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

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

Reasonably anticipated to be human carcinogens


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

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\text{CH}_3
\begin{array}{c}
\text{Cl} \\
\text{NH}_2
\end{array}
\]

**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 (Akaron 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).**

**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 (Gar- 
rigos et al. 2000). \( p \)-Chloro-\( o \)-toluidine hydrochloride has also been 
found as an impurity in the pesticide chloridimeform (IARC 2000). 

\( p \)-Chloro-\( o \)-toluidine could be released to the environment from 
decomposition of chloridimeform. As of 2000, chloridimeform 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 chloridimeform. 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 
aples at less than 0.04 ppm (Kossmann et al. 1971). \( p \)-Chloro-\( o \)-tolui-
dine was also reported to be metabolized from chloridimeform 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 (\( \mu \)g/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 chloridimeform, 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 chloridimeform 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 hy-
droxy 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 biode-
grade slowly in soil or water and has a low potential for bioaccumu-
lization (HSDB 2009).

\( p \)-Chloro-\( o \)-toluidine has been measured in the urine of workers 
exposed to chloridimeform; 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 chloridimeform (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-labora-
tory workers and health aides, but not nursing aides), including 425 
women, potentially were exposed to \( p \)-chloro-\( o \)-toluidine hydrochlor-
ide (NIOSH 1990b).

Regulations

Department of Transportation (DOT)

\( p \)-Chloro-\( o \)-toluidine hydrochloride is considered a hazardous material, and special requirements 
have been set for marking, labeling, and transporting this material.

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.

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For definitions of technical terms, see the Glossary.