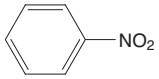
Nitrobenzene

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 from studies in experimental animals.

Cancer Studies in Experimental Animals

Exposure to nitrobenzene by inhalation caused tumors at numerous tissue sites in mice and rats. In mice, inhalation exposure to nitrobenzene caused benign and malignant lung tumors (alveolar/bronchiolar adenoma and carcinoma) and benign thyroid-gland tumors (follicular-cell adenoma) in males and benign mammary-gland tumors (adenocarcinoma) in females. In rats, it caused benign liver tumors (hepatocellular adenoma) in males of both strains tested, kidney tumors (renal adenoma) in males of one strain, and endometrial tumors (stromal polyps) in females. In addition, the incidences of benign liver tumors in female mice and rats and benign thyroid-gland tumors in male rats of one strain were marginally increased with increasing nitrobenzene exposure level (Cattley *et al.* 1994).

Cancer Studies in Humans

The data available from epidemiological studies are inadequate to evaluate the relationship between human cancer and exposure specifically to nitrobenzene. The only relevant study found was a case-control study of children whose fathers were occupationally exposed to nitrobenzene. Paternal exposure was associated with a statistically nonsignificant increase in the risk of childhood brain cancer, based on a small number of cancer patients whose fathers had been exposed to nitrobenzene (Wilkins and Sinks 1990).

Studies on Mechanisms of Carcinogenesis

Nitrobenzene did not cause mutations in bacteria, with or without mammalian metabolic activation, or genetic damage in most mammalian test systems (IARC 1996). It did not cause unscheduled DNA synthesis in cultured human or rat hepatocytes (Butterworth *et al.* 1989). Inhalation exposure of rats to nitrobenzene did not cause sister chromatid exchange in lymphocytes in the spleen or peripheral blood, chromosomal aberrations 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, 1996).

Nitrobenzene is absorbed dermally and by inhalation in both humans and experimental 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 (by bacteria in the intestine) or aerobic conditions (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 condition in which altered hemoglobin cannot carry oxygen) 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 the Report on Carcinogens as *reasonably anticipated to be human carcinogens* and classified by the International Agency for Research on Cancer as possibly carcinogenic to humans (IARC 1989).

Properties

Nitrobenzene is a nitro aromatic compound that exists at room temperature as a greenish-yellow or yellow oily liquid with the odor of bitter almonds. It is slightly soluble in water, soluble in acetone, and freely soluble in alcohol, benzene, ether, and oils. Nitrobenzene is stable when stored under normal temperatures and pressures, but has explosive potential when exposed to heat or flames, especially in the presence of strong alkalis or acids (IARC 1996). Physical and chemical properties of nitrobenzene are listed in the following table.

Property	Information
Molecular weight	123.1[a]
Specific gravity	1.2037 at 20°C/4°C[a]
Melting point	5.7°C[a]
Boiling point	210.8°C[a]
Log K_{ow}	1.85[a]
Water solubility	2.090 g/L at 25°C[b]
Vapor pressure	0.245 mm Hg at 25°C[a]
Vapor density relative to air	4.1[a]

Sources: [a]HSDB 2009, [b]ChemIDplus 2009.

Use

Most nitrobenzene (97%) is used in the manufacture of aniline (IARC 1996, HSDB 2009). 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 2009). 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 increased steadily from 73,000 metric tons (161 million pounds) in 1960 to 1,390,000 metric tons (3,064 million pounds) by 2007 (IARC 1996, Bizzari and Kishi 2007). In 1995, nitrobenzene ranked 49th in volume among chemicals produced in the United States (Kirschner 1996). In 2009, there were 5 U.S. producers and 20 U.S. suppliers of nitrobenzene (ChemSources 2009, SRI 2009). Imports and exports of nitrobenzene are reported to be negligible (ATSDR 1990, HSDB 2009).

Exposure

The general population 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, one of nearly 600 urban and suburban sites in the United

States and one of more than 700 U.S. sites, reported mean concentrations of nitrobenzene in air to be 0.17 ppb and 0.117 ppb, respectively (ATSDR 1990, HSDB 2009). In a survey of 862 hazardous-waste sites, nitrobenzene was detected in groundwater at 3 sites, at a geometric mean concentration of 1.4 ng/L, but was not detected in surface-water samples from any site (ATSDR 1990).

Occupational exposure to nitrobenzene generally is by inhalation of the vapor or dermal contact with the vapor or liquid. The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 5,080 workers, including 475 women, potentially were exposed to nitrobenzene (IARC 1996, HSDB 2009). No more recent data on occupational exposure to nitrobenzene were found. 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

Coast Guard, Department of Homeland Security

Minimum requirements have been established for safe transport of nitrobenzene on ships and barges.

Department of Transportation (DOT)

Nitrobenzene is considered a hazardous material and marine pollutant, and special requirements have been set for marking, labeling, and transporting this material.

Environmental Protection Agency (EPA)

Clean Air Act

National Emission Standards for Hazardous Air Pollutants: Listed as a hazardous air pollutant.
New Source Performance Standards: Manufacture of nitrobenzene is subject to certain provisions for the control of volatile organic compound emissions.

Clean Water Act

Effluent Guidelines: Listed as a toxic pollutant.
Water Quality Criteria: Based on fish or shellfish and water consumption = 10 µg/L; based on fish or shellfish consumption only = 600 µg/L; based on organoleptic-effect criteria = 30 µg/L.
Designated a hazardous substance.

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

Characteristic Hazardous Waste: Toxicity characteristic leaching procedure (TCLP) threshold = 2.0 mg/L.
Listed Hazardous Waste: Waste codes for which the listing is based wholly or partly on the presence of nitrobenzene = U169, F004, K083, K103, K104.
Listed as a hazardous constituent of waste.

Occupational Safety and Health Administration (OSHA)

While this section accurately identifies OSHA's legally enforceable PELs for this substance in 2010, specific PELs may not reflect the more current studies and may not adequately protect workers.
Permissible exposure limit (PEL) = 1 ppm (5 mg/m^3).
Potential for dermal absorption.

Guidelines

American Conference of Governmental Industrial Hygienists (ACGIH)

Threshold limit value – time-weighted average (TLV-TWA) = 1 ppm (5 mg/m^3).
Potential for dermal absorption.

National Institute for Occupational Safety and Health (NIOSH)

Recommended exposure limit (REL) = 1 ppm (5 mg/m^3).
Immediately dangerous to life and health (IDLH) limit = 200 ppm.
Potential for dermal absorption.

References

ATSDR. 1990. *Toxicological Profile for Nitrobenzene*. Agency for Toxic Substances and Disease Registry. http://www.atsdr.cdc.gov/toxprofiles/tp140.html.

Bizzari SN, Kishi A. 2007. Nitrobenzene. In *Chemical Economics Handbook*. Menlo Park, CA: SRI Consulting. Online edition.

Butterworth BE, Smith-Oliver T, Earle L, Loury DJ, White RD, Doolittle DJ, *et al.* 1989. Use of primary cultures of human hepatocytes in toxicology studies. Cancer Res 49(5): 1075-1084.

Cattley RC, Everitt JI, Gross EA, Moss OR, Hamm TE Jr, Popp JA. 1994. Carcinogenicity and toxicity of inhaled nitrobenzene in B6C3F$_1$ mice and F344 and CD rats [published erratum appears in *Fundam Appl Toxicol* 1995 25(1):159]. *Fundam Appl Toxicol* 22(3): 328-340.

ChemIDplus. 2009. *ChemIDplus Advanced*. National Library of Medicine. http://chem.sis.nlm.nih.gov/chemidplus/chemid and select Registry Number and search on CAS number. Last accessed: 11/16/09.

ChemSources. 2009. *Chem Sources – Chemical Search*. Chemical Sources International. http://www.chemsources.com/chemonline.html and search on nitrobenzene. Last accessed: 11/16/09.

Holder JW. 1999. Nitrobenzene carcinogenicity in animals and human hazard evaluation. *Toxicol Ind Health* 15(5): 445-457.

HSDB. 2009. *Hazardous Substances Data Bank*. National Library of Medicine. http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB and search on CAS number. Last accessed: 11/16/09.

Huang Q, Wang L, Han S. 1995. The genotoxicity of substituted nitrobenzenes and the quantitative structure-activity relationship studies. *Chemosphere* 30(5): 915-923.

Huang QG, Kong LR, Liu YB, Wang LS. 1996. Relationships between molecular structure and chromosomal aberrations in *in vitro* human lymphocytes induced by substituted nitrobenzenes. *Bull Environ Contam Toxicol* 57(3): 349-353.

IARC. 1989. *Diesel and Gasoline Engine Exhausts and Some Nitroarenes*. IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans, vol. 46. Lyon, France: International Agency for Research on Cancer. 458 pp.

IARC. 1996. Nitrobenzene. In *Printing Processes, Printing Inks, Carbon Blacks and Some Nitro Compounds*. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, vol. 65. Lyon, France: International Agency for Research on Cancer. pp. 381-408.

Kirschner EM. 1996. Growth of top 50 chemicals slowed in 1995 from very high 1994 rate. *Chem Eng News* 74(15): 16-22.

NTP. 2002. *Report on Carcinogens Background Document for Nitrobenzene*. National Toxicology Program. http://ntp.niehs.nih.gov/ntp/newhomeroc/roc11/NBPub.pdf.

Rickert DE. 1987. Metabolism of nitroaromatic compounds. *Drug Metab Rev* 18(1): 23-53.

SRI. 2009. *Directory of Chemical Producers*. Menlo Park, CA: SRI Consulting. Database edition. Last accessed: 11/16/09.

Wilkins JR 3rd, Sinks T. 1990. Parental occupation and intracranial neoplasms of childhood: results of a case-control interview study. *Am J Epidemiol* 132(2): 275-292.