5-CHLORO-*ortho*-TOLUIDINE

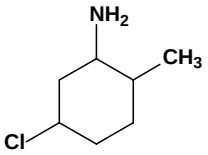
1. Exposure Data

1.1 Chemical and physical data

1.1.1 *Nomenclature*

Chem. Abstr. Serv. Reg. No.: 95-79-4
Chem. Abstr. Name: 5-Chloro-2-methylbenzenamine
IUPAC Systematic Name: 5-Chloro-*ortho*-toluidine
Synonyms: 2-Amino-4-chlorotoluene; 4-chloro-2-aminotoluene; 3-chloro-6-methylaniline; 5-chloro-2-methylaniline; 5-chloro-2-toluidine; 2-methyl-5-chloroaniline

1.1.2 *Structural and molecular formulae and relative molecular mass*



C_7H_8ClN Relative molecular mass: 141.6

1.1.3 *Chemical and physical properties of the pure substance*

(*a*) *Description*: Off-white solid or light brown oil which tends to darken on storage (Lewis, 1993)
(*b*) *Boiling-point*: 239 °C (Lide & Milne, 1996)
(*c*) *Melting-point*: 26 °C (Lide & Milne, 1996)
(*d*) *Spectroscopy data*: Infrared [COB, 2315], ultraviolet [1302] and mass [NIST, 71121] spectral data have been reported (Lide & Milne, 1996)
(*e*) *Solubility*: Very soluble in ethanol (Lide & Milne, 1996)

(*f*) *Conversion factor*[1]: $mg/m^3 = 5.79 \times ppm$

1.1.4 *Technical products and impurities*

Trade names for 5-chloro-*ortho*-toluidine include: Acco Fast Red KB base; Ansibase Red KB; Azoene Fast Red KB base; Fast Red KB amine; Fast Red KB salt; Fast Red KB salt Supra; Fast Red KB-T Base; Fast Red KBS salt; Genazo Red KB soln; Hiltonil Fast Red KB base; Metrogen Red Former KB soln; Naphthosol Fast Red KB base; Pharmazoid Red KB; Red KB base; Spectrolene Red KB; Stable Red KB base.

1.1.5 *Analysis*

No methods have been reported for the analysis of 5-chloro-*ortho*-toluidine in environmental matrices.

1.2 Production

Information available in 1999 indicated that 5-chloro-*ortho*-toluidine was manufactured by three companies in China and by one company each in Germany, India, Japan and the United Kingdom (Chemical Information Services, 1999).

1.3 Use

5-Chloro-*ortho*-toluidine is used as a dye intermediate in the synthesis of Pigment Red 11, Pigment Yellow 77 and for Azoic Coupling Component 21. It is also used as a dye for cotton, silk and nylon (National Library of Medicine, 1999)

1.4 Occurrence

1.4.1 *Natural occurrence*

5-Chloro-*ortho*-toluidine is not known to occur as a natural product.

1.4.2 *Occupational exposure*

No data were available to the Working Group.

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[1] Calculated from: mg/m^3 = (relative molecular mass/24.45) × ppm, assuming a temperature of 25 °C and a pressure of 101 kPa

1.4.3 *Environmental occurrence*

5-Chloro-*ortho*-toluidine is produced in relatively small volume as a dye intermediate and thus may be released into the environment in various waste streams as a result of its production, distribution and use. However, no data on its occurrence in the environment were available that would permit assessment of exposures by the Working Group.

1.5 Regulations and guidelines

5-Chloro-*ortho*-toluidine is listed as a Class 3 carcinogenic substance in Germany; these are substances which cause concern that they could be carcinogenic for man but which cannot be assessed conclusively because of lack of data (Deutsche Forschungsgemeinschaft, 1999).

2. Studies of Cancer in Humans

No data were available to the Working Group.

3. Studies of Cancer in Experimental Animals

3.1 Oral administration

3.1.1 *Mouse*

Groups of 50 male and 50 female B6C3F_1 mice, six weeks of age, were administered 5-chloro-*ortho*-toluidine (technical grade, chromatography showing a single homogeneous peak) in the diet at concentrations 2000 or 4000 mg/kg diet (ppm) for 78 weeks, followed by an observation period of 13 weeks. Concurrent controls consisted of 20 male and 20 female untreated mice. Mean body weights of treated groups of each sex were lower than those of the corresponding control groups. Mortality was dose-related for each sex ($p < 0.001$ and $p = 0.039$ for male and female groups, respectively, Tarone test for dose-related trend). In male mice, the incidence of haemangiosarcomas (mostly originating in the adipose tissue adjacent to the genital organs) was 1/20, 11/50 and 37/47 ($p < 0.001$, Fisher's exact test; $p < 0.001$, trend test) in control, low- and high-dose groups, respectively. In female mice, the incidence of haemangiosarcomas (mostly originating in the adipose tissue adjacent to the genital organs) was 0/20, 6/50 and 22/43 ($p < 0.001$, Fisher's exact test; $p < 0.001$, Cochran-Armitage trend test) in control, low- and high-dose groups, respectively. In male mice, the incidence of hepatocellular carcinomas was 4/20, 19/50 and 25/47 ($p = 0.011$, Fisher's exact test; $p = 0.007$, trend

test) in control, low- and high-dose groups, respectively. In female mice, the incidence of hepatocellular carcinomas was 0/20, 19/50 ($p < 0.001$, Fisher's exact test) and 26/43 ($p < 0.001$, Fisher's exact test; $p < 0.001$, trend test) in control, low- and high-dose groups, respectively (National Cancer Institute, 1979).

3.1.2 *Rat*

Groups of 50 male and 50 female Fischer 344 rats, six weeks of age, were administered 5-chloro-*ortho*-toluidine (technical grade, chromatography showing a single homogeneous peak) in the diet at concentrations of 2500 or 5000 ppm for 78 weeks, followed by an observation period of 25–26 weeks. Concurrent controls consisted of 20 male and 20 female untreated rats. Mean body weights of low- and high-dose females were lower than those of the corresponding control group. Mortality was not affected by treatment in either sex. Although a positive association between dose and the incidence of phaeochromocytomas of the adrenal gland was observed in male rats (control, 0/20; low-dose, 2/49; high-dose, 7/48; $p = 0.019$, trend test), neither of the Fisher's exact tests for comparison of the treated groups with the control group showed statistical significance (National Cancer Institute, 1979). [The Working Group noted the small numbers of animals in the control group.]

4. Other Data Relevant to an Evaluation of Carcinogenicity and its Mechanisms

4.1 Absorption, distribution, metabolism and excretion

4.1.1 *Humans*

No data were available to the Working Group.

4.1.2 *Experimental systems*

5-Chloro-*ortho*-toluidine was given orally to female Wistar rats and female B6C3F$_1$ mice (0.5 mmol [71 mg]/kg bw) and found to bind covalently to haemoglobin. It was concluded that binding of such monocyclic aromatic amines occurs via a reaction of the respective nitrosoarene metabolites with haemoglobin. The haemoglobin binding index of 5-chloro-*ortho*-toluidine was 28-fold higher in rats than in mice. This difference may reflect the proportions of the dose of 5-chloro-*ortho*-toluidine that undergo *N*-oxidation in rats compared with mice (Birner & Neumann, 1988).

4.2 Toxic effects

4.2.1 *Humans*

No data were available to the Working Group.

4.2.2 *Experimental systems*

5-Chloro-*ortho*-toluidine given orally to male mice at a dose of 200 mg/kg bw inhibited testicular DNA synthesis, as measured by tritiated thymidine incorporation (Seiler, 1977).

4.3 Reproductive and developmental effects

No data were available to the Working Group.

[The Working Group noted that many aromatic amines induce methaemglobinaemia (Watanabe *et al*., 1976; Coleman & Coleman, 1996). The effect of methaemoglobinaemia on fetal development has not been well studied, but may be associated with suboptimal fetal outcome (Fan & Steinberg, 1996; Kilpatrick & Laros, 1999).]

4.4 Genetic and related effects

4.4.1 *Humans*

No data were available to the Working Group.

4.4.2 *Experimental systems* (see Table 1 for references)

There are few data available on the genetic toxicology of 5-chloro-*ortho*-toluidine. In single assays, it did not induce mutagenicity in *Salmonella typhimurium*, prophage lambda in *Escherichia coli* or unscheduled DNA synthesis in cultured rat hepatocytes.

4.5 Mechanistic considerations

Like other aromatic amines, 5-chloro-*ortho*-toluidine undergoes an initial metabolic activation step, probably *N*-oxidation, to form a nitrosoarene that can bind covalently to haemoglobin.

Ashby and Tennant (1988) have identified this chemical as showing structural features predictive of genotoxicity. No genotoxic effects were seen in three different assays, but the data-set is inadequate to allow firm conclusions.

Table 1. Genetic and related effects of 5-chloro-*ortho*-toluidine

Test system	Results[a]		Dose[b] (LED or HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
Prophage induction, SOS repair, DNA strand breaks or cross-links	–	–	4.4	DeMarini & Brooks (1992)
Salmonella typhimurium TA100, TA1535, TA1537, TA98, reverse mutation	–	–	666 µg/plate	Haworth *et al*. (1983)
Cell transformation, BALB/c 3T3 mouse cells	+	NT	160	Matthews *et al.* (1993)
Unscheduled DNA synthesis, rat primary hepatocytes *in vitro*	–	NT	14.2	Yoshimi *et al*. (1988)

[a] –, negative; NT, not tested

[b] LED, lowest effective dose; HID, highest ineffective dose; in-vitro test, µg/mL

5. Summary of Data Reported and Evaluation

5.1 Exposure data

5-Chloro-*ortho*-toluidine is an aromatic amine which is produced in relatively small quantities as an intermediate in the manufacture of some pigments and azo dyes. No data were available on human exposure.

5.2 Human carcinogenicity data

No data were available to the Working Group.

5.3 Animal carcinogenicity data

5-Chloro-*ortho*-toluidine was tested for carcinogenicity by oral administration in one experiment in mice and in one experiment in rats. In mice, it increased the incidence of haemangiosarcomas (mostly of adipose tissue) and of hepatocellular carcinomas in both males and females. In rats, no carcinogenic effect was observed.

5.4 Other relevant data

5-Chloro-*ortho*-toluidine undergoes an initial metabolic activation step, probably via *N*-oxidation, to form a nitrosoarene that can bind covalently to haemoglobin.

The few available genotoxicity test results on 5-chloro-*ortho*-toluidine were negative.

5.5 Evaluation

No epidemiological data relevant to the carcinogenicity of 5-chloro-*ortho*-toluidine were available.

There is *limited evidence* in experimental animals for the carcinogenicity of 5-chloro-*ortho*-toluidine.

Overall evaluation

5-Chloro-*ortho*-toluidine is *not classifiable as to its carcinogenicity to humans (Group 3).*

6. References

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