2-NITROPROPANE

Data were last reviewed in IARC (1982) and the compound was classified in *IARC Monographs* Supplement 7 (1987).

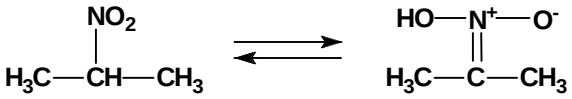
1. Exposure Data

1.1 Chemical and physical data

1.1.1 *Nomenclature*

Chem. Abstr. Serv. Reg. No.: 79-46-9
Chem. Abstr. Name: 2-Nitropropane
IUPAC Systematic Name: 2-Nitropropane
Synonyms: Dimethylnitromethane; isonitropropane

1.1.2 *Structural and molecular formulae and relative molecular mass*



$C_3H_7NO_2$ Relative molecular mass: 89.09

1.1.3 *Chemical and physical properties of the pure substance*

(*a*) *Description*: Colourless liquid (Lewis, 1993)
(*b*) *Boiling-point*: 120.2°C (Lide, 1997)
(*c*) *Melting-point*: –91.3°C (Lide, 1997)
(*d*) *Solubility*: Slightly soluble in water (1.7 mL/100 mL); miscible with many organic solvents (Budavari, 1996)
(*e*) *Vapour pressure*: 1.7 kPa at 20°C; relative vapour density (air = 1), 3.06 (WHO, 1992; Lewis, 1993)
(*f*) *Flash point*: 38°C, open cup (WHO, 1992)
(*g*) *Explosive limits*: Lower flammability limit, 2.6% by volume in air (WHO, 1992)
(*h*) *Conversion factor*: $mg/m^3 = 3.65 \times ppm$

1.2 Production and use

In 1977, production of 2-nitropropane in the United States was estimated to be 13 600 tonnes. 2-Nitropropane is reportedly produced by two companies in the United States and one company in France (WHO, 1992).

A major use of 2-nitropropane is as an industrial solvent. It is used in vinyl inks, generally at low concentrations, for printing, flexography and photogravure, and in adhesives and electrostatic paints (IARC, 1982; Markofsky, 1991). 2-Nitropropane, often mixed with alcohols, dissolves a large number of resins such as epoxy, polyurethane, polyester, vinyl, urea–formaldehyde and phenolic. These solvent–resin mixtures are used for coatings, such as for beverage cans (Markofsky, 1981; WHO, 1992). Minor uses of 2-nitropropane are as a solvent for chemical reactions, a processing solvent to separate natural products, an intermediate for the manufacture of several propane derivatives, a component of explosives and propellants, and in fuels for internal combustion engines (WHO, 1992).

1.3 Occurrence

1.3.1 *Occupational exposure*

According to the 1981–83 National Occupational Exposure Survey (NOES, 1997), as many as 10 000 workers in the United States were potentially exposed to 2-nitropropane (see General Remarks). Occupational exposures may occur in its production and use as a solvent.

1.3.2 *Environmental occurrence*

2-Nitropropane may enter the atmosphere during its manufacture and use as a solvent. A major contributor to these releases is evaporation of 2-nitropropane used as a solvent in printing ink and surface coatings (United States National Library of Medicine, 1997a; WHO, 1992). According to the United States Environmental Protection Agency Toxic Chemical Release Inventory, industrial releases of 2-nitropropane from manufacturing and processing facilities in the United States were approximately 211 000 kg in 1987 and 14 000 kg in 1995 to the atmosphere; 1860 kg in 1987 and 1360 kg in 1995 for water release; and 76 000 kg for 1987 and none for 1995 for underground release (United States National Library of Medicine, 1997b). There appear to be no reports of occurrence of 2-nitropropane in outdoor air or water away from areas of manufacture and use (WHO, 1992).

2-Nitropropane has been detected in cigarette smoke (IARC, 1986).

1.4 Regulations and guidelines

The American Conference of Governmental Industrial Hygienists (ACGIH) (1997) has recommended 36 mg/m^3 as the 8-h time-weighted average threshold limit value for occupational exposures to 2-nitropropane in workplace air. Similar values have been used as standards or guidelines in many countries (International Labour Office, 1991).

No international guideline for 2-nitropropane in drinking-water has been established (WHO, 1993).

2. Studies of Cancer in Humans

The only epidemiological study available was published as an abstract and was considered inadequate for evaluation (IARC, 1982).

3. Studies of Cancer in Experimental Animals

2-Nitropropane was tested for carcinogenicity in two experiments in rats by inhalation exposure. Hepatocellular carcinomas were produced in one experiment and an increased incidence of hepatocellular nodules in the other. An inhalation study in rabbits was considered to be inadequate for evaluation (IARC, 1982).

3.1 Oral administration

Rat: 2-Nitropropane (redistilled) was administered by gavage to weanling male Sprague-Dawley rats at a dose of 1 mmol/kg bw three times per week for 16 weeks. All surviving rats were killed at week 77. Benign liver tumours appeared in 4/22 treated animals versus 1/29 controls and malignant liver tumours occurred in 22/22 treated rats versus 0/29 controls ($p < 0.001$) (Fiala *et al*., 1987a).

3.2 Two-stage initiation/promotion models

Rat: Male and female Sprague-Dawley rats, four to six days of age, were exposed by whole-body inhalation to concentrations of 0, 25, 40, 50, 80 and 125 ppm [0, 91, 146, 182, 292 and 456 mg/m^3] 2-nitropropane (99% pure) for 6 h per day on five days per week for three weeks. One week later, a polychlorinated biphenyl (Clophen A50) was administered orally at a dose of 10 mg/kg bw twice per week for eight weeks. Thirteen weeks after the start of the experiment, the number of preneoplastic adenosine-5-triphosphatase-deficient foci in the liver was found to increase linearly with the exposure concentration, demonstrating the initiating activity of 2-nitropropane (Denk *et al*., 1990).

Male Wistar rats, three to four weeks of age, received six intraperitoneal injections of 25, 50 or 100 mg/kg bw 2-nitropropane (95% pure) every two days. Between the 42nd and 56th day of the experiment, 2-acetylaminofluorene (2-AAF) dissolved in corn oil was added to the diet at a concentration of 50 mg/kg diet (ppm). In the middle of the 2-AAF treatment period (on day 49), rats were subjected to partial hepatectomy. From day 56, phenobarbital sodium was added to the diet at a concentration of 500 ppm for two weeks. After 70 days of the experiment, rats were killed and the livers examined for γ-glutamyl-transpeptidase (γ-GT) and for glutathione *S*-transferase (GST) foci. The numbers of γ-GT-positive foci per cm^2 were 0.6, 3.7, 5.5 and 22.2 in the control, low-dose, mid-dose and high-dose groups, respectively. The numbers of GST-positive foci were 1.4, 10.8, 10.7 and 29.9 in the four groups, respectively (Astorg *et al*., 1994).

4. Other Data Relevant to an Evaluation of Carcinogenicity and its Mechanisms

4.1 Absorption, distribution, metabolism and excretion

4.1.1 *Humans*

No data were available to the Working Group.

4.1.2 *Experimental systems*

Nolan *et al.* (1982) administered 2-nitro[^{14}C]propane to rats by inhalation at levels of 73 or 562 mg/m^3 for 6 h. Over 40% of the administered dose was retained in the body and the bulk of the absorbed dose was rapidly metabolized and excreted. The elimination of total ^{14}C from the blood and by exhalation was biphasic and the two sets of parameters were broadly comparable at the two dose levels. The two elimination half-lives from blood were 71 min and 13.2 h at the high dose and 64 min and 16.4 h at the low dose, while for exhalation the corresponding values were 172 min and 36 h (high dose) and 354 min and 35 h (low dose). At the high dose, the elimination half-life of 2-nitropropane from blood was 48 min; the value could not be calculated at the low dose, since 2-nitropropane levels were 1/12th of those at the high dose and only two levels could be measured before the concentration fell below the detection limit. The blood levels of 2-nitropropane and ^{14}C at the end of the 6-h inhalation exposure at the high dose were 12 and nine times those after the low dose, values to be compared with the 7.5-fold difference between the doses. A 100% recovery of the absorbed dose was obtained in excretion balance studies conducted 48 h after the 6-h inhalation exposure. Some 10% of the dose was excreted in the urine, with a further 5% (high dose) or 10% (low dose) in the faeces. Fifty per cent of the dose was exhaled as $^{14}CO_2$ and 3% (low dose) or 22% (high dose) as 2-nitropropane. The balance of the dose (25%, low dose; 11%, high dose) was present in the carcass.

Suggestions about the metabolic pathway leading to $^{14}CO_2$ were provided by the work of Marker and Kulkarni (1985, 1986). They showed that the microsomal metabolism of 2-nitropropane in mice resulted in the release of nitrite in a cytochrome P450-dependent reaction. In contrast to earlier results in rats, enzymatic denitrification in mice did not require enzyme induction.

2-Nitropropane exists in equilibrium with its tautomer propane-2-nitronic acid, present in physiological media as the anion propane-2-nitronate. Dayal *et al.* (1991) have investigated the metabolism of both 2-nitropropane and propane-2-nitronate in mouse microsomes and found that the oxidative denitrification of propane-2-nitronate was 5–10 times more extensive than that of 2-nitropropane. Acetone formed by this reaction affords the source of $^{14}CO_2$ detected when 2-nitro[^{14}C]propane was administered *in vivo*. However, neither 2-nitropropane nor propane-2-nitronate was cytotoxic to mouse hepatocytes.

After administration of 2-nitropropane to rats, oxidative damage to DNA occurs, notably an increase in 8-hydroxy- and 8-aminodeoxyguanine (Fiala *et al.*, 1989). The

mechanism of this damage is hard to relate to the oxidation of 2-nitropropane (Bors *et al.*, 1993; Kohl *et al.*, 1995). Sodum *et al.* (1994) have advanced a novel pathway of metabolism for both 2-nitropropane and propane-2-nitronate in which an *N*-hydroxy form is *O*-sulfated, giving an amino radical and acetone. Damage to DNA and RNA was markedly inhibited by the sulfotransferase inhibitors pentachlorophenol and 2,6-dichloro-4-nitrophenol. However, the mechanisms of 2-nitropropane metabolism and associated DNA damage remain uncertain (Kohl *et al.*, 1995).

4.2 Toxic effects

4.2.1 *Humans*

An employee health examination including workers exposed to personal time-weighted average levels below 25 ppm [91 mg/m^3] 2-nitropropane revealed no adverse effects in the lung, liver, kidney, skin or haematopoietic and cardiovascular systems (Crawford *et al*., 1985).

Harrison *et al*. (1985, 1987) reported on two construction workers who were exposed to 2-nitropropane while applying epoxy resin coating. One man died 10 days after exposure from fulminant hepatitis, the other man had persistently elevated serum aminotransferase activity. Serum concentrations of 2-nitropropane on admission were 13 mg/L in the man who died and 8.5 mg/L in his co-worker.

4.2.2 *Experimental systems*

Dayal *et al*. (1989) treated BALB/c mice intraperitoneally with a single dose of 9 mmol/kg bw 2-nitropropane. In male mice, plasma activities of the hepatic enzymes sorbitol dehydrogenase, alanine aminotransferase and aspartate aminotransferase were significantly elevated, while doses of 6.7 mmol/kg bw were ineffective. In female mice, a dose of 6.7 mmol/kg bw was sufficient to cause hepatotoxicity. Histopathological evaluation revealed hepatic damage, particularly in the periportal region.

Griffin *et al*. (1981) exposed male and female Sprague-Dawley rats by inhalation to 25 ppm [91 mg/m^3] 2-nitropropane for 7 h per day on five days per week over a period of 22 months. Histopathological examination of all major organs did not show any lesions.

Cunningham and Matthews (1991) treated male Fischer 344 rats with 0.5, 1 or 2 mmol/kg bw 2-nitropropane daily for 10 days by gavage. At the higher dose levels, but not at 0.5 mmol/kg bw, increased hepatic DNA synthesis was found, together with moderate signs of cholestasis and hepatotoxicity.

Inhalation exposure of male Sprague-Dawley rats to 2-nitropropane at air concentrations of 100 ppm [365 mg/m^3] for 7 h per day on four consecutive days did not result in increased hepatic microsomal malonaldehyde content as a measure of lipid peroxidation, or increased levels of serum aspartate transferase or of glutamic oxaloacetic transaminase. Total hepatic glutathione was enhanced by 2-nitropropane treatment (Haas-Jobelius *et al*., 1992).

4.3 Reproductive and developmental effects

4.3.1 *Humans*

No data were available to the Working Group.

4.3.2 *Experimental systems*

Sprague-Dawley rats were treated intraperitoneally with 170 mg/kg bw per day on days 1–15 of gestation. The treatment resulted in reduced pre- and postimplantation survival and reduced fetal body weight or length. No signs of maternal toxicity or teratogenicity were observed (Hardin *et al*., 1981).

4.4 Genetic and related effects

4.4.1 *Humans*

No data were available to the Working Group.

4.4.2 *Experimental systems* (see Table 1 for references)

2-Nitropropane was mutagenic to bacteria both in the presence and in the absence of an exogenous metabolic system.

In vitro, in the absence of an exogenous metabolic system, 2-nitropropane induced unscheduled DNA synthesis in rat and mouse liver cells. It induced gene mutations in Chinese hamster cells and rat hepatoma cells in the absence of an exogenous metabolic system. In the absence of an exogenous metabolic system, 2-nitropropane induced micronuclei in three rat hepatoma cell lines but not in Chinese hamster cells.

In one study, 2-nitropropane induced unscheduled DNA synthesis *in vitro* in hepatocytes from three of six people. In human peripheral lymphocytes, 2-nitropropane induced sister chromatid exchanges and chromosomal aberrations in the presence of an exogenous metabolic system.

The genotoxic effects of 2-nitropropane have been reviewed (WHO, 1992). 2-Nitropropane is genotoxic to a wide range of organisms *in vitro* and *in vivo*. It induced DNA modifications (8-hydroxydeoxyguanosine and 8-aminodeoxyguanosine) in rat liver *in vivo* but not in the kidney. In one study, levels of 8-hydroxydeoxyguanosine in rabbit liver DNA were lower than in DNA from rat liver in animals treated with 2-nitropropane *in vivo*. In another study, 2-nitropropane induced DNA strand breaks in liver, but not in lung, kidney, bone marrow and brain of rats treated *in vivo*. DNA strand breaks and 8-hydroxydeoxyguanosine were detected, in a single study, in bone marrow of rats *in vivo*. It provoked unscheduled DNA synthesis in liver of rats treated *in vivo*. In single studies conducted *in vivo*, 2-nitropropane failed to induce micronuclei in the bone marrow of mice or rats, but did induce them in rat liver.

The production of oxygen free radicals by one-electron oxidation of the nitronate form (De Rycker & Halliwell, 1978; Porter & Bright, 1983; Kido & Soda, 1984) could explain the relatively high mutagenicity in the oxidant-sensitive *Salmonella typhimurium* strain TA102 and the production of 8-hydroxydeoxyguanosine in rat liver *in vivo*. Another modified deoxynucleoside, 8-aminodeoxyguanosine, has been identified in rat

Table 1. Genetic and related effects of 2-nitropropane

Test system	Result[a]		Dose[b] (LED or HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
SA0, *Salmonella typhimurium* TA100, reverse mutation	+	+	1410	Hite & Skeggs (1979)
SA0, *Salmonella typhimurium* TA100, reverse mutation	+	+	1270	Speck *et al.* (1982)
SA0, *Salmonella typhimurium* TA100, reverse mutation	+	+	1280	Haworth *et al.* (1983)
SA0, *Salmonella typhimurium* TA100, reverse mutation	+	+	2207	Fiala *et al.* (1987b)
SA0, *Salmonella typhimurium* TA100, reverse mutation	+	+	233	Göggelmann *et al.* (1988)
SA0, *Salmonella typhimurium* TA100, reverse mutation	+	+	1320	Conaway *et al.* (1991)
SA0, *Salmonella typhimurium* TA100, reverse mutation	+	NT	90	Kohl *et al.* (1994)
SA2, *Salmonella typhimurium* TA102, reverse mutation	+	+	1070	Fiala *et al.* (1987b)
SA2, *Salmonella typhimurium* TA102, reverse mutation	+	+	2640	Conaway *et al.* (1991)
SA2, *Salmonella typhimurium* TA102, reverse mutation	+	NT	90	Kohl *et al.* (1994)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	?	3850	Haworth *et al.* (1983)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	(+)	38150	Hite & Skeggs (1979)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	3850	Haworth *et al.* (1983)
SA9, *Salmonella typhimurium* TA98, reverse mutation	+	+	4200	Hite & Skeggs (1979)
SA9, *Salmonella typhimurium* TA98, reverse mutation	+	+	385	Speck *et al.* (1982)
SA9, *Salmonella typhimurium* TA98, reverse mutation	+	+	1280	Haworth *et al.* (1983)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	2140	Fiala *et al.* (1987b)
SA9, *Salmonella typhimurium* TA98, reverse mutation	+	+	233	Göggelmann *et al.* (1988)
SAS, *Salmonella typhimurium* TA92, reverse mutation	+	+	11450	Hite & Skeggs (1979)
URP, Unscheduled DNA synthesis, rat primary hepatocytes *in vitro*	+	NT	8.9	Davies *et al.* (1993)
URP, Unscheduled DNA synthesis, rat primary hepatocytes *in vitro*	+	NT	22	Kohl *et al.* (1994)
URP, Unscheduled DNA synthesis, rat primary hepatocytes *in vitro*	+	NT	0.89	Fiala *et al.* (1995)
UIA, Unscheduled DNA synthesis, mouse primary hepatocytes *in vitro*	+	NT	89	Davies *et al.* (1993)
G9H, Gene mutation, Chinese hamster lung V79 cells, *hprt* locus *in vitro*	+	NT	45	Roscher *et al.* (1990)

Table 1 (contd)

Test system	Result[a]		Dose[b] (LED or HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
G9H, Gene mutation, Chinese hamster lung V79 cells, *hprt* locus *in vitro*	+	NT	267	Haas-Jobelius *et al.* (1991)
GIA, Gene mutation, rat hepatoma H4IIEC3/G$^-$ cells, *hprt* locus *in vitro*	+[c]	NT	89	Roscher *et al.* (1990)
SIC, Sister chromatid exchange, Chinese hamster ovary cells *in vitro*	–	–	5000	Galloway *et al.* (1987)
MIA, Micronucleus test, H4IIEC3/G$^-$ rat hepatoma cell line *in vitro*	+[c]	NT	267	Roscher *et al.* (1990)
MIA, Micronucleus test, 2sFou rat hepatoma cell line *in vitro*	+[c]	NT	267	Roscher *et al.* (1990)
MIA, Micronucleus test, C_2Rev7 rat hepatoma cell line *in vitro*	+[c]	NT	267	Roscher *et al.* (1990)
MIA, Micronucleus test, Chinese hamster lung V79 cells *in vitro*	–	NT	891	Roscher *et al.* (1990)
MIA, Micronucleus test, Chinese hamster lung V79 cells *in vitro*	–	NT	445	Haas-Jobelius *et al.* (1991)
CIC, Chromosomal aberrations, Chinese hamster ovary cells *in vitro*	–	–	5000	Galloway *et al.* (1987)
UIH, Unscheduled DNA synthesis, human primary hepatocytes *in vitro*	(+)	NT	89	Davies *et al.* (1993)
SHL, Sister chromatid exchange, human lymphocytes *in vitro*	–	+	668	Bauchinger *et al.* (1987)
SHL, Sister chromatid exchange, human lymphocytes *in vitro*	–	+	7120	Göggelmann *et al.* (1988)
CHL, Chromosomal aberrations, human lymphocytes *in vitro*	–	+	5345	Bauchinger *et al.* (1987)
CHL, Chromosomal aberrations, human lymphocytes *in vitro*	–	+	7120	Göggelmann *et al.* (1988)
DVA, 8-Hydroxydeoxyguanosine in Sprague-Dawley rat liver DNA *in vivo*	+		100 ip × 1	Fiala *et al.* (1989)
DVA, 8-Hydroxydeoxyguanosine in Sprague-Dawley rat liver DNA *in vivo*	+		100 ip × 1	Guo *et al.* (1990)
DVA, 8-Hydroxydeoxyguanosine in Sprague-Dawley rat kidney DNA *in vivo*	–		100 ip × 1	Guo *et al.* (1990)
DVA, DNA strand breaks, Sprague-Dawley rat liver *in vivo*	+		45 po × 1	Robbiano *et al.* (1991)
DVA, DNA strand breaks, Sprague-Dawley rat lung, kidney, bone marrow and brain *in vivo*	–		713 po × 1	Robbiano *et al.* (1991)
DVA, 8-Hydroxydeoxyguanosine in Wistar rat liver DNA *in vivo*	+		80 ip × 1	Adachi *et al.* (1993)

Table 1 (contd)

Test system	Result[a]		Dose[b] (LED or HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
DVA, 8-Amino- and 8-hydroxydeoxyguanosine in Sprague-Dawley rat liver DNA *in vivo*	+		100 ip × 1	Fiala *et al.* (1993)
DVA, 8-Amino- and 8-hydroxydeoxyguanosine in New Zealand White rabbit liver DNA *in vivo*	(+)		100 ip × 1	Fiala *et al.* (1993)
DVA, 8-Hydroxydeoxyguanosine in Fischer 344 rat liver DNA *in vivo*	+		100 ip × 1	Hasegawa *et al.* (1995)
DVA, 8-Aminodeoxyguanosine in Fischer 344 rat liver DNA *in vivo*	+		100 ip × 1	Sodum *et al.* (1993)
DVA, 8-Amino- and 8-hydroxydeoxyguanosine in Fischer 344 rat liver DNA *in vivo*	+		100 ip × 1	Sodum *et al.* (1994)
DVA, 8-Hydroxydeoxyguanosine in Fischer 344 rat liver DNA *in vivo*	+		100 ip × 1	Takagi *et al.* (1995)
DVA, DNA strand breaks (comet assay), Wistar rat bone-marrow DNA *in vivo*	+		100 ip × 1	Deng *et al.* (1997)
DVA, 8-Hydroxydeoxyguanosine in Wistar rat bone-marrow DNA *in vivo*	+		100 ip × 1	Deng *et al.* (1997)
DVA, 8-Hydroxydeoxyguanosine in Fischer 344 rat liver DNA *in vivo*	+		100 ip × 1	Fiala *et al.* (1997)
UPR, Unscheduled DNA synthesis, Sprague-Dawley rat hepatocytes *in vivo*	+		50 po × 1	George *et al.* (1989)
MVM, Micronucleus test, CD-1 mouse bone-marrow cells *in vivo*	–		300 po × 2	Hite & Skeggs (1979)
MVM, Micronucleus test, (101/E1 × C3H/E1)F_1 mouse bone-marrow cells *in vivo*	–		300 po × 1	Kliesch & Adler (1987)
MVR, Micronucleus test, Sprague-Dawley rat hepatocytes *in vivo*	+		25 po × 1	George *et al.* (1989)
MVR, Micronucleus test, Sprague-Dawley rat bone-marrow cells *in vivo*	–		300 po × 1	George *et al.* (1989)
8-Hydroxyguanosine in Sprague-Dawley rat liver RNA *in vivo*	+		100 ip × 1	Fiala *et al.* (1989)
8-Hydroxyguanosine in Sprague-Dawley rat liver and kidney RNA *in vivo*	+		100 ip × 1	Guo *et al.* (1990)
8-Amino- and 8-hydroxyguanosine in Sprague-Dawley rat liver RNA *in vivo*	+		100 ip × 1	Fiala *et al.* (1993)

Table 1 (contd)

Test system	Result[a]		Dose[b] (LED or HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
8-Amino- and 8-hydroxyguanosine in New Zealand White rabbit liver RNA *in vivo*	(+)		100 ip × 1	Fiala *et al.* (1993)
8-Aminoguanosine in Fischer 344 rat liver RNA *in vivo*	+		100 ip × 1	Sodum *et al.* (1993)
8-Amino- and 8-hydroxyguanosine in Fischer 344 rat liver RNA *in vivo*	+		100 ip × 1	Sodum *et al.* (1994)
8-Hydroxyguanosine in Fischer 344 rat liver RNA *in vivo*	+		100 ip × 1	Fiala *et al.* (1997)

[a] +, positive; (+), weak positive; –, negative; NT, not tested; ?, inconclusive

[b] LED, lowest effective dose; HID, highest ineffective dose; in-vitro tests, μg/mL; in-vivo tests, mg/kg bw/day; ip, intraperitoneal; po, oral

[c] Cells pre-incubated for 24 h with 2 μM dexamethasone, an inducer of liver-specific cytochrome P450 isoforms; results were negative without this pretreatment.

liver DNA following treatment with 2-nitropropane *in vivo* (Sodum *et al*., 1993, 1994) and in rat hepatocytes treated *in vitro* (Davies *et al*., 1993).

4.4.3 *Mechanistic considerations*

Nitroalkanes are acidic compounds; the dissociation of a proton from a nitroalkane produces the nitroalkane anion, or nitronate, whose chemical and physical properties differ from those of the parent nitroalkane. The nitronate form of 2-nitropropane is more mutagenic in *S. typhimurium* TA100 and TA102 than is the neutral parent compound (Fiala *et al*., 1987b; Dayal *et al*., 1989; Kohl *et al*., 1994), suggesting that propane 2-nitronate may act as an intermediate in the mechanism by which 2-nitropropane exerts its genotoxic and carcinogenic effects. This hypothesis is supported by studies indicating that both bacterial mutagenicity and induction of unscheduled DNA synthesis in rat hepatocytes are decreased by conditions (low pH or deuteration of the secondary carbon atom) that limit formation of the nitronate tautomer, and that the tautomerization of 2-nitropropane can be influenced by hepatic enzymes (Kohl *et al*., 1994).

It has been proposed that 8-aminodeoxyguanosine is formed from the nitronate tautomer of 2-nitropropane either by base nitrosation followed by reduction, or via an enzyme-mediated conversion of the nitronate anion to hydroxylamine-*O*-sulfonate or acetate, which yields the highly reactive nitrenium ion NH_2^+ (Sodum *et al*., 1993). Sodum *et al*. (1994) have provided evidence for the activation of 2-nitropropane to an aminating species by rat liver aryl sulfotransferase *in vitro* and *in vivo*. Pretreatment of rats with the aryl sulfotransferase inhibitors pentachlorophenol or 2,6-dichloro-4-nitrophenol significantly decreased the levels of nucleic acid modifications produced in the liver by 2-nitropropane treatment. Partially purified rat liver aryl sulfotransferase activated 2-nitropropane and its nitronate at neutral pH to a reactive species that aminated guanosine at the C^8 position. This activation was dependent on the presence of the enzyme, its specific cofactor adenosine 3′-phosphate 5′-phosphosulfate, and mercaptoethanol. It was inhibited by 2,6-dichloro-4-nitrophenol.

5. Summary of Data Reported and Evaluation

5.1 Exposure data

2-Nitropropane is produced in low volume and occupational exposures occur primarily in its production and use as a solvent in inks, adhesives, paints and coatings. Exposures of the general population may occur in ambient air and water near industrial sites manufacturing or using 2-nitropropane, in cigarette smoke, and possibly from its solvent uses.

5.2 Human carcinogenicity data

No adequate epidemiological data were available to the Working Group.

5.3 Animal carcinogenicity data

2-Nitropropane was tested for carcinogenicity in one experiment in rats by oral administration and two experiments in rats by inhalation exposure. It induced benign and malignant liver tumours following oral administration and hepatocellular carcinomas in one inhalation experiment and an increased incidence of hepatocellular nodules in the other. 2-Nitropropane showed initiating activity in rat liver in two experiments.

5.4 Other relevant data

Nitropropane shows mainly hepatotoxicity in rats.

It is mutagenic in a wide variety of in-vitro and in-vivo systems by a direct action. It leads to formation of 8-hydroxydeoxyguanosine in DNA *in vivo*.

5.5 Evaluation

There is *inadequate evidence* for the carcinogenicity of 2-nitropropane in humans.

There is *sufficient evidence* in experimental animals for the carcinogenicity of 2-nitropropane.

Overall evaluation

2-Nitropropane is *possibly carcinogenic to humans (Group 2B)*.

6. References

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