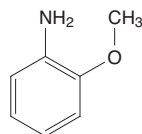


## ***o*-Anisidine and Its Hydrochloride**

### **CAS Nos. 90-04-0 and 134-29-2**

Reasonably anticipated to be human carcinogens

First listed in the *Third Annual Report on Carcinogens* (1983)



### **Carcinogenicity**

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

#### **Cancer Studies in Experimental Animals**

Oral exposure to *o*-anisidine administered as its hydrochloride salt caused tumors in two rodent species and at two different tissue sites. Dietary administration of *o*-anisidine hydrochloride increased the combined incidence of benign and malignant urinary-bladder tumors (transitional-cell papilloma and carcinoma) in rats and mice of both species. In male rats, it also caused kidney cancer (transitional-cell carcinoma of the renal pelvis) and increased the combined incidence of benign and malignant thyroid-gland tumors (follicular-cell adenoma and carcinoma, papillary cystadenoma, and cystadenocarcinoma) (NCI 1978, IARC 1982).

#### **Cancer Studies in Humans**

No epidemiological studies were identified that evaluated the relationship between human cancer and exposure specifically to *o*-anisidine or *o*-anisidine hydrochloride.

### **Properties**

*o*-Anisidine is an aromatic amine that exists at room temperature as a liquid with an amine-like odor and ranging in color from colorless to yellowish, pink, or reddish. It is soluble in water, miscible with ethanol, benzene, diethyl ether, and acetone, and soluble in dilute mineral acids. *o*-Anisidine hydrochloride is a salt of *o*-anisidine. It is a gray-black crystalline solid or light gray powder at room temperature and is soluble in water (HSDB 2009). Physical and chemical properties of *o*-anisidine and its hydrochloride salt are listed in the following table.

| Property                         | <i>o</i> -Anisidine | <i>o</i> -Anisidine HCl |
|----------------------------------|---------------------|-------------------------|
| Molecular weight                 | 123.2               | 159.6                   |
| Specific gravity                 | 1.10 at 15°C/15°C   | NR                      |
| Melting point                    | 5°C                 | 225°C                   |
| Boiling point                    | 225°C               | NR                      |
| Log $K_{ow}$                     | 1.18                | NR                      |
| Water solubility                 | 14 g/L at 25°C      | soluble                 |
| Vapor pressure                   | 0.08 mm Hg at 25°C  | 0.414 mm Hg at 25°C     |
| Vapor density relative to air    | 4.25                | 6.77                    |
| Dissociation constant ( $pK_a$ ) | 4.53                | NR                      |

Source: HSDB 2009. NR = not reported.

### **Use**

*o*-Anisidine hydrochloride is used as a chemical intermediate in the production of numerous azo and triphenylmethane dyes and pigments (e.g., C.I. direct red 72, disperse orange 29, direct yellow 44, direct red 24, and acid red 4); in the production of pharmaceuticals, including the expectorant guaiaicol; as a corrosion inhibitor for

steel; and as an antioxidant for polymercaptan resins (IARC 1999, HSDB 2009).

### **Production**

*o*-Anisidine was produced commercially in the United States from the 1920s until 1957 (IARC 1982). In 2009, six manufacturers of *o*-anisidine were identified worldwide, but none for the hydrochloride salt (SRI 2009). *o*-Anisidine was available from 44 suppliers, including 20 U.S. suppliers, and the hydrochloride salt was available from 8 suppliers, including 5 U.S. suppliers (ChemSources 2009). U.S. imports of *o*-anisidine and its hydrochloride salt are reported in the category “*o*-anisidines, *p*-anisidines, and *p*-phenetidine,” and U.S. exports are reported in the category “anisidines, dianisidines, phenetidines and their salts.” From 1989 to 2008, imports in the category ranged from a high of over 4.6 million kilograms (10.1 million pounds) in 1996 to zero in 2007 and 2008, and exports ranged from zero to 262,000 kg (577,000 lb) (USITC 2009). Reports filed under the U.S. Environmental Protection Agency’s Toxic Substances Control Act Inventory Update Rule indicated that U.S. production plus imports of *o*-anisidine totaled 500,000 lb to 1 million pounds in 1986, 1990, and 2006; 1 million to 10 million pounds in 1990 and 1998; and 10,000 to 500,000 lb in 2002 (EPA 2004, 2009).

### **Exposure**

The primary routes of potential human exposure to *o*-anisidine and *o*-anisidine hydrochloride are inhalation and dermal contact; exposure may also occur by ingestion (HSDB 2009). Individuals in the population could be exposed to *o*-anisidine in the environment. *o*-Anisidine occurs in cigarette smoke and as an environmental pollutant in wastewater from oil refineries and chemical plants (IARC 1982, 1999). Mean concentrations of *o*-anisidine in smoke from market, reference, and other cigarettes were reported to range from less than 0.2 to 5.12 ng per cigarette (Stabbert *et al.* (2003). *o*-Anisidine was detected at concentrations ranging from less than 0.05 to 4.2 µg/L (median = 0.22 µg/L) in urine samples from 20 members of the general population in Germany (Weiss and Angerer 2002). Hemoglobin adducts of *o*-anisidine were detected in all blood samples from 224 children in three German cities; however, adduct levels did not differ significantly between children exposed to environmental tobacco smoke and unexposed children (Richter *et al.* 2001).

According to EPA’s Toxics Release Inventory, environmental releases of *o*-anisidine between 1988 and 1992 peaked in 1989, when 10,000 lb was released, including almost 5,000 lb to surface water. During this period, most releases were to air; however, 250 lb was released to landfills annually from 1989 through 1992, and 2,000 to 3,600 lb to surface impoundments in 1989, 1991, and 1992. From 1993 to 2007, releases were much lower and remained fairly steady; in 2007, releases totaled 638 lb. Releases of hydrochloride salt have not been reported (TRI 2009). If released to air, *o*-anisidine is expected to remain in the vapor phase and to be degraded by reaction with hydroxyl radicals, with a half-life of 6 hours. If released to surface water, it is expected to bind to sediment or suspended solids with high organic matter content and to volatilize from water with an estimated half-life of 31 days from streams and 350 days from lakes. *o*-Anisidine has little potential to bioaccumulate in aquatic organisms. If released to soil, it will likely bind to humic materials; at low concentrations, it will be subject to rapid biodegradation under aerobic conditions (HSDB 2009).

Occupational exposure to *o*-anisidine and its hydrochloride salt may occur during their production and use as a chemical intermediate, corrosion inhibitor, or antioxidant (IARC 1999). The National Occupational Exposure Survey (conducted from 1981 to 1983) es-

estimated that 705 workers in the Chemicals and Allied Products industry potentially were exposed to *o*-anisidine and 1,108 workers in the same industry potentially were exposed to *o*-anisidine hydrochloride (NIOSH 1990).

## Regulations

### Department of Transportation (DOT)

Anisidines are considered hazardous materials, and special requirements have been set for marking, labeling, and transporting these materials.

### Environmental Protection Agency (EPA)

#### Clean Air Act

National Emission Standards for Hazardous Air Pollutants: *o*-Anisidine is listed as a hazardous air pollutant.

#### Comprehensive Environmental Response, Compensation, and Liability Act

Reportable quantity (RQ) = 100 lb.

#### Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: *o*-Anisidine is a listed substance subject to reporting requirements.

#### Resource Conservation and Recovery Act

Listed Hazardous Waste: Waste code for which the listing is based wholly or partly on the presence of *o*-anisidine = K181.

### 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) = 0.5 mg/m<sup>3</sup> for *o*-anisidine.

Potential for dermal absorption for *o*-anisidine.

## Guidelines

### American Conference of Governmental Industrial Hygienists (ACGIH)

Threshold limit value – time-weighted average (TLV-TWA) = 0.5 mg/m<sup>3</sup> for *o*-anisidine.

Potential for dermal absorption for *o*-anisidine.

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

Recommended exposure limit (REL) = 0.5 mg/m<sup>3</sup> for *o*-anisidine.

Immediately dangerous to life and health (IDLH) limit = 50 mg/m<sup>3</sup> for *o*-anisidine.

Potential for dermal absorption for *o*-anisidine.

*o*-Anisidine is listed as a potential occupational carcinogen.

## References

ChemSources. 2009. *Chem Sources - Chemical Search*. Chemical Sources International. <http://www.chemsources.com/chemonline.html> and search on anisidine. Last accessed: 5/4/09.

EPA. 2004. *Non-confidential IUR Production Volume Information*. U.S. Environmental Protection Agency. <http://www.epa.gov/oppt/iur/tools/data/2002-vol.html> and search on CAS number.

EPA. 2009. *Non-confidential 2006 IUR Records by Chemical, Including Manufacturing, Processing and Use Information*. U.S. Environmental Protection Agency. [http://cfpub.epa.gov/iursearch/2006\\_iur\\_natlcheminfo.cfm?id=6566](http://cfpub.epa.gov/iursearch/2006_iur_natlcheminfo.cfm?id=6566).

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: 5/4/09.

IARC. 1982. *ortho*- and *para*-Anisidine and their hydrochlorides. In *Some Aromatic Amines, Anthraquinones and Nitroso Compounds and Inorganic Fluorides Used in Drinking Water and Dental Preparations*. IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans, vol. 27. Lyon, France: International Agency for Research on Cancer. pp. 63-80.

IARC. 1999. *ortho*-Anisidine. In *Some Chemicals That Cause Tumors of the Kidney or Urinary Bladder in Rodents and Some Other Substances*. IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans, vol. 73. Lyon, France: International Agency for Research on Cancer. pp. 49-58.

NCI. 1978. *Bioassay of o-Anisidine Hydrochloride for Possible Carcinogenicity*. National Cancer Institute Technical Report Series no. 89. DHEW (NIH) Publication no. 78-1339. Bethesda, MD: National Institutes of Health. 130 pp.

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/x8301sic.html>, <http://www.cdc.gov/noes/noes1/x8302sic.html>.

Richter E, Rosler S, Scherer G, Gostomzyk JG, Grubl A, Kramer U, Behrendt H. 2001. Haemoglobin adducts from aromatic amines in children in relation to area of residence and exposure to environmental tobacco smoke. *Int Arch Occup Environ Health* 74(6): 421-428.

SRI. 2009. *Directory of Chemical Producers*. Menlo Park, CA: SRI Consulting. Database edition. Last accessed: 5/4/09.

Stabbert R, Schafer KH, Biefel C, Rustemeier K. 2003. Analysis of aromatic amines in cigarette smoke. *Rapid Commun Mass Spectrom* 17(18): 2125-2132.

TRI. 2009. *TRI Explorer Chemical Report*. U.S. Environmental Protection Agency. Last updated: 3/19/09. <http://www.epa.gov/triexplorer> and select *o*-Anisidine.

Weiss T, Angerer J. 2002. Simultaneous determination of various aromatic amines and metabolites of aromatic nitro compounds in urine for low level exposure using gas chromatography-mass spectrometry. *J Chromatogr B Analyt Technol Biomed Life Sci* 778(1-2): 179-192.