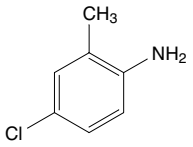
p-Chloro-*o*-toluidine and Its Hydrochloride

CAS Nos. 95-69-2 and 3165-93-3

Reasonably anticipated to be human carcinogens

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

Also known as 4-chloro-*o*-toluidine or 4-chloro-2-methylaniline



Carcinogenicity

p-Chloro-*o*-toluidine and its hydrochloride salt are *reasonably anticipated to be human carcinogens* based on limited evidence of carcinogenicity from studies in humans and evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Humans

There is limited evidence for the carcinogenicity of *p*-chloro-*o*-toluidine from epidemiological studies in humans. Three cohort studies found high relative risks for urinary-bladder cancer among workers exposed to *p*-chloro-*o*-toluidine; however, confounding by co-exposure to other potential urinary-bladder carcinogens could not be ruled out. Documented human exposure to *p*-chloro-*o*-toluidine has occurred primarily in the dye and synthetic-chemical industries (IARC 2000). Between 1982 and 1990, 7 cases of urinary-bladder cancer were detected in a group of 49 German and Danish workers who were involved in producing the insecticide chlordimeform from *p*-chloro-*o*-toluidine on an irregular basis for an average of 18 years (Popp *et al.* 1992). The incidence of urinary-bladder tumors in this group was significantly higher than the expected incidence based on national or regional cancer registries. A brain tumor also occurred in one of the seven workers with urinary-bladder cancer. Exposure levels were not documented, but exposure to *p*-chloro-*o*-toluidine from 1980 to 1986 was demonstrated analytically by monitoring of the workers' urine, where it was reported to be present at minimal levels (concentrations were not reported). There was some evidence that the cohort handled other chemicals (including *o*-chloroaniline); however, none of the resulting exposures were quantified by chemical analysis at the time. In other studies, workers were exposed to *p*-chloro-*o*-toluidine and numerous other compounds, several of which are potential carcinogens. No exposure levels were documented, and the exposures occurred before 1980, when modern industrial-hygiene standards were implemented (Ott and Langner 1983, Stasik 1988, IARC 1990, Hogan 1993).

Cancer Studies in Experimental Animals

Dietary administration of *p*-chloro-*o*-toluidine hydrochloride caused benign or malignant blood-vessel tumors (hemangioma or hemangiosarcoma) in the spleen and adipose tissue in mice of both sexes, in two different mouse strains (Weisburger *et al.* 1978, NCI 1979, IARC 1990).

Studies on Mechanisms of Carcinogenesis

p-Chloro-*o*-toluidine caused genetic damage in a variety of prokaryotic and mammalian *in vitro* and *in vivo* test systems (IARC 1990, Goggelmann *et al.* 1996). *p*-Chloro-*o*-toluidine binding to DNA was demonstrated *in vitro* with calf thymus DNA and *in vivo* following administration to mice and rats by intraperitoneal injection (Hill *et al.* 1979, Bentley *et al.* 1986, IARC 2000). In organs from animals exposed to *p*-chloro-*o*-toluidine, DNA breakage was detected by single-cell gel electrophoresis (comet assay) in mouse liver, urinary bladder, lung, and brain and in rat liver and kidney (Sekihashi *et al.* 2002).

Properties

p-Chloro-*o*-toluidine is a chlorinated aromatic amine that exists as a grayish-white crystalline solid or leaflet, and *p*-chloro-*o*-toluidine hydrochloride is a buff-colored or light-pink powder at room temperature. The base compound is practically insoluble in water or carbon tetrachloride but is soluble in ethanol or dilute acid solutions. It is stable under normal temperatures and pressures (Akron 2009). Physical and chemical properties of *p*-chloro-*o*-toluidine are listed in the following table. No physical and chemical properties for the hydrochloride were found except its molecular weight of 178.1 and melting range of 265°C to 270°C (IARC 2000, Weisburger 1978).

Property	Information
Molecular weight	141.6[a]
Melting point	30°C[a]
Boiling point	241°C[a]
Log K_{ow}	2.27[b]
Water solubility	0.95 g/L at 25°C[b]
Vapor pressure	0.041 mm Hg at 25°C[b]
Vapor density relative to air	4.9[a]
Dissociation constant (pK_a)	3.85 at 25°C[a]

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

Use

p-Chloro-*o*-toluidine and its hydrochloride salt are used in manufacturing azo dyes for cotton, silk, acetate, and nylon and as intermediates in the production of the dyes C.I. 12800, pigment red 7, and pigment yellow 49 (IARC 1990, 2000). *p*-Chloro-*o*-toluidine has also been used since the 1960s in the manufacture of the pesticide (insecticide and acaricide) chlordimeform. It is believed that chlordimeform is no longer produced or used worldwide (IARC 1990).

Production

Commercial production of *p*-chloro-*o*-toluidine began in Germany in 1924 and was first reported in the United States in 1939 (IARC 1990, 2000). In 2009, *p*-chloro-*o*-toluidine was produced by two manufacturers in China and one in India (SRI 2009); worldwide, *p*-chloro-*o*-toluidine free base was available from 25 suppliers and the hydrochloride from 5 suppliers (ChemSources 2009). In 1976, U.S. imports of the free base were 25,000 lb (NCI 1979). U.S. imports in a category of substances including *p*-chloro-*o*-toluidine (toluidines and their salts) were 680,000 kg (1.5 million pounds) in 1995, reached a high of 708,000 kg (1.6 million pounds) in 2000, and declined to 209,000 kg (461,000 lb) in 2004. No imports in this category were reported from 1989 to 1994. From 1989 to 2004, U.S. exports in this category ranged from a high of 9.8 million kilograms (22 million pounds) in 1992 to a low of 1.8 million kilograms (3.7 million pounds) in 2002 (USITC 2009). Reports filed in 1986 and 1990 under the U.S. Environmental Protection Agency's Toxic Substances Control Act Inventory Update Rule indicated that U.S. production plus imports of *p*-chloro-*o*-toluidine totaled 10,000 to 500,000 lb. No inventory update reports for *p*-chloro-*o*-toluidine were filed in 1994 or 1998, and reports in 2002 indicated a quantity of less than 10,000 lb (EPA 2004).

Exposure

The routes of potential human exposure to *p*-chloro-*o*-toluidine are inhalation, ingestion, and dermal contact. The general population can be exposed to *p*-chloro-*o*-toluidine from the use of products that contain it as an impurity; for example, *p*-chloro-*o*-toluidine was found in

five samples of finger paints tested in a study in Spain (Garrigos *et al.* 2000). *p*-Chloro-*o*-toluidine hydrochloride has also been found as an impurity in the pesticide chlordimeform (IARC 2000).

p-Chloro-*o*-toluidine could be released to the environment from decomposition of chlordimeform. As of 2000, chlordimeform was not believed to be produced or used anywhere in the world (IARC 2000). Previously, *p*-chloro-*o*-toluidine was isolated and identified in field samples of plant materials treated with chlordimeform. It was measured in young bean leaves at concentrations of less than 0.1 to 0.2 ppm (mg/kg), in grape stems at 0.02 to 0.3 ppm, in a mixture of grape stems and berries at 0.02 to 0.05 ppm, and in prunes and apples at less than 0.04 ppm (Kossmann *et al.* 1971). *p*-Chloro-*o*-toluidine was also reported to be metabolized from chlordimeform by enzymes present in the leaves of apple seedlings and in cotton plants (IARC 1990, 2000). In an experimental field application, residual concentrations of *p*-chloro-*o*-toluidine were found in rice grains at 3 to 61 ppb (µg/kg), in straw parts at 80 to 7,200 ppb, in the upper layer of soil (0 to 5 cm) at 2 to 68 ppb, and in the lower layer of soil (5 to 10 cm) at trace levels to 20 ppb. In another experimental field application of chlordimeform, no residues of *p*-chloro-*o*-toluidine were detected in rice grains or husks tested 20 to 55 days after pesticide application (IARC 1990). Mammals (including dogs, rats, goats, and humans) also metabolize chlordimeform to *p*-chloro-*o*-toluidine.

If *p*-chloro-*o*-toluidine is released to air, it will exist as a vapor and degrade by direct photolysis or photochemically produced hydroxyl radicals, with an estimated half-life of 9 hours. If it is present in water, it will slowly volatilize. It is expected to be moderately mobile in mainly inorganic soils but to bind tightly to soils with high humus or organic-matter content. *p*-Chloro-*o*-toluidine will biodegrade slowly in soil or water and has a low potential for bioaccumulation (HSDB 2009).

p-Chloro-*o*-toluidine has been measured in the urine of workers exposed to chlordimeform; however, no data were found on the levels detected (IARC 1983, 1990). Occupations with the greatest potential for exposure to *p*-chloro-*o*-toluidine include manufacturers of pigments, dyes, and chlordimeform (IARC 2000). Exposures to *p*-chloro-*o*-toluidine were reported to occur during the charging of mixing vats and at the basification stage at a chemical purification facility in England, at a batch-operated chemical processing plant in the United States, and during its production and processing at a facility in Germany. Data on exposure levels were not provided for any of these studies (IARC 1990). The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 250 workers (health-services workers and chemists, but not biochemists), all of whom were women, potentially were exposed to *p*-chloro-*o*-toluidine and that 682 workers (health-services and clinical-laboratory workers and health aides, but not nursing aides), including 425 women, potentially were exposed to *p*-chloro-*o*-toluidine hydrochloride (NIOSH 1990b).

Regulations

Environmental Protection Agency (EPA)

Comprehensive Environmental Response, Compensation, and Liability Act

Reportable quantity (RQ) = 100 lb for *p*-chloro-*o*-toluidine hydrochloride.

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: *p*-Chloro-*o*-toluidine 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 *p*-chloro-*o*-toluidine hydrochloride = U049.

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