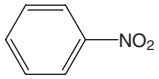
Nitrobenzene
CAS No. 98-95-3

Reasonably anticipated to be a human carcinogen
First Listed in the *Eleventh Report on Carcinogens* (2004)



Carcinogenicity

Nitrobenzene is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity in experimental animals. The carcinogenicity of nitrobenzene was evaluated in male and female mice ($B6C3F_1$), male rats of two strains (F344/N and Sprague-Dawley) and in female rats of one strain (F344/N). When administered to mice and rats by inhalation, nitrobenzene caused significantly increased incidences of tumors at multiple tissue sites in both species. Exposure to nitrobenzene caused lung and thyroid tumors in male and mammary gland tumors in female $B6C3F_1$ mice (Cattley *et al.* 1994). Exposure to nitrobenzene caused liver tumors in males of both strains, kidney tumors in F344/N males, and endometrial tumors in females. In addition, marginal increases in the incidences of liver tumors in the female mice and female rats and thyroid tumors in male F344/N rats were observed with increasing nitrobenzene exposure level (Cattley *et al.* 1994).

Only one study evaluating the possible relationship between human cancer and exposure to nitrobenzene was found in the literature; a case-control study of children whose fathers were occupationally exposed to nitrobenzene. Paternal exposure was associated with a non-statistically significant increase in the risk of childhood brain cancer. This risk estimate was based on a small number of cancer patients whose fathers had been exposed to nitrobenzene (Wilkins and Sinks 1990). The data are insufficient for evaluation of nitrobenzene's carcinogenicity in humans.

Additional Information Relevant to Carcinogenicity

Nitrobenzene did not cause mutations in bacteria, with or without metabolic activation (addition of rodent liver microsomes to simulate mammalian metabolism of the test substance). Nitrobenzene did not cause genetic damage in most mammalian test systems (IARC 1996). It did not cause unscheduled DNA synthesis (a DNA repair response) in cultured human or rat hepatocytes (liver cells) (Butterworth *et al.* 1989). Inhalation exposure of rats to nitrobenzene did not cause sister chromatid exchange in lymphocytes (white blood cells) from the spleen or peripheral (circulating) blood, chromosomal aberrations (changes in chromosome number or structure) in peripheral blood lymphocytes, or unscheduled DNA synthesis in hepatocytes (IARC 1996). However, in humans, inhalation exposure to nitrobenzene did cause chromosomal aberrations in peripheral blood lymphocytes (Huang *et al.* 1995, Huang *et al.* 1996).

Nitrobenzene is absorbed dermally and by inhalation in both humans and laboratory animals, and its metabolism appears to be similar in humans and animals. Nitrobenzene metabolites are excreted primarily in the urine. Two pathways for nitrobenzene metabolism have been proposed: (1) reduction of the nitro group to form aniline, followed by ring oxidation to form aminophenols, which can conjugate with glucuronide or sulfate, and (2) ring oxidation to form nitrophenols, which can conjugate with glucuronide or sulfate (Rickert 1987). Nitrobenzene can be reduced to aniline under anaerobic conditions (in the absence of oxygen, by bacteria in the intestine) or aerobic conditions (in the presence of oxygen, in the microsomes of mammalian cells). The former is more likely to occur when nitrobenzene is ingested, and the latter when nitrobenzene is inhaled. Reduction of nitrobenzene to aniline appears to be an important step in development of methemoglobinemia (a form of anemia) observed in humans and experimental animals exposed to nitrobenzene (IARC 1996, Holder 1999, NTP 2002).

The mechanism by which nitrobenzene causes cancer has not been determined. Nitrobenzene is structurally related to other aromatic nitro and amino compounds, including several nitroarenes listed in this report as *reasonably anticipated to be human carcinogens* and classified by the International Agency for Research on Cancer as possibly carcinogenic to humans (Group 2B) (IARC 1989).

Properties

Nitrobenzene is an aromatic nitro compound with a molecular weight of 123.1. It occurs as a colorless to pale yellow, oily liquid or as greenish-yellow crystals, with an odor resembling that of bitter almonds. It melts at 5.8°C, boils at 210.8°C, and has a density of 1.2 g/cm^3 at 20°C. Its vapor pressure is 0.15 mm Hg at 20°C and 0.245 mm Hg at 25°C, and its vapor density is 4.1. Nitrobenzene is moderately soluble in water (1.9 g/L at 20°C) and soluble in acetone, benzene, diethyl ether, and ethanol. The log octanol-water partition coefficient is 1.85. Though stable under normal laboratory conditions, nitrobenzene is combustible (with a flash point of 88°C) and reacts explosively when heated with concentrated alkalies, nitric acid, sulfuric acid, aluminum chloride and phenol, aniline, or oxidants. Toxic combustion products include nitrogen oxides (IARC 1996, HSDB 2003).

Use

Most nitrobenzene (97%) is used in the manufacture of aniline (IARC 1996, HSDB 2003). Miscellaneous uses include the manufacture of benzidine, quinoline, azobenzene, pyroxylin compounds, isocyanates, pesticides, rubber chemicals, pharmaceuticals, and dyes such as nigrosines and magenta. Nitrobenzene is found in soaps and shoe and metal polishes and is used as a solvent for cellulose ester, in modifying esterification of cellulose acetate, and in refining lubricating oils (HSDB 2003). Nitrobenzene also is used as a solvent in petroleum refining and the synthesis of other organic compounds, such as acetaminophen (ATSDR 1990).

Production

Nitrobenzene is produced in a continuous process by the direct nitration of benzene (IARC 1996). The demand for nitrobenzene and its U.S. production have increased steadily from 73,000 metric tons (161 million pounds) in 1960 to about 1,080,000 metric tons (2,381 million pounds) by 2000 (IARC 1996, Chinn *et al.* 2001). In 1995, nitrobenzene ranked 49th in volume among chemicals produced in the United States (Kirschner 1996). In 2003, there were five U.S. producers and 24 U.S. suppliers of nitrobenzene (ChemSources 2003, SRI 2003). Imports and exports of nitrobenzene are reported to be negligible (ATSDR 1990, HSDB 2003).

Exposure

The general public potentially is exposed to nitrobenzene in the environment through inhalation of ambient air, ingestion of water, or dermal contact with products or water containing nitrobenzene. Two surveys of the air, one of almost 600 urban and suburban sites in the United States and one of more than 700 U.S. sites, reported mean concentrations of nitrobenzene to be 0.17 ppb and 0.117 ppb, respectively (ATSDR 1990, HSDB 2003). In a survey of 862 hazardous waste sites, nitrobenzene was detected in groundwater at three sites, at a geometric mean concentration of 1.4 ng/L, but was not detected in surface-water samples from any of the 862 sites (ATSDR 1990).

Occupational exposure to nitrobenzene generally is by inhalation of the vapor or dermal contact with the vapor or liquid. The most recent information available for occupational exposures is from the National Institute of Occupational Safety and Health's National Occupational Exposure Survey, conducted from 1981 to 1983, which estimated that 5,080 employees (including 475 women) potentially were exposed to nitrobenzene (IARC 1996, HSDB 2003). Direct release of nitrobenzene

to air during its manufacture is minimized by passage of contaminated air through activated charcoal. Most (97% to 98%) of the nitrobenzene produced is retained in closed systems for use in synthesis of aniline and other substituted nitrobenzenes and anilines, thus limiting its release into air (ATSDR 1990).

Regulations

EPA

Clean Air Act
- NESHAP: Listed as a Hazardous Air Pollutant (HAP)
- NSPS: Manufacture of substance is subject to certain provisions for the control of Volatile Organic Compound (VOC) emissions

Clean Water Act
- Effluent Guidelines: Listed as a Toxic Pollutant
- Water Quality Criteria: Based on fish/shellfish and water consumption = 17 µg/L; based on fish/shellfish consumption only = 690 µg/L

Comprehensive Environmental Response, Compensation, and Liability Act
- Reportable Quantity (RQ) = 1,000 lb

Emergency Planning and Community Right-To-Know Act
- Toxics Release Inventory: Listed substance subject to reporting requirements
- Reportable Quantity (RQ) = 1,000 lb
- Threshold Planning Quantity (TPQ) = 10,000 lb

Resource Conservation and Recovery Act
- Listed Hazardous Waste: Waste codes in which listing is based wholly or partly on substance - U169, F004, K083, K103, K104
- Characteristic Toxic Hazardous Waste: TCLP Threshold = 2.0 mg/L
- Listed as a Hazardous Constituent of Waste

OSHA

Permissible Exposure Limit (PEL) = 1 ppm (5 mg/m^3)

Guidelines

ACGIH

Threshold Limit Value - Time-Weighted Average Limit (TLV-TWA) = 1 ppm

NIOSH

Recommended Exposure Limit (REL) = 1 ppm (5 mg/m^3)

Immediately Dangerous to Life and Health (IDLH) = 200 ppm

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