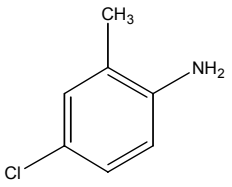
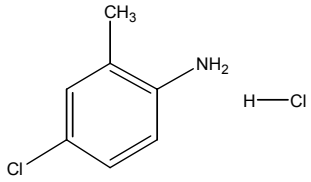
p-CHLORO-*o*-TOLUIDINE and *p*-CHLORO-*o*-TOLUIDINE HYDROCHLORIDE

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

First Listed in the *Eighth Report on Carcinogens*



p-Chloro-*o*-toluidine



p-Chloro-*o*-toluidine hydrochloride

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 malignant tumor formation in experimental animals (IARC 2000).

There is limited evidence for the carcinogenicity of *p*-chloro-*o*-toluidine in humans. High relative risks of bladder cancer have been observed in small cohort studies of workers exposed to *p*-chloro-*o*-toluidine; however, confounding cannot be excluded due to the simultaneous exposure of these workers to other potential bladder carcinogens (IARC 2000). Documented human exposure has occurred primarily in the dye and synthetic chemistry industries. Between 1982 and 1990, seven cases of urinary bladder cancer were detected in a group of 49 workers producing the insecticide chlordimeform from *p*-chloro-*o*-toluidine on an irregular basis for an average of 18 years. The incidence of bladder tumors in this group was significantly higher than that of the cancer registers. Exposure levels were not documented, but from 1980 to 1986, exposure to *p*-chloro-*o*-toluidine was analytically checked by monitoring of urine and was found to be minimal (quantitation of exposure not given). Increased incidences of tumors were observed primarily in the urinary bladder, and 1 of the 7 workers that had bladder cancer also developed a brain tumor. There was some evidence that the cohort studied handled other chemicals (including 4-chloroaniline); however, none of the resulting exposures were quantified by chemical analysis at the time (Popp *et al*. 1992). In other studies, workers were exposed to *p*-chloro-*o*-toluidine and numerous other compounds, several of which are known or possible carcinogens. Levels of exposure to all compounds were undocumented and occurred prior to the implementation of modern industrial hygiene standards in 1980 (Ott and Langer 1983, IARC 1990, Stasik 1988, Hogan 1993).

p-Chloro-*o*-toluidine or its hydrochloride salt was orally administered in two experiments in mice and two experiments in rats. Both compounds increased the incidence of hemangiosarcomas in the spleen and adipose tissue in both male and female mice; however, no increased incidence of tumors in rats was observed. A significant increase of hemangiosarcomas or hemangiomas was observed in both sexes of two strains of mice that received chronic dietary administration of *p*-chloro-*o*-toluidine hydrochloride. *p*-Chloro-*o*-toluidine hydrochloride, however, was not a carcinogen when administered chronically in the diet of both sexes of two strains of rats (Weisburger *et al*. 1978, NCI 1979, IARC 2000).

ADDITIONAL INFORMATION RELEVANT TO CARCINOGENESIS OR POSSIBLE MECHANISMS OF CARCINOGENESIS

p-Chloro-*o*-toluidine has been demonstrated to be genotoxic in a variety of prokaryotic and mammalian *in vitro* and *in vivo* test systems (IARC 1990). *p*-Chloro-*o*-toluidine binding to DNA was demonstrated *in vitro* with calf thymus DNA (Bently *et al*. 1986) and *in vivo* when it was administered by intraperitoneal injection to rats (Hill *et al*. 1979, IARC 1990).

No data were available that would suggest that the mechanisms thought to account for tumor induction by *p*-chloro-*o*-toluidine in mice would not also operate in humans.

PROPERTIES

p-Chloro-*o*-toluidine occurs in the form of leaflets (from ethanol). It has a boiling point of 244°C and a melting point of 30°C. It is soluble in hot alcohol and sparingly soluble in water, ethanol, and dilute acids. *p*-Chloro-*o*-toluidine hydrochloride occurs as a buff-colored powder or a light-pink powder (IARC 2000, HSDB 2000).

USE

p-Chloro-*o*-toluidine and its hydrochloride salt have been used commercially to produce azo dyes for cotton, silk, acetate, and nylon and as intermediates in the production of Pigment Red 7 and Pigment Yellow 49. As an azoic diazo component, *p*-chloro-*o*-toluidine is used in the synthesis of some azoic dyes, which are made by a two-step process involving diazotization of a primary amine component and coupling of the diazotized amine with a naphthol-derived coupling component (IARC 1990, 2000, NCI 1979). *p*-Chloro-*o*-toluidine has also been used in the manufacture of the pesticide chlordimeform (IARC 1990).

p-Chloro-*o*-toluidine is also an impurity in (as the hydrochloride salt) and a metabolite of chlordimeform, which is an insecticide and acaricide. It has been used in the production of chlordimeform since the 1960s (IARC 1983, 1990, 2000).

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). The USITC reported that 89,753 lb of *p*-chloro-*o*-toluidine and *p*-chloro-*o*-toluidine hydrochloride were imported in 1980, 83,098 lb in 1981, 31,747 lb in 1982, and 44,147 lb in 1983 (USITC 1981-1984). An IARC Working Group reported that production of *p*-chloro-*o*-toluidine in the United States stopped in 1979, and all importation and distribution of the compound were discontinued in 1986 (IARC 1990). Chem Sources (1996) identified eleven U.S. suppliers of *p*-chloro-*o*-toluidine and four U.S. suppliers of *p*-chloro-*o*-toluidine hydrochloride. More recently, Chem Sources (2001) identified eight U.S. suppliers of *p*-chloro-*o*-toluidine and two U.S. suppliers of *p*-chloro-*o*-toluidine hydrochloride.

EXPOSURE

The routes of potential human exposure to *p*-chloro-*o*-toluidine and *p*-chloro-*o*-toluidine hydrochloride are inhalation, ingestion, and dermal contact. *p*-Chloro-*o*-toluidine may be found in the environment as a decomposition product of chlordimeform. The compounds are not known to occur naturally. Occupations with the greatest potential for exposure include pigment manufacturers and dyemakers and manufacturers of chlordimeform. Exposures to *p*-chloro-*o*-toluidine have been reported to occur during the charging of mixing vats and at the basification stage in a purification plant in England, by inhalation and dermal contact at a batch-operated chemical processing plant in the United States, and during production and processing at a facility in Germany. Data on exposure levels were not provided for any of these studies (IARC 1990).

p-Chloro-*o*-toluidine has been isolated and identified in field samples of plant materials treated with chlordimeform in young bean leaves at concentrations of less than 0.1 to 0.2 ppm, 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. The compound was also reported to be formed from chlordimeform by enzymes present in the leaves of apple seedlings and in cotton plants (IARC 1990, 2000).

In an experimental field application, residue concentrations of *p*-chloro-*o*-toluidine were found in rice grains at 3 to 61 ppb, in straw parts at 80 to 7,200 ppb, in the upper 0 to 5 cm layer of soil at 2 to 68 ppb, and in the lower 5 to 10 cm of soil at trace to 20 ppb. In another experimental field application, residues of the compound were not detected in rice grains or husks (IARC 1990).

p-Chloro-*o*-toluidine has been found in the urine of workers exposed to chlordimeform. It is a major metabolite of chlordimeform in dogs, rats, and goats (IARC 1990).

The National Occupational Hazard Survey, conducted by NIOSH from 1972 to 1974, estimated that 1,397 workers were potentially exposed to *p*-chloro-*o*-toluidine in the workplace (NIOSH 1976). The National Occupational Exposure Survey (1981-1983) indicated that 250 workers (all women) were potentially exposed to *p*-chloro-*o*-toluidine, and 682 workers, including 425 women, were potentially exposed to *p*-chloro-*o*-toluidine hydrochloride (NIOSH l990).

REGULATIONS

EPA regulates p-chloro-o-toluidine hydrochloride under the Resource Conservation and Recovery Act (RCRA), Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA), Superfund Amendments and Reauthorization Act (SARA); and the Toxic Substances Control Act (TSCA). *p*-Chloro-*o*-toluidine hydrochloride is regulated as a hazardous constituent of waste under RCRA and is subject to reporting and record-keeping requirements under RCRA and SARA. A reportable quantity (RQ) of 100 lb (4.54 kg) was established for *p*-chloro-*o*-toluidine hydrochloride under RCRA. Under TSCA, EPA subjects *p*-chloro-*o*-toluidine and p-chloro-o-toluidine hydrochloride to reporting requirements applicable to any significant new use.

OSHA regulates p-chloro-o-toluidine and p-chloro-o-toluidine hydrochloride under the Hazard Communication Standard and as a chemical hazard in laboratories. The Department of Transportation (DOT) has its own regulations concerning the transportation of *p*-chloro-*o*-toluidine hydrochloride. Regulations are summarized in Volume II, Table 43.

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