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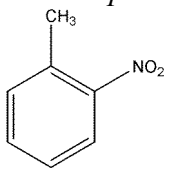
o-Nitrotoluene
CAS No: 88-72-2
Reasonably anticipated to be a human carcinogen
First listed in the *12th Report on Carcinogens*



Carcinogenicity

o-Nitrotoluene is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals and supporting mechanistic data. When administered in the diet, *o*-nitrotoluene caused malignant and benign tumors at multiple tissue sites in rats and mice and early onset of cancer in male rats. Malignant mesothelioma (cancer of the membrane covering an internal organ or cavity) and mesothelial-cell hyperplasia (overproliferation of cells) of the tunica vaginalis of the epididymis (the membrane that covers the ducts leading out of the testis) were observed in male rats administered *o*-nitrotoluene in their feed for 13 weeks (NTP 1992). Bile-duct cancer (cholangiocarcinoma) was observed after 26 weeks, both in animals exposed to *o*-nitrotoluene for 26 weeks and in animals exposed for 13 weeks and 13 more weeks without exposure (NTP 1996). *o*-Nitrotoluene was a multi-site carcinogen in a two-year stop-exposure study of male rats (in which the animals were exposed to *o*-nitrotoluene for 13 weeks and evaluated at two years) and in two-year chronic exposure studies of rats and mice of both sexes (NTP 2002). In rats, exposure to *o*-nitrotoluene caused (1) subcutaneous skin tumors and mammary gland (fibroadenoma) tumors in both sexes, (2) malignant mesothelioma, liver (hepatocellular carcinoma or adenoma and cholangiocarcinoma), and lung (alveolar/bronchiolar adenoma or carcinoma) tumors in males, and (3) benign liver tumors (hepatocellular adenoma) in females. In mice, it caused (1) malignant blood-vessel tumors (hemangiosarcoma) in both sexes, (2) malignant tumors of the large intestine (cecal carcinoma) in males, and (3) liver tumors (hepatocellular adenoma or carcinoma) in females (NTP 2002).

The data available from epidemiological studies are inadequate to evaluate the relationship between human cancer and exposure specifically to *o*-nitrotoluene. One cohort study of workers involved in the manufacture of magenta dye mentioned exposure of workers to *o*-nitrotoluene as part of the manufacturing process. A large excess of bladder cancer was reported; however, the workers were also exposed to other chemicals (*o*-toluidine and 4,4'-methylenebis(2-methylaniline) that are suspected of causing bladder cancer (Rubino *et al.* 1982). Two other studies of magenta manufacturing workers also reported an excess of bladder cancer, but did not report whether the workers were exposed to *o*-nitrotoluene (Case and Pearson 1954, Vineis and Magnani 1985).

Additional Information Relevant to Carcinogenicity

After oral administration to rats and mice, *o*-nitrotoluene is absorbed into the blood and rapidly cleared; the serum half-life is 1.5 hours in rats (NTP 2002). In the rat liver, *o*-nitrotoluene is metabolized to *o*-nitrobenzyl alcohol, followed by glucuronidation, sulfation, or oxidation to *o*-nitrobenzoic acid. The metabolites are eliminated primarily in

the urine. The glucuronidated form can also be excreted in the bile; when the glucuronidated form in the bile is excreted into the small intestine, intestinal bacteria can deconjugate it and reduce the nitro group to an amino group, forming aminobenzyl alcohol. Aminobenzyl alcohol can be reabsorbed from the intestine and further metabolized by the liver to reactive compounds (carbonium and nitrenium ions) that can covalently bind to DNA or to proteins (Chism and Rickert 1985, NTP 2002, NTP 2008). However, neither *o*-aminobenzyl alcohol nor its metabolites have been detected in mouse urine after exposure to *o*-nitrotoluene (NTP 2002); therefore, other unidentified biochemical pathways leading to tumor formation most likely are involved.

o-Nitrotoluene did not cause mutations in bacteria. In studies of its ability to cause genetic damage in cultured mammalian cells, the results were mixed. *o*-Nitrotoluene caused (1) sister chromatid exchange in Chinese hamster ovary (CHO) cells, (2) chromosomal aberrations in Chinese hamster lung (CHL) cells and human peripheral lymphocytes (circulating white blood cells) but not in CHO cells, (3) micronucleus formation in CHL cells but not in CHO-K1 cells, and (4) DNA damage in L5178Y mouse lymphoma cells (NTP 2008). It did not induce DNA repair in rat or human hepatocytes (liver cells) (NTP 2008).

In rats and mice exposed *in vivo*, *o*-nitrotoluene caused a slight increase in micronucleus formation in peripheral normochromatic erythrocytes (circulating mature red blood cells) in male mice at a high dose level; this finding was not considered conclusive. *o*-Nitrotoluene did not induce micronucleus formation in peripheral normochromatic erythrocytes in female mice or in polychromatic erythrocytes (immature red blood cells) in the bone marrow of male rats or mice (NTP 2002).

Following *in vivo* exposure of rats to *o*-nitrotoluene, DNA repair was increased in liver cells isolated from males, but not in cells isolated from females or from germ-free males. These results, together with the failure of *o*-nitrotoluene to induce DNA repair in hepatocytes *in vitro,* suggest that activation of *o*-nitrotoluene to become genotoxic is sex-specific and depends on both mammalian metabolism and metabolism by intestinal bacteria (Doolittle *et al*. 1983). However, *o*-nitrotoluene also caused tumors in other tissues in rats and mice of both sexes, suggesting that other activation mechanisms exist.

In rats exposed to *o*-nitrotoluene *in vivo,* DNA adducts were detected in the liver of males but not females (NTP 2008). Formation of DNA adducts was consistent with the reaction of intermediate compounds derived from *o*-aminobenzyl alcohol with guanine or adenine bases (Jones *et al.* 2003). The pattern of mutations in oncogenes from *o*-nitrotoluene-induced tumors was also consistent with guanine adduct formation: the majority of *p53* mutations in hemangiosarcomas were G·C → A·T transitions, and almost all the K-*ras* mutations in cecal carcinomas were G·C → T·A transversions (Sills *et al.* 2004, Hong *et al.* 2003). Mutations in the *p53*, *ß-catenin*, and K-*ras* genes also were found in hemangiosarcomas from mice exposed to *o*-nitrotoluene, but not in spontaneously occurring hemangiosarcomas from unexposed mice (Hong *et al.* 2003).

In factory workers exposed to *o*-nitrotoluene, hemoglobin adducts were detected in the blood (Jones *et al.* 2005a), and *o*-nitrobenzoic acid and *o*-nitrobenzyl alcohol were detected in the urine (Jones *et al.* 2005b), providing evidence that human exposure to *o*-nitrotoluene results in production of a reactive metabolite(s). In addition, 2-methylaniline

hemoglobin adducts were identified in exposed workers and were also identified in exposed rats, and the hemoglobin adduct levels in the blood of rats were proportional to the 2-methylaniline DNA adduct levels in the livers of rats (Jones *et al.* 2003, Jones and Sabbioni 2003).

Properties

o-Nitrotoluene (also known as 2-nitrotoluene) is a nitroaromatic compound. It is one of three isomers of nitrotoluene; the other two are *m*-nitrotoluene (also known as 3-nitrotoluene) and *p*-nitrotoluene (also known as 4-nitrotoluene). At room temperature, *o*-nitrotoluene is a yellow liquid with an odor of bitter almonds. It is slightly soluble in water and soluble in acetone, benzene, chloroform, diethyl ether, ethanol, and petroleum ether. It has a flash point of 106°C (closed cup) and an autoignition temperature of 305°C (PTCL 2003). It does not ignite easily; however, it may burn, and containers of *o*-nitrotoluene may explode when heated (HSDB 2008). The physical and chemical properties of *o*-nitrotoluene are summarized in the following table.

Property	Information
Molecular weight	137.1
Specific gravity	1.162 at 19°C/15°C
Melting point	–9.5°C (needles); –2.9°C (crystals)
Boiling point	222°C at 760 mm Hg
Octanol-water partition coefficient (log K_{ow})	2.30
Water solubility	650 mg/L at 30°C
Vapor pressure (mm Hg)	0.188 at 25°C
Vapor density relative to air	4.73

Source: HSDB 2008.

Use

o-Nitrotoluene is used primarily in the production of *o*-toluidine (*o*-aminotoluene), 2-amino-4-chlorotoluene, 2-amino-6-chlorotoluene, *o*-toluidine-4-sulfonic acid, and other chemicals that are intermediates in the production of various azo dyes (IARC 1996). It is also used in the manufacture of (or manufacture of intermediates for) other dyes such as magenta and various sulfur dyes for cotton, wool, silk, leather, and paper (HSDB 2008, IARC 1996). In addition, it is used as an intermediate in the synthesis of (or synthesis of intermediates for) explosives and a variety of organic chemicals, including compounds used in the agricultural chemical, pesticide, petrochemical, pharmaceutical, and rubber industries (HSDB 2008).

Production

o-Nitrotoluene is produced principally by the nitration of toluene with a mixture of nitric acid and either sulfuric, aromatic sulfonic, or phosphoric acid (IARC 1996). SRI (2007) reported that in 2007 *o*-nitrotoluene was produced in only one U.S. facility. Eleven U.S. suppliers of *o*-nitrotoluene were identified in 2007 (ChemSources 2007). The U.S.

Environmental Protection Agency lists *o*-nitrotoluene as a "high production volume" chemical; according to data submitted by companies under the Toxic Substances Control Act Inventory Update Rule, annual U.S. production of *o*-nitrotoluene was between 10 million and 50 million pounds for every four-year reporting period from 1986 to 2002 (EPA 2007). U.S. production of *o*-nitrotoluene was calculated as 13 billion grams (29 million pounds) for 1981 (HSDB 2008) and was estimated at 16,120 metric tons (35.5 million pounds) for 1993 (Kirk-Othmer 1996). No data on U.S. imports or exports of *o*-nitrotoluene were found.

Exposure

Exposure to *o*-nitrotoluene in the United States is expected to result primarily from occupational exposure during the production and use of this chemical. No information was found on the number of U.S. workers potentially exposed to *o*-nitrotoluene in the production of chemical intermediates. *o*-Nitrotoluene was detected in ambient air at a chemical manufacturing plant in New Jersey, where a concentration of 47 ng/m^3 was reported (IARC 1996). In Sweden, it also was detected in air at concentrations of up to 2.0 mg/m^3 in the nitrotoluene production area of a chemical plant producing pharmaceuticals and explosives (Ahlborg *et al.* 1985).

The general population may be exposed to *o*-nitrotoluene as a result of its occurrence in the environment from (1) inadvertent spills of *o*-nitrotoluene or chemical mixtures containing *o*-nitrotoluene, (2) emissions directly into the environment, and (3) breakdown products of dinitrotoluenes (DNT) and trinitrotoluenes (TNT). *o*-Nitrotoluene has been detected in U.S. air and water. The National Response Center (NRC 2008) database contains reports of two spills reported as *o*-nitrotoluene in 1990 and one spill reported as nitrotoluene (*o*-, *p*-, and mixtures) in 2000. Two ambient air samples collected in Boise, ID, in the winter of 1986–1987 contained 0.03 and 0.29 ng/m^3 of *o*-nitrotoluene vapor (Nishioka and Lewtas 1992). *o*-Nitrotoluene also was detected in a paper-mill waste-treatment lagoon (concentration and location not reported) (HSDB 2008) and at concentrations ranging from 320 to 16,000 μg/L in the effluent of a U.S. plant producing TNT (IARC 1996, HSDB 2008).

DNT and TNT are used in the production of commercial and military explosives, and *o*-nitrotoluene has been found in groundwater, private well water, surface water, and soil at or near munitions production facilities and military training grounds. *o*-Nitrotoluene was found at average concentrations of 42.6 mg/L (42,600 μg/L) (Best *et al.* 2001) and 2.9 mg/L (2,900 μg/L) (Spain *et al.* 1999) in groundwater at a Tennessee munitions arsenal. At a facility that has produced munitions since World War II, *o*-nitrotoluene has been detected sporadically during routine groundwater monitoring of both the Ogallala aquifer, at concentrations of 0.12 μg/L to 2.9 μg/L (both measured in 2004), and a perched aquifer above the Ogallala, at concentrations of 0.14 μg/L (in 2003) to 5 μg/L (in 2004) (Pantex 2008). At a former munitions production site in Wisconsin, *o*-nitrotoluene was detected in off-site private well water at concentrations of up to 0.095 μg/L (ATSDR 2007, WDHFS 2002). In surface water, *o*-nitrotoluene was detected at concentrations of up to 0.12 μg/L at a munitions facility in Missouri and up to 25 μg/L at a military training facility in Massachusetts (ATSDR 2007). At a historical testing ground in Idaho, soil

contaminated with TNT at a concentration of 39,100 ppm contained *o*-nitrotoluene at a concentration of 1.4 ppm (Radtke *et al.* 2002).

Regulations

U.S. Department of Homeland Security

Minimum requirements have been established for the safe transport of *o*-nitrotoluene on barges.

U.S. Department of Transportation (DOT)

Considered a hazardous material; special requirements have been set for marking, labeling, and transporting

Safety measures after spills or leaks are prescribed in accordance with *o*-nitrotoluene being a combustible toxic hazardous material

U.S. Environmental Protection Agency[1]

Comprehensive Environmental Response, Compensation, and Liability Act

Reportable quantity (RQ) = 1,000 lb

Occupational Safety and Health Administration (OSHA)

Permissible exposure limit (PEL) = 5 ppm (30 mg/m^3) [skin][2]

Guidelines

American Conference of Governmental Industrial Hygienists (ACGIH)

Threshold limit value–time-weighted average (TLV-TWA) limit = 2 ppm [skin]

Biological Exposure Index (BEI): methemoglobin in blood not to exceed 1.5% of hemoglobin measured during or at the end of a shift

National Institute for Occupational Safety and Health (NIOSH)

Immediately dangerous to life and health (IDLH) = 200 ppm

Recommended exposure limit (REL) = 2 ppm (11 mg/m^3) [skin]

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[1] EPA has not carried out an Integrated Risk Information System (IRIS) assessment for *o*-nitrotoluene.
[2] The [skin] designation indicates the potential for dermal absorption; skin exposure should be prevented as necessary through the use of good work practices and gloves, coveralls, goggles, and other appropriate equipment.

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