane by horseradish peroxidase. Biochem J, 175: 601-606.

Dhawale MR & Hornemann U (1979) Nitroalkane oxidation by Streptomycetes. J Bacteriol, 137: 916-924.

Estes FL & Gast JH (1960) The *in vitro* effects of aliphatic nitro compounds on tissues. Arch Environ Health, 1: 59-64.

FAO/WHO (1984) Evaluation of certain food additives and contaminants. Twenty-eighth report of the Joint FAO/WHO Expert Committee on Food Additives. Geneva, World Health Organization, 44 pp (WHO Technical Report Series 710).

FAO/WHO (1990a) Evaluation of certain food additives and contaminants. Thirty-fifth report of the Joint FAO/WHO Expert Committee on Food Additives. Geneva, World Health Organization, 48 pp (WHO Technical Report Series 789).

FAO/WHO (1990b) Toxicological evaluation of certain food additives and contaminants, prepared by the 35th meeting of the Joint FAO/WHO Expert Committee on Food Additives (JECFA). Geneva, World Health Organization, 189 pp (WHO Food Additives Series 26).

Fiala ES, Czerniak R, & Williams GM (1986) Formation of carcinogenic and/or genotoxic aliphatic azoxy compounds from the respective nitroalkanes by direct mild chemical reduction. Toxicologist, 6: 40.

Fiala ES, Conaway CC, Biles WT, & Johnson B (1987a) Enhanced mutagenicity of 2-nitropropane nitronate with respect to 2-nitropropane possible involvement of free radical species. Mutat Res, 179: 15-22.

Fiala ES, Czerniak R, Castonguay A, Conaway CC, & Rivenson A (1987b) Assay of 1-nitropropane, 2-nitropane, 1-azoxypropane and 2-azoxypropane for cancinogenicity by gavage in Sprague-Dawley rats. Carcinogenesis, 8: 1947-1949.

Fiala ES, Conaway CC, & Mathis JE (1989) Oxidative DNA and RNA damage in the livers of Sprague-Dawley rats treated with the hepatocarcinogen 2-nitropropane. Cancer Res, 49: 5518-5522.

Fieser LF & Fieser M (1972) Reagents for organic synthesis. New York, Wiley-Interscience, vol 3, pp 213-214.

Fieser LF & Fieser M (1974) Reagents for organic synthesis. New York, Wiley-Interscience, vol 4, p 256.

Filser JG & Baumann M (1988) Pharmokinetics of 2-nitropropane in rats and determination of enzymes in serum specific for liver injury. Naunyn Schmiedeberg's Arch Pharmacol, 337(suppl): R17.

Fine DH, Challis BC, Hartman P, & Van Ryzin J (1982) Endogenous synthesis of volatile nitrosamines: model calculations and risk assessment. In: N-nitroso compounds: Occurrence and biological effects. Proceedings of the VIIth International Symposium on N-Nitroso Compounds, Tokyo, 28 September-1 October 1981. Lyon, International Agency for Research on Cancer, pp 379-396 (IARC Scientific Publications No. 41).

Finklea JF (1977) Current NIOSH intelligence bulletin: 2-nitropropane. Am Ind Hyg Assoc J, 38(7): A-15, A-17, A-19.

Fishbein L (1981) Carcinogenicity and mutagenicity of solvents. I. Glycidyl ethers, dioxane, nitroalkanes, dimethylformamide and allyl derivatives. Sci Total Environ, 17: 97-110.

Flanner LT (1972) 2-Nitropropane or nitromethane for inhibiting the corrosion of tin-plated steel aerosol cans: US Patent US 3650982 (21 March 1972). USA, Allied Chemical Corporation, 2 pp (Abstract only).

Freitag D, Geyer H, Kraus A, Viswanathan R, Kotzias D, Attar A, Klein W, & Korte F (1982) Ecotoxicological profile analysis. VII. Screening chemicals for their environmental behavior by comparative evaluation. Ecotoxicol Environ Saf, 6: 60-81.

Freitag D, Ballhorn L, Geyer H, & Korte F (1985) Environmental hazard profile of organic chemicals. Chemosphere, 14: 1589-1616.

Friedman MA, Greene EJ, & Epstein SS (1972) Rapid gastric absorption of sodium nitrite in mice. J Pharm Sci, 61: 1492-1494.

Friedman AL, Zalesov VS, Surkov VD, Kratynskaya LV, & Plaksina AN (1976) [Synthesis and study of the physiological activity of aliphatic nitro compounds. X. Relation among structure, toxicity, and antimicrobial activity in a series of nitroalkanes and their α-halo derivatives.] Khim-Farm Zh, 10: 53-56 (in Russian).

Galloway SM, Armstrong MJ, Reuben C, Colman S, Brown B, Cannon C, Bloom AD, Nakamura F, Ahmed M, Duk S, Rimpo J, Margolin BH, Resnick MA, Anderson B, & Zeiger E (1987) Chromosome aberrations and sister chromatid exchanges in Chinese hamster ovary cells: Evaluations of 108 chemicals. Environ Mol Mutagen, 10(suppl 10): 1-175.

Gautier M, Fournier P-E, Gervais P, & Sicot C (1964) Intoxication par le nitropropane. Arch Mal Prof, 25: 425-428.

George E, Burlinson B, & Gatehouse D (1989) Genotoxicity of 1- and 2-nitropropane in the rat. Carcinogenesis, 10: 2329-2334.

Glaser RA, & Woodfin WJ (1981) A method for sampling and analysis of 2-nitropropane in air. Am Ind Hyg Assoc J, 42: 18-22.

Goggelmann W, Bauchinger M, Kulka U, & Schmid E. (1988) Genotoxicity of 2-nitropropane and 1-nitropropane in Salmonella typhimurium and human lymphocytes. Mutagenesis, 3: 137-140.

Goldwhite H (1965) Nitrogen derivatives of the aliphatic hydrocarbons. In: Coffey S ed. Rodd's chemistry of carbon compounds, Part B, 2nd ed. Amsterdam, Oxford, New York, Elsevier Science Publishers, vol. 1, pp 93-164.

Griffin TB & Coulston F (1983) Final report. Chronic inhalation exposure of rats to vapors of 2-nitropropane at 100 ppm. Alamogordo, New Mexico, Coulston International Corporation, 13 pp.

Griffin TB, Benitz K-F, Coulston F, & Rosenblum I (1978) Chronic inhalation toxicity of 2-nitropropane in rats. Pharmacologist, 20: 145.

Griffin TB, Coulston F, & Stein AA (1980) Chronic inhalation exposure of rats to vapors of 2-nitropropane at 25 ppm. Ecotoxicol Environ Saf, 4: 267-281.

Griffin TB, Stein AA, & Coulston F (1981) Histologic study of tissues and organs from rats exposed to vapors of 2-nitropropane at 25 ppm. Ecotoxicol Environ Saf, 5: 194-201.

Griffin T, Coulston F, & Stein AA (1984) Chronic inhalation exposure of mice to 2-nitropropane. Preliminary report: Laboratory findings and histopathology of liver. Alamogordo, New Mexico, Coulston International Corporation, 14 pp (Unpublished report).

Griffin T, Coulston F, & Stein AA (1986) Long-term effects of acute exposure of rats to 2-nitropropane. Final Report, Study No. 820202. Alamogordo, New Mexico, Coulston International Corporation, 17 pp (Unpublished report).

Griffin T, Coulston F, & Stein AA (1987) Chronic inhalation exposure of mice to 2-nitropropane (100 ppm): Final report. Alamogordo, New Mexico, Coulston International Corporation, 24 pp (Unpublished report).

Guo N, Conaway CC, Hussain NS, & Fiala ES (1990) Sex and organ differences in oxidative DNA and RNA damage due to treatment of Sprague-Dawley rats with acetoxime or 2-nitropropane. Carcinogenesis, 11: 1659-1662.

Haas-Jobelius M, Ziegler-Skylakakis K, & Andrae U (1991) Nitroreduction is not involved in the genotoxicity of 2-nitropropane in cultured mammalian cells. Mutagenesis, 6: 87-91.

Hardin BD, Bond GP, Sikov MR, Andrew FD, Beliles RP, & Niemeier RW (1981) Testing of selected workplace chemicals for teratogenic potential. Scand J Work Environ Health, 7(suppl 4): 66-75.

Harris SJ, Bond GP, & Niemeier RW (1979) The effects of 2-nitropropane, naphthalene, and hexachlorobutadiene on fetal rat development. Toxicol Appl Pharmacol, 48: A35.

Harrison RJ, Pasternak G, Blanc P, Basuk P, & Letz G (1985) Acute hepatic failure after occupational exposure to 2-nitropropane. J Am Med Assoc, 254(24): 3415-3416.

Harrison RJ, Letz G, Pasternak G, & Blanc P (1987) Fulminant hepatic failure after occupation exposure to 2-nitropropane. Ann Intern Med, 107: 466-468.

Hartle RW (1980) Health hazard evaluation report No. 80-057-781 at Long Island Railroad, Richmond Hill, New York, Cincinnati, Ohio, National Institute for Occupational Safety and Health, 17 pp.

Haworth S, Lawlor T, Mortelmans K, Speck W, & Zeiger E (1983) Salmonella mutagenicity test results for 250 chemicals. Environ Mutagen, 5 (suppl 1): 3-142.

Hine CH, Pasi A, & Stephens BG (1978) Fatalities following exposure to 2-nitropropane. J Occup Med, 20: 333-337.

Hite M & Skeggs H (1979) Mutagenic evaluation of nitroparaffins in the Salmonella typhimurium/mammalian microsome test and the micronucleus test. Environ Mutagen, 1: 383-389.

Hoar RM (1976) Chapter 3. Biomethodology. In: Wagner JE & Manning PJ ed. The biology of the guinea pig. New York, London, Academic Press, p 16.

Hoffmann D & Rathkamp C (1968) Chemical studies on tobacco smoke. III. Primary and secondary nitroalkanes in cigarette smoke. Beitr Tabakforsch, 4: 124-134.

Hollett BA & Schloemer J (1978) Hazard evaluation technical assistance report No. TA 76-90: Newport Industrial Products Firestone Tire Rubber Co., Newport, Tennessee. Cincinnati, Ohio, National Institute for Occupational Safety and Health, 52 pp.

Hughes TJ, Simmons DS, Monteith LG, Myers LD, & Claxton LD (1987) Mutagenicity of 31 organic compounds in a modified preincubation Ames assay with *Salmonella typhimumium* strains TA100 and TA102. Environ Mutagen, 9 (suppl 8): 49.

Hussain NS, Conaway CC, Guo N, Asaad W, & Fiala ES (1990) Oxidative DNA and RNA damage in rat liver due to acetoxime: similarity to effects of 2-nitropropane. Carcinogenesis, 11: 1013-1016.

Indig GL & Cilento G (1987) Peroxidase-promoted aerobic oxidation of 2-nitropropane: Mechanism of excited state formation. Biochim Biophys Acta, 923: 347-354.

IARC (1982) 2-Nitropropane. In: Some industrial chemicals and dyestuffs. Lyon, International Agency for Research on Cancer, pp 331-343 (IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans, Volume 29).

IARC (1987) Overall evaluations of carconogenicity: An updating of IARC monographs, volumes 1 to 42. Lyon, International Agency for Research on Cancer, p 67 (IARC Monographs on the Evaluation of the Carconogenic Risk of Chemicals to Humans, Supplement 7).

IRPTC (1986) IRPTC data profile on 2-nitropropane. Geneva, International Register of Potentially Toxic Chemicals, United Nations Environment Programme, pp 17/1-17/3.

Ivanetich KM, Lucas S, Marsh JA, Ziman MR, Katz ID, & Bradshaw JJ (1978) Organic compounds. Their interaction with and degradation of hepatic microsomal drug-metabolizing enzymes *in vitro*. Drug Metab Disp, 6: 218-225.

Jones LR (1963) The determination of 2-nitropropane in air. Ind Hyg J, January-February: 11-16.

Jones LR & Riddick JA (1952) Colorimetric determination of nitroparaffins. Anal Chem, 24: 1533-1536.

Jonsson J, Kammerer RC, & Cho AK (1977) Metabolism of 2-nitro-1-phenylpropane by rabbit liver microsomes. Res Commun chem Pathol Pharmacol, 18: 75-82.

Kaplan HM, Brewer NR, & Blair WH (1983) Physiology. In: Foster HL, Small JD, & Fox JG ed. The mouse in biomedical research. Volume III Normative biology, immunology, and husbandry. New York, London, Academic Press, p 255.

Kawai A, Goto S, Matsumoto Y, & Matsushita H (1987) [Mutagenicity of aliphatic and aromatic nitro compounds. Industrial materials and related compounds.] Jpn J ind Health, 29: 34-54 (in Japanese).

Kenaga EE (1980) Predicted bioconcentration factors and soil sorption coefficients of pesticides and other chemicals. Ecotoxicol environ Saf, 4: 26-38.

Kido T, Yamamoto T, & Soda K (1975) Microbial assimilation of alkyl nitro compounds and formation of nitrite. Arch Microbiol, 106: 165-169.

Kido T, Tanizawa K, Inagaki K, Yoshimura T, Ishida M, Hashizume K, & Soda K (1984) 2-Nitropropane dioxygenase from *Hansenula mrakii*: Re-characterization of the enzyme and oxidation of anionic nitroalkanes. Agric Biol Chem, **48**: 2549-2554.

Kliesch U & Adler I-D (1987) Micronucleus test in bone marrow of mice treated with 1-nitropropane, 2-nitropropane and cisplatin. Mutat Res, **192**: 181-184.

Korte F, Freitag D, Geyer H, Klein W, Kraus AG, & Lahaniatis E (1978) Ecotoxicologic profile analysis. Chemosphere, 1: 79-102.

Kozma C, Macklin W, Cummins LM, & Mauer R (1974) Chapter 3. Anatomy, physiology, and biochemistry of the rabbit. In: Weisbroth SH, Flatt RE, & Kraus AL ed. The biology of the laboratory rabbit. New York, London, Academic Press, pp 56-57.

Krotoszynski BK, Bruneau GM, & O'Neill HJ (1979) Measurement of chemical inhalation exposure in urban population in the presence of endogenous effluents. J Anal Toxicol, **3**: 225-234.

Kuo FK & Fridovich (1986) Free-radical chain oxidation of 2-NP initiated and propagated by superoxide. Biochem J, **237**: 505-510.

Levy A (1973) The photochemical smog reactivity of organic solvents. Adv Chem Ser, **124**: 70-94.

Lewis TR, Ulrich CE, & Busey WM (1979) Subchronic inhalation toxicity of nitromethane and 2-nitropropane. J Environ Pathol Toxicol, 2: 233-249.

Life Extension Institute (1983) Summary report of medical findings for selected employees at one plant. Rockville, Maryland, Life Extension Institute, 12 pp.

Little HN (1951) Oxidation of nitroethane by extracts from Neurospora. J Biol Chem, **193**: 347-358.

Little HN (1957) The oxidation of 2-nitropropane by extracts of pea plants. J Biol Chem, **229**: 231-238.

Litton Bionetics, Inc. (1977) Mutagenicity evaluation of P-1357 66459T: Final report. Terre Haute, Indiana, IMC Chemical Group, Inc., 10 pp (Unpublished report).

Löfroth G, Nilsson L, & Andersen JR (1986) Structure-activity relationship of nitroalkane-induced mutagenicity in the Ames *Salmonella* assay. In: Genetic toxicology of environmental chemicals. Part B: Genetic effects and applied mutagenesis. New York, Alan R. Liss, Inc., pp 149-155.

Lotz F, Nitz S, & Korte F (1979) [Photomineralization of adsorbed organic chemicals on a microscale.] Chemosphere, 10: 763-768 (in German).

Love JR & Kern M (1981) Health hazard evaluation report no. 81-065-938. Metro bus maintenance shop, Washington, DC. Cincinnati, Ohio, National Institute for Occupational Safety and Health, 13 pp.

Mabuchi H (1979) [Urinary and serum volatile substances in diabetics.] Nippon Naika Gakkai Zasshi, **58**: 731-743 (Abstract only) (in Japanese).

McGregor DB (1981) Tier II mutagenic screening of 13 NIOSH priority compounds. Individual compound report: 2-Nitropropane. Musselburgh, Scotland, Inveresk Research International Ltd, 194 pp (Report No. 31).

Machle W, Scott EW, & Treon J (1940) The physiological response of animals to some simple mononitroparaffins and to certain derivatives of these compounds. J Ind Hyg Toxicol, **22**: 315-332.

Malkinson FD & Gehlmann L (1977) Factors affecting percutaneous absorption. In: Drill VA & Lazar P, ed. Cutaneous toxicity. New York, London, Academic Press, pp 63-82.

Marcstrom A (1967) Studies on the connection between physicochemical properties and stimulating abilities of some sweet and bitter compounds. Ark Zool, **19**: 421-535.

Marker EK & Kulkarni AP (1985) Enzymatic denitrification of 2-nitropropane in uninduced mouse liver microsomes. Toxicol Lett, **26**: 181-185.

Marker EK & Kulkarni AP (1986a) Cumene hydroperoxide-supported denitrification of 2-nitropropane in uninduced mouse liver microsomes. Int J Biochem, **18**: 595-601.

Marker EK & Kulkarni AP (1986b) Cytochrome P-450-mediated denitrification of 2-nitropropane in mouse liver microsomes. J Biochem Toxicol, **1**: 71-83.

Miller ME & Temple GW (1979) 2-NP mortality epidemiology study of the Sterlington, LA Employees, 1-1-46 thru 6-30-77. Northbrook, Illinois, International Minerals and Chemical Corporation, 34 pp (Unpublished report).

Mochizuki H, Kominami S, & Takemori S (1988) Examination of differences between benzo[*a*]pyrene and steroid hydroxylases in guinea pig adrenal microsomes. Biochem Biophys Acta, 964: 83-89.

Müller WF, Coulston F, & Korte F (1983) Comparative metabolism of 2-nitropropane in rats and chimpanzees. Chemosphere, **12**: 231-237.

National Fire Protection Association (1968) Hazardous chemicals data. J Chem Educ, 45: A313-A314, A317-A318, 320-322.

National Library of Medicine (1989) Toxic chemical release inventory. Washington, DC, National Library of Medicine (TOXNET system, TRI data base, 12 June 1989).

Nielsen AT (1981) Nitronic acids and esters. In: Feurer H ed. The chemistry of the nitro and nitroso groups. Huntington, New York, Robert Krieger Publishing Co., Part 1, pp 349-386.

Nolan RJ, Unger SM, & Muller CJ (1982) Pharmacokinetics of inhaled [^{14}C]-2-nitropropane in male Sprague-Dawley rats. Ecotoxicol Environ Saf, 6: 388-397.

Occupational Health Services, Inc. (1982) An evaluation of the number of workers occupationally exposed to 2-nitropropane. Cambridge, Massachusetts, Occupational Health Services, Inc., 22 pp (Unpublished report prepared for IMC Corporation, Des Plaines, Illinois).

Parks NJ, Krohn KA, Mathis CA, Chasko JH, Geiger KR, Gregor ME, & Peek NF (1981) Nitrogen-13-labeled nitrite and nitrate: Distribution and metabolism after intratracheal administration. Science, **212**: 58-61.

Paszyc S (1971) [Photolysis of 2-nitropropane in gaseous and liquid phases.] Poznan Tow Przyj Nauk Pr Kom Mat-Przyr, Pr Chem, **12**: 79-85 (in Polish).

Patel RN, Hou CT, Laskin AI, & Felix A (1982) Epoxidation of alkenes and hydroxylation of alkanes by soluble methane monooxygenase: Regeneration of cofactor $NADH_2$. J Appl Biochem, **4**: 175-184.

Porter DJ & Bright HJ (1983) The mechanism of oxidation of nitroalkanes by horseradish peroxidase. J Biol Chem, **258**: 9913-9924.

Purcell RF (1967) Use of 2-nitropropane under rule 66. West Paint Rev, **53**: 22A, 24A.

Reece WO (1984) Respiration in mammals. In: Swenson MJ ed. Duke's physiology of domestic animals, 10th ed. Cornell, New York, Comstalk Press, p 231.

Robbiano L, Mattioli F, & Brambilla G (1991) DNA fragmentation by 2-nitropropane in rat tissues, and effects of the modulation of biotransformation processes. Cancer Lett. **57**: 61-66.

Rondia D (1979) 2-nitropropane: One more death. Vet Hum Toxicol, **21**: 183-185.

Roscher E, Ziegler-Skylakakis K, & Andrae U (1990) Involvement of different pathways in the genotoxicity of nitropropanes in cultured mammalian cells. Mutagenesis, **5**: 375-380.

Sadtler SP (1961) Sadtler standard ultraviolet spectra. Philadelphia, Pennsylvania, Sadtler Research Laboratory, p 1.

Sakurai H, Hermann G, Ruf HH, & Ullrich V (1980) The interaction of aliphatic nitro compounds with the liver microsomal monooxygenase system. Biochem Pharmacol, **29**: 341-345.

Sander J & Schweinsberg F (1972) [Interrelationships between nitrate, nitrite and carcinogenic N-nitroso-compounds. 1. Communication: nitrate, nitrite and nitrosable amino-compounds in food and drugs, chemistry of N-nitroso compounds.] Zentrabl Bakeriol Parasitenkd Infektionsk Hyg Abt 1: Orig Reihe B, **156**: 299-340 (in German).

Schneider NR & Yeary RA (1975) Nitrite and nitrate pharmacokinetics in the dog, sheep, and pony. Am J Vet Res, **36**: 941-947.

Scott EW (1943) The metabolism of monoparaffins. III. The concentration of nitroethane, nitrite and nitrate in the blood of rabbits during exposure by inhalation and oral administration. J Ind Hyg Toxicol, **25**: 20-25.

Seizinger DC & Dimitrades B (1972) Oxygenates in exhaust from simple hydrocarbon fuels. J Air Pollut Control Assoc, **22**: 47-51.

Simmons DM, Monteith LG, Hughes TJ, & Claxton LD (1986) Effect of preincubation time on mutagenic activity in the Ames/*Salmonella* assay. Environ Mutagen, **8**(suppl 6): 78.

Skinner JB (1947) The toxicity of 2-nitropropane. Ind Med, 16: 441-443.

Smith EL, Hill RL, Lehman IR, Lefkowitz RJ, Handler P, & White A (1983) Principles of biochemistry. General aspects. New York, McGraw-Hill, pp 539-541.

Soda K, Kido T, & Asada K (1977) 2-Nitropropane dioxygenase from *Hansenula mrakii*: Generation and participation of superoxide anion in the reaction. In: Hayashi O & Asada K ed. Biochemical and medical aspects of active oxygen. Baltimore, Maryland, University Park Press, pp 119-133.

Speck WT, Meyer LW, Zeiger E, & Rosenkranz HS (1982) Mutagenicity and DNA-modifying activity of 2-nitropropane. Mutat Res, 104: 49-54.

SRI International (1988) 1988 Directory of chemical producers, United States of America. Menlo Park, California, SRI International, pp 29, 168, 803.

SRI International (1990) 1990 Directory of chemical producers, United States of America. Menlo Park, California, SRI International, p 815.

Stokinger HE (1982) Aliphatic nitro compounds, nitrates, nitrites. In: Clayton GD & Clayton FE ed. Patty's industrial hygiene and toxicology, 3rd revised ed. New York, John Wiley and Sons, vol 2C, pp 4141-4208.

Swann RL, Laskowski DA, McCall PJ, Vander Kuy K, & Dishburger HJ (1983) A rapid method for the estimation of the environmental parameters octanol/water partition coefficient, soil sorption constant, water to air ratio, and water solubility. Residue Rev, 85: 17-28.

Tabershaw Occupational Medicine Association (1980) Cross-sectional morbidity study of workers. Rockville, Maryland, Tabershaw Occupational Medicine Association, 68 pp (Unpublished report).

Treon JF & Dutra FR (1952) Physiological response of experimental animals to the vapor of 2-nitropropane. Arch Ind Hyg Occup Med, 5: 52-61.

Ullrich V & Schnabel KN (1973) Formation and binding of carbanions by cytochrome P-450 of liver microsomes. Drug Metab Disp, 1: 176-183.

Ullrich V, Hermann G, & Weber P (1978) Nitrite formation from 2-nitropropane by microsomal monooxygenases. Biochem Pharmacol, 27: 2301-2304.

US Bureau of the Census (1987) Statistical abstract of the United States: 1988, 108th ed. Washington, DC, US Bureau of the Census, p 368.

US EPA (1977) TSCA chemical assessment series. Chemical hazard information profiles (CHIPS), August 1976-August 1978. Washington, DC, US Environmental Protection Agency, pp 212-217 (EPA-560/11-80-011).

US EPA (1980) Materials balance 2-nitropropane, Level 1. Washington, DC, US Environmental Protection Agency, 70 pp (EPA-560/13-89-011).

US EPA (1985) Health and environmental effects profile for 2-nitropropane. Washington, DC, US Environmental Protection Agency, pp 3-4 (EPA-600/X-85-112).

US EPA (1986) Notice of potential risk, 2-nitropropane. Washington, DC, US Environmental Protection Agency, 5 pp.

US FDA (Food and Drug Administration) (1987) 2-Nitropropane. Code Fed Regul, 27 (Parts 1 to 199): Docket No. 78N-0221.

USITC (1990) Synthetic organic chemicals. United States production and sales, 1989. Washington, DC, United States International Trade Commission, pp 15-17, 15-35-15-36 (USITC Publication No. 2338).

US NIOSH (1983) National occupational exposure survey, 1981-83: Actual observation and trade-name exposure to 2-nitropropane. Cincinnati, Ohio, National Institute for Occupational Safety and Health (Unpublished database).

US NIOSH (1987a) NIOSH manual of analytical methods. Second supplement, 3rd ed. Cincinnati, Ohio, National Institute for Occupational Safety and Health, pp 2528/1-2528/4 (NIOSH Publication No. 87-117).

US NIOSH (1987b) Safe sheet #1: Summary of accidental fatality evaluations, confined spaces, Case #3. Morgantown, West Virginia, National Institute for Occupational Safety and Health, Environmental Investigations Branch, Division of Respiratory Disease Studies, p 2.

US NIOSH (1988) Current intelligence bulletins: Summaries, September 1988. Cincinnati, Ohio, National Institute for Occupational Safety and Health, p 6.

US OSHA (Occupational Safety and Health Administration) (1988) 1-Nitropropane and 2-nitropropane. Code Fed Regul, 29: 705, 708 (Parts 1900 to 1910).

Weast RC ed. (1986) CRC handbook of chemistry and physics, 67th ed. Boca Raton, Florida, CRC Press, p C-444.

Wester PW, Van Leeuwen FXR, & De Vries T (1989) 4-Week toxicity study with 2-nitropropane (2-NP) by gavage in rats. Bilthoven, The Netherlands, National Institute of Public Health and Environmental Protection, 20 pp (Report No. 658501 001).

Wilbur SZ & Parekh CK (1982) Dermal toxicity potential of 2-nitropropane (P-1357). Northbrook, Illinois, International Minerals and Mining Corporation, 5 pp (Unpublished report No. PLR-281/AMR-072).

Wilks RA & Gilbert SG (1972a) Sensory and instrumental evaluation in model systems of residues migrating from can coatings. J Food Sci, 37: 72-76.

Wilks RA & Gilbert SG (1972b) Quick test for liner solvents. Modern Packag, May: 52-55.

Williams SV, Bryan JA, Burk JR, & Wolf FS (1974) Toxic hepatitis and methylenedianiline. New Engl J Med, 291: 1256.

Windholz M ed. (1983) The Merck index, 10th ed. Rahway, New Jersey, Merck & Co., p 6482.

Woo Y-T, Lai DY, Arcos JC, & Argus MF (1985) Chemical induction of cancer: structural bases and biological mechanisms, Vol. III B: Aliphatic and polyhalogenated carcinogens. New York, London, Academic Press, pp 329-341.

Yasuhara A, Yamanaka Y, & Ogawa T (1986) Volatile compounds in machine cutting-fluid emulsion. Agric Biol Chem, 50: 1765-1770.

Ziegler-Skylakakis K, Homfeldt H, & Andrae U (1987) *In vitro* and *in vivo* genotoxicity of 2-nitropropane and 1-nitropropane in mammalian cells. Naunyn-Schmiedeberg's Arch Pharmacol, 335(suppl): R25.

Zimmering S, Mason JM, Valencia R, & Woodruff RC (1985) Chemical mutagenesis testing in *Drosophila*. II. Results of 20 coded compounds tested for the National Toxicology Program. Environ Mutagen, 7: 87-100.

Zitting A, Savolainen H, & Nickels J (1981) Acute effects of 2-nitropropane on rat liver and brain. Toxicol Lett, 9: 237-246.

RESUME

1. Propriétés et méthodes d'analyse

Le 2-nitropropane (2-NP) est un liquide huileux, incolore, à l'odeur douceâtre. Il est inflammable, moyennement volatil et stable dans les conditions ordinaires. Il n'est que légèrement soluble dans l'eau mais miscible à de nombreux liquides organiques et c'est un excellent solvant de nombreux composés organiques. Il existe de bonnes méthodes d'analyse pour la recherche et le dosage du 2-nitropropane présent dans l'environnement. On a actuellement recours à la chromatographie en phase gazeuse avec détection par ionisation de flamme ou capture d'électrons, ou bien à la chromatographie en phase liquide à haute performance avec détecteur u.v. Pour le dosage dans l'air, il faut tout d'abord piéger le 2-nitropropane et le concentrer par adsorption sur phase solide.

2. Emploi et sources d'exposition

2.1 Production

Les chiffres de production actuels ne sont pas connus. En 1977 les Etats-Unis d'Amérique en ont produit environ 13 600 tonnes. Le 2-nitropropane est actuellement produit par deux firmes américaines et une firme française. Il peut prendre naissance naturellement à l'état de traces lors de la combustion du tabac et d'autres matières organiques riches en nitrates mais rien n'indique qu'il puisse se former à l'issue d'un processus biologique quelconque.

2.2 Emploi et passage dans l'environnement

Le 2-nitropropane est utilisé comme solvant, principalement en mélange, et il a de nombreuses applications industrielles en tant que tel pour la confection d'encres d'imprimerie, de peintures, de vernis, d'adhésifs et autres revêtements, comme par exemple ceux que l'on utilise dans les récipients contenant des boissons. On l'utilise également comme solvant pour séparer des composés très voisins comme les acides gras, comme intermédiaire en synthèse chimique et comme additif dans les carburants. C'est principalement par l'intermédiaire de l'air qu'il passe dans

l'environnement, surtout par évaporation à partir des surfaces enduites de produits qui en contiennent.

3. Transport et distribution dans l'environnement

Le 2-nitropropane se révèle très mobile dans le milieu naturel. Du fait que sa solubilité dans l'eau, son adsorption par les sédiments et sa bioaccumulation sont faibles et qu'il s'évapore rapidement dans l'atmosphère, il se répartit dans l'air et l'eau sans s'accumuler dans un compartiment particulier du milieu. Le 2-nitropropane absorbe le rayonnement ultra-violet aux longueurs d'onde que l'on rencontre dans l'environnement et il est donc probable qu'il subisse une lente photolyse dans l'atmosphère. Il est également probable qu'il soit lentement transformé par voie biologique en composés moins toxiques, tant dans l'environnement aquatique que dans l'environnement terrestre.

4. Concentrations dans l'environnement et exposition humaine

Il semble que l'exposition de la population générale au 2-nitropropane soit très faible et provienne de la fumée de cigarettes (1,1 à 1,2 μg/cigarette), de résidus présents dans des enduits ou revêtements tels qu'on en utilise pour les récipients contenant des boissons, dans les adhésifs, les encres d'imprimerie, ainsi que dans les huiles végétales que l'on fractionne au moyen de ce solvant. On ignore quelle est l'importance de l'exposition des travailleurs de l'industrie dans le monde, mais aux Etats-Unis d'Amérique, il semble qu'elle soit limitée à 0,02-0,19 % du personnel. Dans ce même pays, environ 4000 travailleurs (soit à peu près 0,005 % de la main-d'oeuvre) subissent sans doute une exposition notable (de l'ordre de 9,1 mg/m^3(2,5 ppm) ou davantage). Selon les pays, les limites d'exposition professionnelle dans l'air vont de 36 mg/m^3 (1 ppm) (TWA) à 146 mg/m^3 (40 ppm) (STEL). La production du 2-nitropropane s'effectue en circuit fermé et en général, le personnel n'est guère exposé; toutefois dans certaines industries (peinture, imprimerie ou extraction par solvant), il est arrivé que des travailleurs soient exposés à des concentrations dépassant largement les limites d'exposition professionnelle. C'est ainsi que des concentrations atteignant 6 g/m^3 (1640 ppm) dans l'air ont été enregistrées lors du remplissage de fûts.

5. Cinétique et métabolisme

Le 2-nitropropane est principalement résorbé au niveau des poumons. Chez l'animal de laboratoire, on a montré qu'il était rapidement absorbé non seulement à ce niveau mais également au niveau de la cavité péritonéale et des voies digestives. On est mal renseigné sur son absorption percutanée. Quant aux données concernant sa distribution dans l'organisme du rat, elles sont quelque peu contradictoires. Le 2-nitropropane est rapidement métabolisé, essentiellement sous forme d'acétone et de nitrite. Il se forme peut-être aussi un peu d'alcool isopropylique. Après injection par voie intrapéritonéale, le 2-nitropropane et ses métabolites carbonés se concentrent d'abord dans les graisses, puis dans la moelle osseuse ainsi que dans les surrénales et les autres organes internes; après inhalation, ils se concentrent dans le foie et les reins, mais relativement peu dans les graisses. Il est possible que plusieurs systèmes enzymatiques interviennent dans ce métabolisme et les vitesses, de même que les voies de métabolisation, varient selon les espèces. Le 2-nitropropane et ses métabolites carbonés disparaissent rapidement de l'organisme par métabolisation, exhalation ou excrétion dans les urines et les matières fécales. On manque de données satisfaisantes sur la distribution et l'excrétion de la fraction nitrée de ces métabolites.

6. Effets sur les mammifères de laboratoire et les systèmes *in vitro*

La toxicité aiguë du 2-nitropropane pour les mammifères est modérée. Les mâles sont plus sensibles que les femelles, tout au moins en ce qui concerne le rat, et l'expérience montre que la sensibilité varie largement d'une espèce à l'autre. La CL_{50} (concentration produisant une mortalité de 50 % en 14 jours) a été de 1,5 g/m^3 (400 ppm) pour les rats mâles et de 2,6 g/m^3 (720 ppm) pour les rats femelles. Il semble que la mortalité soit associée principalement aux effets narcotiques, mais les mammifères exposés à des concentrations d'au moins 8,4 g/m^3 (2300 ppm) pendant une heure ou davantage ont présenté des anomalies anatomopathologiques graves, notamment des lésions hépatocellulaires, un oedème du poumon et des hémorragies.

Il est indiscutable que le 2-nitropropane est cancérogène pour le rat. L'exposition de rats pendant de longues durées à du 2-nitropropane par voie respiratoire à raison de 0,36 g/m^3 (100 ppm) (pendant 18 mois à raison de sept heures par jour et

cinq jours par semaine) a causé des lésions destructrices au niveau du foie, et en particulier des carcinomes hépatocellulaires chez certains rats mâles. A la concentration de 0,75 g/m^3 (207 ppm) les lésions étaient encore plus graves, avec une forte incidence de carcinomes hépatocellulaires à survenue plus rapide. L'administration chronique de doses modérées par voie orale a également provoqué une surincidence de carcinomes hépatocellulaires. Toutefois, l'inhalation prolongée par des rats de 2-nitropropane aux doses respectives de 91 ou 98,3 mg/m^3 (25 ou 27 ppm) n'a pas provoqué de lésions décelables. L'exposition de souris et de lapins à des concentrations de 2-nitropropane capables de provoquer des carcinomes hépatocellulaires chez le rat n'a guère eu d'effets chez ces animaux, mais il est vrai que les études en question étaient trop limitées pour qu'on puisse exclure totalement un effet cancérogène du 2-nitropropane chez ces deux espèces. Le 2-nitropropane a légèrement retardé le développement foetal des rats mais les données relatives à l'embryotoxicité, à la tératogénicité et à la toxicité du 2-NP pour la fonction de reproduction restent très fragmentaires. Le produit s'est révélé fortement génotoxique pour les hépatocytes de rats tant *in vivo* qu'*in vitro*; en revanche aucune génotoxicité sensible n'a été observée au niveau des autres organes chez le rat ou sur des lignées cellulaires d'origine extrahépatique, en l'absence d'activation métabolique exogène. On a également montré que le 2-nitropropane était mutagène chez les bactéries en présence ou en l'absence d'activation métabolique exogène.

7. Effets sur l'homme

L'exposition humaine à de fortes concentrations de 2-nitropropane est largement, voire totalement d'origine professionnelle. A concentration élevée, le 2-nitropropane présente une forte toxicité aiguë et il a provoqué des accidents mortels dans l'industrie - encore qu'on ignore la valeur exacte de cette concentration, sauf dans un cas où on a pu estimer l'exposition à 2184 mg/m^3, soit 600 ppm. Les premiers symptômes consistaient en céphalées, nausées, somnolence, vomissements, diarrhées et douleurs. Malgré une amélioration temporaire de l'état général, la mort est quelquefois survenue dans les 4 à 26 jours suivant l'exposition. La cause initiale de la mort était une insuffisance hépatique à laquelle s'ajoutaient un oedème du poumon, des hémorragies des voies digestives et une insuffisance respiratoire et rénale. A des doses évaluées à 73-164 mg/m^3 (20 à 45 ppm) on a constaté que l'exposition professionnelle

provoquait des nausées et une perte d'appétit pouvant persister plusieurs heures après le départ du lieu de travail, aucun effet indésirable n'étant observé après exposition à des doses de 36,4 à 109 mg/m^3 (10 à 30 ppm) (moins de quatre heures par jour pendant une durée inférieure ou égale à trois jours par semaine).

Malgré l'insuffisance des données disponibles, rien n'indique qu'une exposition professionelle de longue durée au 2-nitropropane aux concentrations généralement présentes sur les lieux de travail puisse provoquer des cancers du foie ou d'autres organes, ni plus généralement des effets indésirables à longue échéance.

8. Effets sur les autres organismes au laboratoire et dans leur milieu naturel

Les quelques études effectuées sur des microorganismes, des invertébrés et des poissons montrent que le 2-nitropropane est peu toxique pour les organismes non mammaliens.

RESUMEN

1. Propiedades y métodos analíticos

El 2-nitropropano (2-NP) es un líquido incoloro y oleoso de olor ligero. Es inflamable, moderadamente volátil, y estable en condiciones normales. Es sólo ligeramente hidrosoluble pero miscible con numerosos líquidos orgánicos, y es un excelente disolvente para muchos tipos de compuestos orgánicos. Existen métodos analíticos adecuados para identificar y medir el 2-NP en concentraciones ambientales. Los métodos de uso corriente son la cromatografía de gases y un detector de ionización de llama o de captura electrónica; también se usa la cromatografía líquida de alto rendimiento con detector de ultravioleta. Para medirlo en el aire, primero es necesario capturarlo y concentrarlo en un sorbente sólido.

2. Usos y fuentes de exposición

2.1 Producción

No se dispone de cifras recientes de producción mundial. En 1977, la producción en los Estados Unidos fue de aproximadamente 13 600 toneladas. Actualmente, el 2-NP se fabrica en dos empresas estadounidenses y una francesa. Se origina por mecanismos naturales como trazas en la combustión del tabaco y de otras sustancias orgánicas ricas en nitratos, pero nada indica que se origine en procesos biológicos.

2.2 Usos y pérdidas al medio ambiente

El 2-NP se utiliza como disolvente, principalmente en mezclas, y tiene numerosas aplicaciones industriales como disolvente para tintas de impresión, pinturas, barnices, adhesivos y otros revestimientos como los de recipientes de bebidas. Se ha utilizado asimismo como disolvente para separar sustancias estrechamente relacionadas como ácidos grasos, como intermediario en síntesis químicas, y como aditivo en combustibles. Las pérdidas al medio ambiente ingresan principalmente en el aire y se deben sobre todo a la evaporación del disolvente a partir de superficies revestidas.

3. Transporte y distribución en el medio ambiente

El 2-NP parece tener gran movilidad en el medio ambiente natural. Dada su baja solubilidad en el agua, escasa absorción por el sedimento, reducida bioacumulación y facil evaporación a la atmósfera, se distribuye tanto en el aire como en el agua y no se acumula en ningún compartimento ambiental definido. La fotoabsorción ultravioleta del 2-NP se encuentra en la escala de frecuencias normales en el medio ambiente, por lo que es probable que la sustancia sea objeto de fotólisis lenta en la atmósfera. La biotransformación lenta del 2-NP a compuestos menos tóxicos también parece probable en los medios acuático y terrestre.

4. Niveles ambientales y exposición humana

La exposición de la población general al 2-NP parece ser muy baja y se debe al humo de cigarrillos (1,1 a 1,2 μg/cigarrillo), a los residuos en revestimientos, como los de las latas de bebidas, adhesivos y material impreso, y a los aceites vegetales fraccionados con esa sustancia. Se desconoce la exposición industrial a escala mundial, pero en los Estados Unidos parece limitarse al 0,02-0,19% de la población trabajadora. Los niveles de exposición de cierta importancia (exposición a 9,1 mg/m^3 (2,5 ppm) o más) en los Estados Unidos probablemente no afectan más que a unos 4000 trabajadores (aproximadamente 0,005% de la población trabajadora). Los límites de exposición ocupacional en el aire varían de un país a otro y van desde 3,6 mg/m^3 (1 ppm) (promedio ponderado en función del tiempo) a 146 mg/m^3 (40 ppm) (STEL). La fabricación del 2-NP es un proceso cerrado y entraña por lo general una exposición reducida de los trabajadores, pero algunos obreros de industrias como la pintura, la impresión y la extracción de disolventes se han visto expuestos en otras épocas a niveles muy superiores a los límites de exposición ocupacional. Durante ciertas operaciones industriales han llegado a registrarse concentraciones de hasta 6 g/m^3 (1640 ppm) en el aire.

5. Cinética y metabolismo

En el ser humano, la absorción de 2-NP se produce principalmente por los pulmones. En animales de experimentación, se ha demostrado que el 2-NP se absorbe rápidamente no sólo por vía pulmonar sino también a partir de la cavidad peritoneal y del tracto gastrointestinal. No se dispone de

datos satisfactorios sobre la absorción por vía cutánea. La información sobre la distribución en la rata es ligeramente contradictoria. El 2-NP se metaboliza rápidamente, principalmente a acetona y nitrito. También puede formarse isopropil alcohol en pequeñas cantidades. Tras la inyección intraperitoneal, el 2-NP y sus metabolitos carbonados se concentran inicialmente en la grasa y después en la médula ósea, así como en las glándulas suprarrenales y otros órganos internos. Tras la inhalación, el 2-NP y sus metabolitos carbonados se concentran en el hígado y el riñón; la cantidad que se acumula en la grasa es relativamente pequeña. Varios sistemas enzimáticos diferentes pueden participar y existen diferencias de unas especies a otras en cuanto a la velocidad y las rutas metabólicas. El 2-NP y sus metabolitos carbonados desaparecen rápidamente del organismo por transformación metabólica, exhalación y excreción en orina y heces. No se dispone de datos satisfactorios sobre la distribución y la excreción de metabolitos que llevan el radical nitro.

1.6 *Efectos en mamíferos de laboratorio y sistemas* in vitro

El 2-NP tiene una toxicidad aguda moderada para los mamíferos. Los machos son más sensibles que las hembras, por lo menos en la rata, y la sensibilidad difiere ampliamente entre las especies que se han ensayado. La CL_{50} (concentración que causa una mortalidad del 50% en un plazo de 14 días) para la rata tras una exposición de 6 horas fue de 1,5 g/m^3 (400 ppm) en los machos y 2,6 g/m^3 (720 ppm) en las hembras. La letalidad parecía asociada principalmente a los efectos narcóticos, si bien los mamíferos expuestos a concentraciones de al menos 8,4 g/m^3 (2300 ppm) durante una hora o más mostraron alteraciones patológicas graves, entre ellas lesiones hepatocelulares, edema pulmonar y hemorragia.

Existen pruebas claras de que el 2-NP es carcinogénico en la rata. La exposición prolongada de ratas por inhalación de 0,36 g/m^3 (100 ppm) durante 18 meses (7 h/día, 5 días/semana) indujo cambios destructivos en el hígado, inclusive carcinomas hepatocelulares en algunos machos. Una concentración de 0,75 g/m^3 (207 ppm) indujo lesiones más graves, entre ellas una elevada incidencia de carcinomas hepatocelulares, con más rapidez. La administración crónica de dosis orales moderadas indujo también un exceso de carcinomas hepatocelulares en ratas. En cambio, la inhalación prolongada de 91 o 98,3 mg/m^3 (25 ó 27

ppm) no produjo lesiones detectables en las ratas. La exposición de ratones y conejos a concentraciones de 2-NP que inducían carcinomas hepatocelulares en la rata tuvieron escaso efecto o ninguno, pero esos estudios eran demasiado limitados para descartar por completo la carcinogenicidad de la sustancia en ambas especies. El 2-NP retrasó ligeramente el desarrollo fetal en la rata, pero escasean los datos sobre embriotoxicidad, teratogenicidad y toxicidad reproductiva. Se observó que el 2-NP era sumamente genotóxico en hepatocitos de rata tanto *in vitro* como *in vivo*, pero no se observó genotoxicidad significativa en otros órganos de la rata ni en líneas celulares de origen extrahepático sin activación metabólica exógena. Se ha demostrado que el 2-NP es mutagénico en bacterias tanto en presencia como en ausencia de activación metabólica exógena.

7. Efectos en el ser humano

La exposición humana a concentraciones elevadas de 2-NP es en su mayor parte o totalmente de origen ocupacional. Las concentraciones elevadas (se desconocen los valores reales, si bien en un caso se calcularon en 2184 mg/m^3 (600 ppm)) producen toxicidad aguda y accidentes mortales en la industria. Entre los síntomas iniciales figuran dolores de cabeza, náuseas, mareos, vómitos, diarrea y dolores. Las víctimas a menudo mostraban una mejoría temporal, aunque en algunos casos sobrevino la muerte entre 4 y 26 días despues de la exposición. El fallo hepático fue la principal causa de muerte, con edema pulmonar, hemorragias gastrointestinales fallo respiratorio y renal como factores contribuyentes. La exposición ocupacional a niveles estimados en 73 a 164 mg/m^3 (20 a 45 ppm) indujo náuseas y pérdida de apetito, que persistieron durante varias horas tras abandonar el lugar de trabajo, mientras que la exposición ocupacional a niveles estimados en 36,4 a 109 mg/m^3 (10 a 30 ppm) (< de 4 h/día durante $\leq$ 3 días/semana) no produjo efectos nocivos detectables.

Aunque los datos disponibles son insuficientes, nada indica que la exposición ocupacional crónica al 2-NP en concentraciones normales en el lugar de trabajo induzca neoplasmas hepáticos o de otro tipo ni otros efectos adversos a largo plazo.

8. Efectos en otros organismos en el laboratorio y sobre el terreno

Los escasos estudios realizados en microorganismos, invertebrados y peces indican una baja toxicidad del 2-NP para organismos no mamíferos.

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