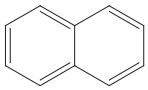
Naphthalene

CAS No. 91-20-3

Reasonably anticipated to be a human carcinogen

First listed in the *Eleventh Report on Carcinogens* (2004)



Carcinogenicity

Naphthalene is *reasonably anticipated to be a human carcinogen* based on sufficient evidence from studies in experimental animals.

Cancer Studies in Experimental Animals

Exposure of rats to naphthalene by inhalation caused nasal tumors, which are rare in this species. Two types of nasal tumor were observed: olfactory epithelial neuroblastoma of the nose, which is a highly malignant and extremely rare tumor of the lining of the nose, and respiratory epithelial adenoma, which also is rare (NTP 2000). At the time the National Toxicology Program study was published, neither type of tumor had been observed in the historical controls (299 males and females) in NTP two-year studies that used the same feed as the naphthalene bioassay. (As of 2010, no nasal tumors had been observed in 1,297 male or 1,247 female controls.) The incidence of neuroblastoma of the olfactory epithelium increased with increasing exposure level in both sexes and was significantly increased at the highest exposure level in females. Some of the neuroblastomas also invaded the brain. The incidence of respiratory epithelial adenoma was significantly increased in males, but not in females. These findings are supported by a significantly increased incidence of benign lung tumors (adenoma) in female B6C3F$_1$ mice exposed to naphthalene by inhalation (NTP 1992). The International Agency for Research on Cancer (2002) concluded that there was sufficient evidence for the carcinogenicity of naphthalene in experimental animals.

Cancer Studies in Humans

The data available from epidemiological studies are inadequate to evaluate the relationship between human cancer and exposure specifically to naphthalene. Two case-series studies of cancer in individuals exposed to naphthalene were identified; the first study reported cancer of the larynx and at other tissue sites among German workers occupationally exposed to naphthalene, and the second reported colorectal cancer among Africans who had used a naphthalene compound for medicinal purposes (Ajao *et al.* 1988, NTP 2002).

Studies on Mechanisms of Carcinogenesis

Naphthalene caused mutations in insects, but not in bacteria or cultured human lymphoblastoid cells (Sasaki *et al.* 1997, Grosovsky *et al.* 1999, NTP 2002). It caused other types of genetic damage in some but not all test systems. In newt larvae, naphthalene induced micronucleus formation. In cultured mammalian cells, it caused chromosomal aberrations, sister chromatid exchange, and formation of kinetochore-negative micronuclei, but did not cause DNA strand breaks, formation of kinetochore-positive micronuclei, or cell transformation. Inhalation exposure of rats to naphthalene caused oxidative stress and DNA damage in liver and brain tissue (IARC 2002, NTP 2002).

When administered to experimental animals dermally, orally, or by inhalation, naphthalene is rapidly absorbed and metabolized (NTP 2000). Evidence suggesting that naphthalene is absorbed in humans comes from studies of workers in a coke plant, which found that concentrations of naphthalene metabolites in the urine were significantly correlated with concentrations of naphthalene in personal air samples (Bieniek 1994, 1997). The first step in the metabolism of naphthalene is formation of naphthalene-1,2-oxide (as two stereoisomers, 1*R*,2*S*-oxide and 1*S*,2*R*-oxide) through the action of cytochrome P450 enzymes in the presence of the coenzyme NADPH. These oxides are metabolized further by three pathways: (1) hydration by epoxide hydrolases into dihydrodiols, (2) conjugation by glutathione transferases, and (3) spontaneous rearrangement into 1-naphthol and 2-naphthol, which are converted to naphthoquinones (Chichester *et al.* 1994, Shultz *et al.* 1999). Naphthalene is excreted in the urine as the unchanged parent compound or as metabolites, including 1-naphthol, 2-naphthol, naphthoquinones, dihydroxynaphthalenes, and conjugated forms, including glutathione, cysteine, glucuronic acid, and sulfate conjugates (NTP 2002).

The mechanism by which naphthalene causes cancer is unknown. A strong correlation has been observed between the rates of formation of the stereoisomer (1*R*,2*S*)-naphthalene oxide in various tissues and the selective toxicity of naphthalene to these tissues, suggesting that this metabolite may play a role in naphthalene's toxicity to the lung and other tissues (Buckpitt and Franklin 1989). Oxidative damage and DNA breakage, observed in rat liver and brain tissue, may contribute to naphthalene's toxicity and carcinogenicity.

Properties

Naphthalene is a polycyclic aromatic hydrocarbon that exists at room temperature as a white crystalline solid with an aromatic odor. It is insoluble in water but soluble in methanol, ethanol, benzene, toluene, olive oil, turpentine, chloroform, carbon tetrachloride, ether, hydronaphthalenes, fixed and volatile oils, and ethylene dichloride. It is stable in closed containers under normal temperatures and pressures (Akron 2009). Physical and chemical properties of naphthalene are listed in the following table.

Property	Information
Molecular weight	128.2
Density	1.162 g/cm^3 at 20°C
Melting point	80.2°C
Boiling point	217.9°C
Log K_{ow}	3.3
Water solubility	0.031 g/L at 25°C
Vapor pressure	0.085 mm Hg at 25°C
Vapor density relative to air	4.42

Source: HSDB 2009.

Use

The principal use of naphthalene in the United States is as an intermediate in the production of phthalic anhydride, which in turn is an intermediate in the production of phthalate plasticizers, pharmaceuticals, insect repellents, and other materials. Naphthalene has also been used as an intermediate in the production of 1-naphthyl-*N*-methylcarbamate insecticides, β-naphthol, synthetic leather-tanning chemicals, surfactants (e.g., naphthalene sulfonates), moth repellents, and toilet-bowl deodorizers (ATSDR 2005, HSDB 2009). In 1999, 59% of naphthalene was used for production of phthalic anhydride, 21% for production of surfactant and dispersant chemicals, 11% for production of insecticides, and 9% in moth repellents and for other purposes (CMR 1999). The Naphthalene Panel of the American Chemistry Council reported in 2002 that naphthalene was no longer used directly in tanneries, in the textile industry, or in the production of toilet-bowl deodorizers and that β-naphthol was not manufactured in the United States (ACC 2002).

Production

Naphthalene is produced from either coal tar (which contains approximately 10% naphthalene), by condensation and separation of coal tar from coke-oven gases, or from petroleum, by dealkylation of methylnaphthalenes. In the United States, most naphthalene was produced from petroleum through the 1980s. U.S. production of naphthalene peaked in 1968, at 900 million pounds (ATSDR 2003). By 2000, over 90% of the 235 million pounds produced was from coal tar (CEH 2000), a volume in the same range of 100 million to 250 million pounds reported to the U.S. Environmental Protection Agency (EPA) for combined U.S. production and imports of naphthalene in 2015 (EPA 2016). From 1989 to 1998, U.S. demand for naphthalene grew 0.5% per year, reaching 248 million pounds in 1999. Demand for naphthalene sulfonates, used primarily as superplasticizer additives to increase the flowability of concrete, grew steadily in the late 1990s (ChemExpo 1999). In 2017, U.S. naphthalene imports totaled 40.1 million pounds (USITC 2018). Exports were as high as 17.1 million gallons in 1998 (USITC 2009), but totaled only 60,000 gallons in 2017 (USITC 2018).

Exposure

The highest levels of exposure to naphthalene occur in the workplace. Workplace air concentrations of naphthalene have been measured in many studies and vary by industry. In the vulcanization step of tire manufacturing, naphthalene was measured at concentrations of up to 1.09 mg/m^3, resulting in an estimated daily intake of 0.0029 mg/kg of body weight (Durmusoglu 2007). A survey by the National Institute for Occupational Safety and Health in 1980 reported air concentrations of naphthalene as high as 10.2 µg/m^3 in an area sample and 19.3 µg/m^3 in a personal sample (ATSDR 2003). The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 112,700 workers potentially were exposed to naphthalene (NIOSH 1990). Workers identified by EPA as potentially exposed to naphthalene include beta-naphthol makers, celluloid makers, coal-tar workers, dye-chemical makers, fungicide makers, hydronaphthalene makers, moth-repellent workers, phthalic anhydride makers, smokeless-powder makers, tannery workers, textile-chemical workers, and aluminum reduction plant workers (EPA 1980). No more recent occupational exposure surveys were found. However, industry estimates in 2002 indicated that about 1,000 workers were employed by the largest U.S. tar-distillation and wood-preservation company and that fewer than 50 workers in the moth-repellent industry potentially were exposed to naphthalene (ACC 2002). These estimates did not include workers potentially exposed to naphthalene in production of phthalic anhydride and other uses.

Evidence that the U.S. general population is exposed to naphthalene comes from the 2013–2014 National Health and Nutrition Examination Survey, which detected the urinary naphthalene metabolites 1-hydroxynaphthalene and 2-hydroxynaphthalene in a sample of 2,640 individuals of all ages, both genders, and all race and ethnicity groups. The geometric mean concentrations were 1.52 µg/L for 1-hydroxynaphthalene and 4.22 µg/L for 2-hydroxynaphthalene (CDC 2018). The general population potentially is exposed to naphthalene through inhalation of ambient and indoor air. Accidental ingestion of household products containing naphthalene, mainly by children, has been reported. Dermal exposure to naphthalene may occur through handling or wearing of clothing stored with moth repellents containing naphthalene. The average daily intake of naphthalene from ambient air was estimated at 19 µg, based on an average naphthalene concentration of 0.95 µg/m^3 in urban and suburban air and an inhalation rate of 20 m^3/day (ATSDR 2003). According to EPA's Toxics Release Inventory, environmental releases of naphthalene have decreased annually since 1998, when almost 6 million pounds (2,700 metric tons) was released. In 2007, 983 facilities released over 2.7 million pounds (1,231 metric tons) of naphthalene, of which more than half was released to air (TRI 2009).

Regulations

Coast Guard (Dept. of Homeland Security)

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

Department of Transportation (DOT)

Naphthalene 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

Mobile Source Air Toxics: Listed as a substance for which regulations are to be developed.
National Emission Standards for Hazardous Air Pollutants: Listed as a hazardous air pollutant.

Clean Water Act

Effluent Guidelines: Listed as a toxic pollutant.
Designated a hazardous substance.

Comprehensive Environmental Response, Compensation, and Liability Act

Reportable quantity (RQ) = 100 lb.

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Listed substance subject to reporting requirements.

Resource Conservation and Recovery Act

Listed Hazardous Waste: Waste codes for which the listing is based wholly or partly on the presence of naphthalene = U165, F024, F025, F034, K001, K035, K087, K145.
Listed as a hazardous constituent of waste.

Occupational Safety and Health Administration (OSHA, Dept. of Labor)

While this section accurately identifies OSHA's legally enforceable PELs for this substance in 2018, specific PELs may not reflect the more current studies and may not adequately protect workers.
Permissible exposure limit (PEL) = 10 ppm (50 mg/m^3).

Guidelines

American Conference of Governmental Industrial Hygienists (ACGIH)

Threshold limit value – time-weighted average (TLV-TWA) = 10 ppm (50 mg/m^3).
Potential for dermal absorption.

National Institute for Occupational Safety and Health (NIOSH, CDC, HHS)

Recommended exposure limit (REL) = 10 ppm (50 mg/m^3).
Short-term exposure limit (STEL) = 15 ppm (75 mg/m^3).
Immediately dangerous to life and health (IDLH) limit = 250 ppm (1,250 mg/m^3).

References

ACC. 2002. Price CM, American Chemical Council, Arlington, VA, letter to Jameson CW, National Toxicology Program, Research Triangle Park, NC, 10/2/2002.

Ajao OG, Adenuga MO, Ladipo JK. 1988. Colorectal carcinoma in patients under the age of 30 years: A review of 11 cases. *J R Coll Surg Edinb* 33(5): 277-279.

Akron. 2009. *The Chemical Database*. The Department of Chemistry at the University of Akron. http://ull.chemistry.uakron.edu/erd and search on CAS number. Last accessed: 10/22/09.

ATSDR. 2005. *Toxicological Profile for Naphthalene, 1-Methylnaphthalene, and 2-Methylnaphthalene.* Agency for Toxic Substances and Disease Registry. http://www.atsdr.cdc.gov/toxprofiles/tp67.pdf.

Bieniek G. 1994. The presence of 1-naphthol in the urine of industrial workers exposed to naphthalene. *Occup Environ Med* 51(5): 357-359.

Bieniek G. 1997. Urinary naphthols as an indicator of exposure to naphthalene. *Scand J Work Environ Health* 23(6): 414-420.

Buckpitt AR, Franklin RB. 1989. Relationship of naphthalene and 2-methylnaphthalene metabolism to pulmonary bronchiolar epithelial cell necrosis. *Pharmacol Ther* 41(1-2): 393-410.

CDC. 2018. 1-Hydroxynaphthalene and 2-Hydroxynaphthalene. In *Fourth National Report on Human Exposure to Environmental Chemicals, Updated Tables, March 2018,* vol. 1. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention. pp. 593-604.

CEH. 2000. *Chemical Economics Handbook*, vol. 27. Menlo Park, CA: SRI International.

ChemSources. 2009. *Chem Sources - Chemical Search*. Chemical Sources International. http://www.chemsources.com/chemonline.html and search on naphthalene. Last accessed: 10/22/09.

Chichester CH, Buckpitt AR, Chang A, Plopper CG. 1994. Metabolism and cytotoxicity of naphthalene and its metabolites in isolated murine Clara cells. *Mol Pharmacol* 45(4): 664-672.

CMR. 2002. Chemical profile — naphthalene. *Chem Mark Rep* 5/31/99.

Durmusoglu E, Aslan S, Can E, Bulut Z. 2007. Health risk assessment of workers' exposure to organic compounds in a tire factory. *Hum Ecol Risk Assess* 13: 209-222.

EPA. 1980. *Ambient Water Quality Criteria for Naphthalene*. EPA 440-5-80-059. Washington, DC: U.S. Environmental Protection Agency.

EPA. 2016. *Chemical Data Reporting Summary: Naphthalene.* U.S. Environmental Protection Agency. https://chemview.epa.gov/chemview and search on CAS number or substance name and select Manufacturing, Processing, Use, and Release Data Maintained by EPA and select Chemical Data Reporting Details.

Grosovsky AJ, Sasaki JC, Arey J, Eastmond DA, Parks KK, Atkinson R. 1999. Evaluation of the potential health effects of the atmospheric reaction products of polycyclic aromatic hydrocarbons. *Res Rep Health Eff Inst* 84: 1-22.

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: 8/12/09.

IARC. 2002. Naphthalene. In *Traditional Herbal Medicines, Some Mycotoxins, Naphthalene and Styrene*. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, vol. 82. Lyon, France: International Agency for Research on Cancer. pp. 367-435.

NIOSH. 1990. *National Occupational Exposure Survey (1981-83)*. National Institute for Occupational Safety and Health. Last updated 7/1/90. http://www.cdc.gov/noes/noes1/49600sic.html.

NTP. 1992. *Toxicology and Carcinogenesis Studies of Naphthalene (CAS No. 91-20-3) in B6C3F$_1$ Mice (Inhalation Studies)*. Technical Report Series no. 410. Research Triangle Park, NC: National Toxicology Program. 172 pp.

NTP. 2000. *Toxicology and Carcinogenesis Studies of Naphthalene (CAS No. 91-20-3) in F344/N Rats (Inhalation Studies)*. Technical Report Series no. 500. Research Triangle Park, NC: National Toxicology Program. 176 pp.

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

Sasaki JC, Arey J, Eastmond DA, Parks KK, Grosovsky AJ. 1997. Genotoxicity induced in human lymphoblasts by atmospheric reaction products of naphthalene and phenanthrene. *Mutat Res* 393(1-2): 23-35.

Shultz MA, Choudary PV, Buckpitt AR. 1999. Role of murine cytochrome P-450 2F2 in metabolic activation of naphthalene and metabolism of other xenobiotics. *J Pharmacol Exp Ther* 290(1): 281-288.

TRI. 2009. *TRI Explorer Chemical Report.* U.S. Environmental Protection Agency. http://www.epa.gov/triexplorer and select Naphthalene. Last accessed: 10/26/09.

USITC. 2009. *USITC Interactive Tariff and Trade DataWeb.* United States International Trade Commission. http://dataweb.usitc.gov/scripts/user_set.asp and search on HTS no. 270740.

USITC. 2018. *USITC Interactive Tariff and Trade DataWeb.* United States International Trade Commission. http://dataweb.usitc.gov/scripts/user_set.asp and search on HTS no. 2707400000. Last accessed: 10/9/18.