

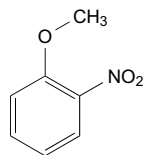
***o*-Nitroanisole**

CAS No. 91-23-6

Reasonably anticipated to be a human carcinogen

First listed in the *Eighth Report on Carcinogens* (1998)

Also known as 2-nitroanisole



Carcinogenicity

o-Nitroanisole is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

Oral exposure to *o*-nitroanisole caused tumors in two rodent species and at several different tissue sites. In rats of both sexes, dietary administration of *o*-nitroanisole caused mononuclear-cell leukemia and increased the combined incidences of benign and malignant tumors of the urinary bladder, kidney, and large intestine (NTP 1993, IARC 1996). In mice, it caused benign and malignant liver tumors (hepatocellular adenoma and carcinoma and hepatoblastoma) in males and benign liver tumors (hepatocellular adenoma) in females (NTP 1993).

Studies on Mechanisms of Carcinogenesis

Orally administered *o*-nitroanisole is metabolized predominantly to *o*-nitrophenol, which is conjugated to sulfate or glucuronide and eliminated in the urine. Less than 1% of *o*-nitroanisole is metabolized to *o*-anisidine, which is listed in the Report on Carcinogens as *reasonably anticipated to be a human carcinogen*. Dietary administration of *o*-anisidine hydrochloride caused tumors of the urinary bladder (transitional-cell neoplasia) in mice and rats and the kidney (transitional-cell carcinoma of the renal pelvis) in rats. *o*-Nitroanisole causes genetic damage in a wide variety of bacterial and *in vitro* mammalian test systems (NTP 1993, IARC 1996).

Since *o*-nitroanisole was listed in the *Eighth Report on Carcinogens*, additional studies relevant to mechanisms of carcinogenesis have been identified. *In vitro*, *o*-nitroanisole is metabolized by O-demethylation to 2-nitrophenol, which is oxidized to 2,5-dihydroxynitrobenzene and 2,6-dihydroxynitrobenzene (Miksanova *et al.* 2004a,b, Stiborova *et al.* 2004, Dracinska *et al.* 2006). *o*-Nitroanisole is also metabolized by nitroreduction to the DNA-reactive products 2-anisidine and *N*-(2-methoxyphenyl)hydroxylamine. DNA adducts similar to those found *in vitro* were found in the urinary bladder, liver, kidney, and spleen of male rats following intraperitoneal injection with *o*-nitroanisole. There is no evidence to suggest that mechanisms by which *o*-nitroanisole causes tumors in experimental animals would not also operate in humans.

Cancer Studies in Humans

The data available from epidemiological studies are inadequate to evaluate the relationship between human cancer and exposure specifically to *o*-nitroanisole.

Properties

o-Nitroanisole is a colorless to yellowish liquid at room temperature. It is slightly soluble in water and soluble in alcohol and ether.

It is stable under normal temperatures and pressures but is explosively reactive with sodium hydroxide and zinc (Akron 2009, HSDB 2009). Physical and chemical properties of *o*-nitroanisole are listed in the following table.

Property	Information
Molecular weight	153.1 ^a
Specific gravity	1.254 at 20°C/4°C ^a
Melting point	9.4°C ^a
Boiling point	277°C ^a
Log <i>K</i> _{ow}	1.73 ^a
Water solubility	1.690 g/L at 30°C ^a
Vapor pressure	3.6 × 10 ⁻³ mm Hg at 25°C ^b

Sources: ^aHSDB 2009, ^bChemIDplus 2009.

Use

o-Nitroanisole is used primarily as a precursor for *o*-anisidine, which is produced through direct nitroreduction (NTP 1993). *o*-Anisidine is used extensively in the synthesis of over 100 azo dyes, either directly after being converted to a diazonium salt or as a precursor for dianisidine, which is diazotized and coupled. *o*-Nitroanisole has also been used as an intermediate in pharmaceutical production (IARC 1996).

Production

o-Nitroanisole is produced by treatment of 2-chloronitrobenzene with sodium methoxide under heat and pressure. The product separates as an oil after dilution with water (IARC 1996). In 2009, *o*-nitroanisole was produced by two manufacturers in India (SRI 2009) and was available from 17 suppliers worldwide, including 9 U.S. suppliers (ChemSources 2009). U.S. imports of *o*-nitroanisole totaled over 700,000 lb in 1976 and 540,000 lb in 1978 (HSDB 2009). No more recent data on U.S. imports or exports of *o*-nitroanisole were found.

Exposure

The routes of potential human exposure to *o*-nitroanisole are dermal contact, ingestion, and inhalation. *o*-Nitroanisole may be released into the environment by dye and pharmaceutical manufacturing facilities through various waste streams (HSDB 2009). When released to air, *o*-nitroanisole will remain in the vapor phase and will be degraded by reactions with photochemically produced hydroxyl radicals, with an estimated half-life of 109 hours. When released to water, it may adsorb to sediments and suspended solids. Volatilization is very slow, with a half-life of 105 days in a model river and 772 days in a model pond. When released to soil, *o*-nitroanisole has moderate mobility. It is not expected to bioaccumulate in aquatic organisms. *o*-Nitroanisole has been identified in drinking water, but no concentrations have been reported. Occupational exposure is associated with the widespread use of *o*-nitroanisole in the manufacture of azo dyes (NTP 1993); however, no estimates of occupational exposure to *o*-nitroanisole were found.

Regulations

Department of Transportation (DOT)

o-Nitroanisole is considered a hazardous material, and special requirements have been set for marking, labeling, and transporting this material.

Environmental Protection Agency (EPA)

Clean Air Act

New Source Performance Standards: Manufacture of *o*-nitroanisole is subject to certain provisions for the control of volatile organic compound emissions.

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Listed substance subject to reporting requirements.

Report on Carcinogens, Fourteenth Edition

References

- 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: 2/19/09.
- ChemIDplus. 2009. *ChemIDplus Advanced*. National Library of Medicine. <http://chem.sis.nlm.nih.gov/chemidplus/chemidheavy.jsp> and select Registry Number and search on CAS number. Last accessed: 2/19/09.
- ChemSources. 2009. *Chem Sources - Chemical Search*. Chemical Sources International. <http://www.chemsources.com/chemonline.html> and search on nitroanisole. Last accessed: 2/19/09.
- Dracinska H, Miksanova M, Svobodova M, Smrcek S, Frei E, Schmeiser HH, Stiborova M. 2006. Oxidative detoxication of carcinogenic 2-nitroanisole by human, rat and rabbit cytochrome P450. *Neuro Endocrinol Lett* 27(Suppl 2): 9-13.
- 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: 2/19/09.
- IARC. 1996. 2-Nitroanisole. In *Printing Processes and Printing Inks, Carbon Black and Some Nitro Compounds*. IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans, vol 65. Lyon, France: International Agency for Research on Cancer. pp. 369-380.
- Miksanova M, Novak P, Frei E, Stiborova M. 2004a. Metabolism of carcinogenic 2-nitroanisole in rat, rabbit, porcine and human hepatic cytosol. *Collec Czech Chem Commun* 69(3): 589-602.
- Miksanova M, Sulc M, Rydlova H, Schmeiser HH, Frei E, Stiborova M. 2004b. Enzymes involved in the metabolism of the carcinogen 2-nitroanisole: evidence for its oxidative detoxication by human cytochromes P450. *Chem Res Toxicol* 17(5): 663-671.
- NTP. 1993. *Toxicology and Carcinogenesis Studies of o-Nitroanisole (CAS No. 91-23-6) in F344 Rats and B6C3F₁ Mice (Feed Studies)*. NTP Technical Report Series no. 416, NIH Publication no. 93-3147. Research Triangle Park, NC: National Toxicology Program. 482 pp.
- SRI. 2009. *Directory of Chemical Producers*. Menlo Park, CA: SRI Consulting. Database edition. Last accessed: 2/19/09.
- Stiborova M, Miksanova M, Smrcek S, Bieler CA, Breuer A, Klokow KA, Schmeiser HH, Frei E. 2004. Identification of a genotoxic mechanism for 2-nitroanisole carcinogenicity and of its carcinogenic potential for humans. *Carcinogenesis* 25(5): 833-840.