para-CHLOROANILINE

1. Exposure Data

1.1 Chemical and physical data

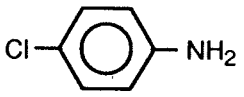
1.1.1 *Synonyms, structural and molecular data*

Chem. Abstr. Serv. Reg. No.: 106-47-8

Chem. Abstr. Name: 4-Chlorobenzenamine

IUPAC Systematic Name: *para*-Chloroaniline

Synonyms: 4-Aminochlorobenzene; *para*-aminochlorobenzene; 1-amino-4-chlorobenzene; 4-amino-1-chlorobenzene; 4-chloro-1-aminobenzene; 4-chloroaniline; 4-chlorophenylamine; *para*-chlorophenylamine



C_6H_6ClN Mol. wt: 127.57

1.1.2 *Chemical and physical properties of the pure substance*

(*a*) *Description*: Rhombic prisms (Lide, 1991); technical material: crystalline, colourless to light-amber; flakes, light-yellow to tan (DuPont Co., 1991a,b)

(*b*) *Boiling-point*: 232 °C (Lide, 1991)

(*c*) *Melting-point*: 72.5 °C (Lide, 1991)

(*d*) *Density*: 1.429 at 19 °C/4 °C (Lide, 1991)

(*e*) *Spectroscopy data*: Infrared, ultraviolet, nuclear magnetic resonance and mass spectral data have been reported (Pouchert, 1981, 1983; Sadtler Research Laboratories, 1980, 1991; Weast & Astle, 1985).

(*f*) *Solubility*: Slightly soluble in water (0.237 wt%), acetone, ethanol and diethyl ether (Lide, 1991; DuPont Co., 1991a,b)

(*g*) *Volatility*: Vapour pressure, 0.15 mm Hg [20 Pa] at 25 °C (technical material); relative vapour density (air = 1), 4.4 (DuPont Co., 1991a,b)

(*h*) *Octanol/water partition coefficient (P)*: log P, 1.83 (Hansch & Leo, 1979)

(*i*) *Conversion factor*: $mg/m^3 = 5.22 \times ppm$[1]

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[1]Calculated from: mg/m^3 = (molecular weight/24.45) × ppm, assuming normal temperature (25 °C) and pressure (760 mm Hg [101.3 kPa])

1.1.3 *Trade names, technical products and impurities*

para-Chloroaniline is commercially available as a technical-grade product with the following specifications: purity, 98.5–99.0% min.; water, 0.10% max.; aniline (see IARC, 1982a, 1987a), 0.1% max.; and isomeric chloroanilines, 0.5% max. (DuPont Co., 1991a; Hoechst Celanese Corp., 1989). It is also available in research quantities at purities ranging from 98 to > 99% (Janssen Chimica, 1990; Riedel-de-Haen, 1990; Heraeus, 1991; Lancaster Synthesis, 1991; TCI America, 1991; Aldrich Chemical Co., 1992; Fluka Chemie AG, 1993).

1.1.4 *Analysis*

A simple gas chromatographic method was developed which provides sensitivity and specificity for the analysis of complex mixtures of common herbicide metabolites, including *para*-chloroaniline, in aqueous solution. The anilines were converted to *N*-acetyl,*N*-trifluoroacetyl derivatives and analysed by gas chromatography with electron capture detection (Hargesheimer *et al.*, 1981).

A thin-layer chromatographic method was reported for the analysis of primary aromatic amines, including *para*-chloroaniline, in mixtures with a low-nanogram detection level. Thin-layer chromatograms are developed by diazotization of the amines with nitrogen oxide vapour, followed by coupling with *N*-(1-naphthyl)ethylenediamine dihydrochloride to produce sharp spots with distinctly different colours (Narang *et al.*, 1982).

In order to assess the applicability of methods developed by the US Environmental Protection Agency and similar survey methods for the determination of a broad range of principal organic hazardous constituents, James *et al.* (1983) evaluated gas chromatography with flame ionization detection and with mass spectrometry for the analysis of complex mixtures containing *para*-chloroaniline. The limit of detection for this compound was 0.20 ng by the first method and 1.9 ng by the second.

A macroporous cation exchanger in the hydrogen form was developed to retain organic bases, including *para*-chloroaniline, as cations from aqueous samples. Neutral organic compounds are removed by washing with methanol and ethyl ether, and the protonated bases are converted to their free base forms with ammonia. After evaporation, the individual bases are separated by gas chromatography with flame ionization detection (Kaczvinsky *et al.*, 1983).

Different adsorption–desorption techniques were compared, including capillary gas chromatography with flame ionization and/or electrochemical detection and a reverse-osmosis technique using reverse-phase high-performance liquid chromatography, for the analysis of selected organic pollutants, including *para*-chloroaniline (Malaiyandi *et al.*, 1987).

Polar aniline derivatives, including *para*-chloroaniline, were determined in aqueous environmental samples by on-line liquid chromatographic preconcentration techniques. The limit of detection using ultraviolet absorption at 235 nm or electrochemical detection was 10 ppt (Hennion *et al.*, 1991).

Fourier transform-infrared techniques were applied to environmental samples to allow identification of trace components at a nanogram level. The precision of the techniques was

shown to be comparable to that obtainable by gas chromatography–mass spectrometry (Gurka *et al.*, 1991).

1.2 Production and use

1.2.1 *Production*

para-Chloroaniline is prepared primarily by the reduction of *para*-nitrochlorobenzene (Dunlap, 1981). It has also been produced by the reaction of 1,4-dichlorobenzene (*para*-dichlorobenzene; see IARC, 1982b, 1987b) with ammonia (US National Library of Medicine, 1992).

Production of *para*-chloroaniline in the USA has been estimated to be 45–450 tonnes per year. The compound (or its hydrochloride salt) is produced by one company each in India, Japan, the United Kingdom and the USA and by two companies in Germany (Chemical Information Services, 1991).

1.2.2 *Use*

para-Chloroaniline is used as an intermediate in the manufacture of dyes (Vat Red 32; Azoic Coupling Agents 5 and 10) and pigments (Pigment Green 10) and as an intermediate in the production of some pharmaceuticals and agricultural chemicals (urea herbicides, e.g., monuron; see IARC, 1976) (US National Library of Medicine, 1992).

1.3 Occurrence

1.3.1 *Natural occurrence*

para-Chloroaniline is not known to occur as a natural product.

1.3.2 *Occupational exposure*

No data were available to the Working Group.

1.3.3 *Water and sediments*

Aniline and chlorinated anilines enter the estuarine environment by various routes, since they are formed during the microbial degradation of phenylcarbamate, phenylurea and acylanilide herbicides and nitroaniline fungicides. They can also enter as waste effluents from dye manufacturing plants. In laboratory studies, photolysis was shown to be an important degradation route for *para*-chloroaniline in estuarine water. There was no microbial degradation of chloroanilines during short-term (up to three days) incubations; however, there was rapid microbial degradation of chloroaniline and aniline photoproducts (Schaefer *et al.*, 1980; Sakagami *et al.*, 1986; Huang *et al.*, 1987; Mutanen *et al.*, 1988).

During 1976–78, the water of the Rhine River contained about 0.1 µg/l *para*-chloroaniline. Following bank or dune filtration of the water, the levels were 0.03–0.1 µg/l or < 0.01 µg/l *para*-chloroaniline, respectively. The half-life of the compound in water was

estimated to be 0.3–3 days in river water and 30–300 days in groundwater (Zoeteman *et al.*, 1980).

In 1979, the mean concentration of *para*-chloroaniline in the Rhine River at Lobith, the Netherlands, was 0.22 μg/l (max., 0.74). Mean concentrations in the Rhine tributaries, Boven Merwede and Ijssel, were 0.14 (max., 0.24) and 0.13 (max., 0.29) μg/l, respectively. *para*-Chloroaniline was frequently detected in the Meuse River at Eijsden and Lith, but the mean concentrations were only 0.02 (max., 0.08) and 0.03 (max., 0.12) μg/l, respectively (Wegman & De Korte, 1981).

para-Chloroaniline was not detected in two tap-water samples from municipal sources in the Lake Ontario region (Kingston and Trenton), Canada; the estimated detection threshold was 20–30 pg (Malaiyandi *et al.*, 1987).

1.3.4 *Soil*

In soil, *para*-chloroaniline binds to humic materials and is slowly degraded by aerobic and anaerobic processes (Hargesheimer *et al.*, 1981; Freitag *et al.*, 1984; Dao *et al.*, 1986). Residues of *para*-chloroaniline were detected in soil up to 12 years after application of the herbicide buturon (Reiml *et al.*, 1989).

1.3.5 *Other*

Levels of *para*-chloroaniline were determined in goldfish (*Carassius auratus*) after experimental pond water had been treated to maintain a *para*-chloroaniline concentration of 50 ppb (μg/l) for four to six weeks. The highest levels after 10 weeks were found in fat (about 7 mg/kg) (Gebefuegi *et al.*, 1988).

1.4 Regulations and guidelines

Occupational exposure limits have been set in several countries: Bulgaria, 0.3 mg/m^3 (time-weighted average, TWA) with a notation that the compound may irritate skin; Romania, 5 mg/m^3 (average), 10 mg/m^3 (max.), with skin irritation notation; the former USSR, 0.3 mg/m^3 (maximal acceptable concentration) with a skin irritation notation; and the former Yugoslavia, 0.05 mg/m^3 (TWA) (Cook, 1987).

DuPont Co. (1991b) proposed an acceptable exposure limit of 0.5 mg/m^3 for an 8-h TWA and 0.3 mg/m^3 for a 12-h TWA, with a skin irritation notation.

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 fed a diet containing 2500 or 5000 mg/kg (ppm) *para*-chloroaniline (technical grade [purity

unspecified], melting-point, 68–71 °C) for 78 weeks, followed by a 13-week observation period. A group of 20 male and 20 female controls received the diet alone. Decreased body weight gain was observed in both treated males and females relative to that of controls. The numbers of surviving animals at 91 weeks were: males—control, 18/20; low-dose, 44/50; high-dose, 44/50; females—control, 20/20; low-dose, 41/50; high-dose, 39/50. Haemangiosarcomas occurred in different organs (subcutaneous tissue, spleen, liver, kidney) in 2/20 control, 9/50 low-dose and 14/50 high dose males; one haemangioma was observed in the low-dose group. The increased incidence of all vascular tumours was significant [$p < 0.025$, Cochran-Armitage trend test]. Among females, haemangiosarcomas occurred at all of the sites in 0/18 control, 3/49 low-dose and 7/42 high-dose animals; one haemangioma was observed in the high-dose group. The increased incidence of combined vascular tumours in females was significant ($p = 0.012$, Cochran-Armitage trend test) (US National Cancer Institute, 1979).

Groups of 50 male and 50 female $B6C3F_1$ mice, seven to eight weeks old, were administered 3, 10 or 30 mg/kg bw *para*-chloroaniline (99.1% pure) in aqueous hydrochloric acid (molar equivalents) by gavage on five days a week for 103 weeks. Controls received deionized water at a volume of 5 ml/kg. Survival at 104 weeks was: males—controls, 43/50; low-dose, 36/50; mid-dose, 29/50 ($p = 0.005$); high-dose 35/50; females—controls, 39/50; low-dose, 42/50, mid-dose; 44/50, high-dose, 41/50. Hepatocellular adenomas were observed in male mice: controls, 9/50; low-dose, 15/49; mid-dose, 10/50; high-dose, 4/50; and hepatocellular carcinomas occurred with a significantly positive trend: controls, 3/50; low-dose, 7/49; mid-dose, 11/50; high-dose, 17/50 ($p < 0.001$, logistic regression trend test). The incidence in males of hepatocellular adenomas and carcinomas combined was: controls, 11/50; low-dose, 21/49 ($p = 0.019$, logistic regression test); mid-dose, 20/50 ($p = 0.045$, logistic regression test); high-dose, 21/50 ($p = 0.027$, logistic regression test). The incidence of haemangiosarcomas of liver and spleen combined was 4/50 controls, 4/49 low-dose, 1/50 mid-dose and 10/50 high-dose male mice ($p = 0.014$, logistic regression trend test). No significant increase in the incidence of such tumours occurred in females (US National Toxicology Program, 1989; Chhabra *et al.*, 1991).

3.1.2 *Rat*

Groups of 50 male and 50 female Fischer 344 rats, six weeks of age, were fed diets containing 250 or 500 ppm (mg/kg) *para*-chloroaniline (technical grade [purity unspecified]) for 78 weeks. A group of 20 male and 20 female controls received the diet alone. Following a 24-week observation period, the surviving animals were sacrificed. There was no difference in body weight gain in the treated animals compared to the controls. Survival at week 102 was: males—controls, 18/20; low-dose, 46/50; high-dose, 38/50; females—controls, 18/20; low-dose, 49/50; high-dose, 45/50. Mesenchymal tumours (fibroma, fibrosarcoma, haemangiosarcoma, osteosarcoma, sarcoma not otherwise specified) of the spleen or splenic capsule occurred in 0/20 control, 0/49 low-dose and 10/49 high-dose male rats ($p = 0.001$, Cochran-Armitage trend test) and in 0/18 control, 2/49 low-dose and 5/42 high-dose females (US National Cancer Institute, 1979; Goodman *et al.*, 1984).

Groups of 50 male and 50 female Fischer 344 rats, eight to nine weeks old, were administered 2, 6 or 18 mg/kg bw *para*-chloroaniline (99.1% pure) in aqueous hydrochloric

acid (molar equivalents) by gavage on five days per week for 103 weeks. A group of 50 male and 50 female controls received deionized water at 5 ml/kg. Survival at 105 weeks in low-dose and mid-dose males was significantly greater than that in the control group: controls, 18/50; low-dose, 32/50 ($p = 0.007$); mid-dose, 32/50 ($p = 0.005$); high-dose 21/50; as was that of high-dose females: controls, 27/50; low-dose, 39/50; mid-dose, 36/50; high-dose, 37/50 ($p = 0.043$). The incidences of proliferative mesenchymal lesions and fatty metamorphosis of the spleen were increased in high-dose males and females. The incidences of fibromas and sarcomas in males are shown in Table 1. Adrenal phaeochromocytomas, including a few malignant phaeochromocytomas, were observed in 13/49 controls, 14/48 low-dose, 15/48 mid-dose and 26/49 high-dose male rats ($p = 0.001$, logistic regression trend test). The incidence of mononuclear cell leukaemias was decreased in all treated groups: males—controls, 21/49; low-dose, 3/50; mid-dose, 2/50; high-dose, 3/50; females—controls, 10/50; low-dose, 2/50; mid-dose, 1/50; high-dose, 1/50 (US National Toxicology Program, 1989; Chhabra *et al.*, 1991).

Table 1. Incidences of tumours of the spleen in male rats treated with *para*-chloroaniline

Tumour	Control	Low-dose	Mid-dose	High-dose
Fibroma	0/49	0/50	0/50	2/50
Fibrosarcoma	0/49	1/50	2/50	17/50**
Osteosarcoma	0/49	0/50	1/50	19/50**
Haemangiosarcoma	0/49	0/50	0/50	4/50*
Sarcomas,combined	0/49	1/50	3/50	38/50**

From US National Toxicology Program (1989); *, $p = 0.07$, logistic regression pair-wise comparison; **, $p < 0.001$, logistic regression trend test

4. Other Relevant Data

4.1 Absorption, distribution, metabolism and excretion

4.1.1 *Humans*

In a patient suffering from acute poisoning by *para*-chloroaniline, conjugates of the parent compound and 2-hydroxy-4-chloroaniline (2-amino-5-chlorophenol) were detected as major urinary metabolites (Yoshida *et al.* 1992).

Other evidence for the metabolism of *para*-chloroaniline in humans is indirect and is derived from studies on the anticancer drug, sulofenur [*N*-(5-indanesulfonyl)-*N'*-(4-chlorophenyl)urea]. 4-Chloroaniline-2-sulfate (2-amino-5-chlorophenyl sulfate) and *para*-chlorooxanilic acid, which are major and minor metabolites, respectively, of *para*-chloroaniline in experimental animals, were identified together with free *para*-chloroaniline as minor urinary metabolites of sulofenur after administration of an oral dose of [^{14}C-*para*-chlorophenyl]-sulofenur (31 mg/kg bw; 91.7 μCi; radiochemical purity, > 99%) to a patient who had previously received the same dose of unlabelled drug daily for six days (Ehlhardt, 1991).

4.1.2 *Experimental systems*

Metabolism of *para*-chloroaniline *in vitro* by human granulocyte myeloperoxidase has been reported, resulting in at least 10 unknown peroxidation products (Bakkenist *et al.*, 1981).

The pharmacokinetics and metabolism of *para*-chloroaniline have been studied extensively in Fischer 344 rats. In male rats administered ^{14}C-labelled compound (5 mCi/mmol [0.04 mCi/mg] [radiochemical purity unspecified]) at 0.3–30 mg/kg bw by gavage in 0.01 N hydrochloric acid, 75–85% of the dose was excreted in urine and 8–12% in faeces by 24 h; only 4% was excreted as unchanged amine in urine, 2.5% in bile and 1% in faeces. At seven days, appreciable radiolabel was still present in blood cells, accounting for 1–2% of the dose. After an intravenous dose of 3.0 mg/kg bw in ethanol:propylene glycol:water (1:1:8), 60% of the dose was excreted in urine after 4 h, 25% was excreted in bile after 6 h, and 90% was eliminated in urine and faeces by 8 h. Initial levels in tissues were highest in muscle > fat > skin > liver > blood; and the kinetics of elimination was biphasic, with an initial half-time of 8 min and terminal half-times of 3–4 h in most tissues, except small intestine and fat (23–29 h). *para*-Chloroacetanilide was detected as a metabolite in bile and in blood, but not in urine or faeces, indicating further metabolism prior to excretion (US National Toxicology Program, 1989).

Additional studies of the metabolism of ^{14}C-*para*-chloroaniline (133 μCi/mg [17 mCi/mmol]; radiochemical purity, > 98%) were carried out in male Fischer 344 rats, female C3H mice and male rhesus monkeys. The compound was given by oral intubation at a dose of 20 mg/kg bw in an aqueous solution adjusted to pH 5 with hydrochloric acid. In rats, mice and monkeys, respectively, the urine contained 90, 82 and 67–74%, and the faeces contained 8, 5 and 1% of the dose after 48 h. The major urinary metabolite in all three species was 4-chloroaniline-2-sulfate; in rats and monkeys, its *N*-acetyl derivative was also detected as a minor urinary metabolite. In rats and to a lesser extent in mice, two additional metabolites, *para*-chloro-oxanilic acid and *para*-chloroglycolanilide, were observed as major and minor urinary metabolites, respectively. In monkeys, *para*-chloroacetanilide, which was not detected in urine or faeces, and 4-chloroaniline-2-sulfate were the major metabolites found in plasma (Ehlhardt & Howbert, 1991).

After oral dosing of female Wistar rats with *para*-chloroaniline [purity unspecified] in propylene glycol at 0.6 mmol [77 mg]/kg bw by gavage, higher levels of haemoglobin binding (569 mmol bound/mol haemoglobin per (mmol compound/kg bw)) were observed than with 12 other monocyclic aromatic amines. The release of free *para*-chloroaniline after alkaline hydrolysis is consistent with the presence of a circulating *N*-hydroxy-*para*-chloroaniline metabolite that enters erythrocytes, is oxidized to *para*-chloronitrosobenzene and forms a sulfinamide adduct with haemoglobin (Birner & Neumann, 1988). These data are also consistent with the observation that at seven days radiolabel persisted in blood cells of Fischer 344 rats treated with radiolabelled *para*-chloroaniline (US National Toxicology Program, 1989).

N-Hydroxylation of *para*-chloroaniline has been demonstrated *in vitro* and shown to be catalysed by hepatic microsomal cytochromes P450 in a wide variety of species, including rats, mice, hamsters, guinea-pigs, rabbits, rainbow trout and red-winged blackbirds. In

mammals, multiple isozymes appear to be involved in the catalysis, since enzymes are induced by both phenobarbital- and 3-methylcholanthrene-type inducers (for reviews, see Golly & Hlavica, 1987; Dady *et al.*, 1991). Peroxidative metabolism of *para*-chloroaniline has also been shown to be mediated by horseradish peroxidase, fungal chloroperoxidases, ram seminal vesicle prostaglandin synthase, rabbit liver microsomal lipid peroxides and by rabbit haemoglobin in the presence of erythrocyte reductases. These results indicate that the *N*-hydroxy derivative may be the initial product but that it is further oxidized enzymatically or non-enzymatically to *para*-chloronitrosobenzene. Several dimeric or halogen-containing oxidation products have also been detected (Kaufman *et al.*, 1973; Corbett *et al.*, 1978, 1980; Golly & Hlavica, 1983; Golly *et al.*, 1984; Golly & Hlavica, 1985; Doerge & Corbett, 1991).

4.2 Toxic effects

4.2.1 *Humans*

Methaemoglobinaemia, which is also consistent with the presence of a circulating *N*-hydroxy-*para*-chloroaniline metabolite, has been reported in workers exposed to *para*-chloroaniline and in neonates inadvertantly exposed in incubators to chlorhexidine gluconate, which is known to decompose spontaneously to *para*-chloroaniline (Faivre *et al.*, 1971; Linch, 1974; van der Vorst *et al.*, 1990). Methaemoglobinaemia and haemolytic anaemia have also been observed (Hainsworth *et al.*, 1989; Taylor *et al.*, 1989) in phase I clinical trials after high doses of sulofenur (Ehlhardt, 1991).

4.2.2 *Experimental systems*

High levels of methaemoglobinaemia have been demonstrated after oral treatment of female Wistar rats with *para*-chloroaniline [purity unspecified] in propylene glycol at 0.6 mmol [77 mg]/kg bw; of male and female Fischer 344 rats with *para*-chloroaniline hydrochloride (purity, > 99%) in water at 5–80 mg/kg, five days per week for 13 weeks; of male and female B6C3F$_1$ mice with *para*-chloroaniline hydrochloride (purity, > 99%) in water at 7.5–120 mg/kg, five days per week for 13 weeks; and of cats with *para*-chloroaniline [purity and vehicle unspecified] at 0.0625 mmol [8 mg]/kg bw (McLean *et al.*, 1969; Birner & Neumann, 1988; Chhabra *et al.*, 1990). Fischer rats given 80 mg/kg for a further 13 weeks had lowered body weights; and both rats and mice showed dose-related decreases in erythrocyte haemoglobin and increases in spleen weight. Numerous lesions indicative of haemolytic anaemia and methaemoglobinaemia were observed, including haemosiderosis in the kidney, liver and spleen and increased haematopoiesis in the liver and spleen in mice and rats; bone-marrow hyperplasia was seen only in rats (Chhabra *et al.*, 1990). Nephrotoxicity was also reported in male Fischer 344 rats given a single intraperitoneal dose of *para*-chloroaniline [purity unspecified] at 1.5 mmol [191 mg]/kg bw in saline, which induced decreased urine volume, haematuria, elevated blood urea nitrogen and decreased renal cortical uptake of *para*-aminohippurate (Rankin *et al.*, 1986).

LD_{50} values for *para*-chloroaniline [purity and vehicle unspecified] were estimated to be 200–480 mg/kg bw after single gavage doses to male Carworth-Wistar rats and 360 mg/kg bw after dermal administration to male New Zealand rabbits (Smyth *et al.*, 1962).

In the 103-week carcinogenicity study described on p. 309, several treatment-related non-neoplastic lesions were observed, including haemolytic anaemia, methaemoglobinaemia and fibrosis and fatty metaplasia of the spleen (US National Toxicology Program, 1989; Chhabra *et al.*, 1991).

4.3 Reproductive and developmental effects

4.3.1 *Humans*

No data were available to the Working Group.

4.3.2 *Experimental systems*

In a study conducted in Germany, zebrafish (*Brachydanio rerio*) were kept in tap-water to which 0, 0.04, 0.2 or 1.0 mg/l *para*-chloroaniline (technical grade; purity, > 99%) had been added (Bresch *et al.*, 1990). The concentrations in the aquaria were analysed weekly by high-performance liquid chromatography. No adverse effect was noted in the F_0 fish or on the numbers and viability of eggs produced. Eggs collected during the 22nd week of exposure were allowed to develop with continuing exposure to 4-chloroaniline. Mortality was not increased, but, at sexual maturity, over 90% of the F_1 fish raised in 1.0 mg/l had spinal abnormalities and abnormal abdominal swellings. Significantly fewer eggs were produced by F_1 fish in all three exposed groups, and the viability of eggs was reduced in the 1.0 mg/l group. An F_2 generation exhibited the same effects: morphological abnormalities, reduced egg counts and reduced viability of eggs at 1.0 mg/l, and reduced egg counts at 0.04 and 0.2 mg/l.

4.4 Genetic and related effects

4.4.1 *Humans*

No data were available to the Working Group.

4.4.2 *Experimental systems* (see also Table 2 and Appendices 1 and 2)

para-Chloroaniline preferentially killed the pol A^- strain in the *Escherichia coli* pol A^-/pol A^+ assay, both in the presence and absence of an exogenous metabolic system. It was not mutagenic to *Salmonella typhimurium*, except to strain TA98, for which conflicting data were obtained. It induced mutations in *Aspergillus nidulans* and in mouse lymphoma L5178Y cells at the *tk* locus. it did not induce mitotic recombination in *Saccharomyces cerevisiae*. *para*-Chloroaniline transformed primary cultures of Syrian hamster embryo cells, only in the later of two studies from the same laboratory. It induced sister chromatid exchange and chromosomal aberrations in Chinese hamster ovary cells *in vitro*.

5. Summary of Data Reported and Evaluation

5.1 Exposure data

para-Chloroaniline is used as an intermediate in the manufacture of dyes, pigments, agricultural chemicals and pharmaceuticals. It is a persistent environmental degradation product of some herbicides and fungicides.

Table 2. Genetic and related effects of *para*-chloroaniline

Test system	Result		Dose[a] (LED/HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
ECL, *Escherichia coli* pol A/N3110-P3478, differential toxicity	+	+	5.0000	Rosenkranz & Poirier (1979)
ECW, *Escherichia coli*, differential toxicity WP2 *uvr*A	–	–	1667.0000	Dunkel *et al.* (1985)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	500.0000	Simmon (1979a)
SA0, *Salmonella typhimurium* TA100, reverse mutation	0	–	0.0000	Zimmer *et al.* (1980)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	1667.0000	Dunkel *et al.* (1985)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	500.0000	Mortelmans *et al.* (1986)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	–	125.0000	Rosenkranz & Poirier (1979)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	–	500.0000	Simmon (1979a)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	–	1667.0000	Dunkel *et al.* (1985)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	–	1667.0000	Mortelmans et al. (1986)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	500.0000	Simmon (1979a)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	1667.0000	Dunkel *et al.* (1985)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	500.0000	Mortelmans *et al.* (1986)
SA&, *Salmonella typhimurium* TA1537, reverse mutation	0	–	0.0000	Zimmer *et al.* (1980)
SA8, *Salmonella typhimurium* TA1538, reverse mutation	–	–	125.0000	Rosenkranz & Poirier (1979)
SA8, *Salmonella typhimurium* TA1538, reverse mutation	–	–	500.0000	Simmon (1979a)
SA8, *Salmonella typhimurium* TA1538, reverse mutation	–	–	1667.0000	Dunkel *et al.* (1985)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	500.0000	Simmon (1979a)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	+	333.0000	Dunkel & Simmon (1980)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	+[b]	500.0000	Dunkel *et al.* (1985)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	+[c]	333.0000	Mortelmans *et al.* (1986)
SA9, *Salmonella typhimurium* TA98, reverse mutation	0	–	0.0000	Zimmer *et al.* (1980)
SCH, *Saccharomyces cerevisiae*, mitotic recombination	–	–	2000.0000	Simmon (1979b)
ANR, *Aspergillus nidulans*, reverse mutation	+	0	200.0000	Prasad (1970)
G5T, Gene mutation, mouse lymphoma L5178Y cells, *tk* locus	+	(+)	16.0000	Mitchell *et al.* (1988)
G5T, Gene mutation, mouse lymphoma L5178Y cells, *tk* locus	(+)	+	16.0000	Myhr & Caspary (1988)

Table 2 (contd)

Test system	Result		Dose[a] (LED/HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
G5T, Gene mutation, mouse lymphoma L5178Y cells, *tk* locus	+	+	25.0000	Myhr *et al.* (1990)
TCS, Cell transformation, Syrian hamster embryo cells, clonal assay	+	0	0.0100	Pienta & Kawalek (1981)
TCS, Cell transformation, Syrian hamster embryo cells, clonal assay	–	0	100.0000	Pienta *et al.* (1977)
CIC, Chromosomal aberrations, CHO cells *in vitro*	+[c]	+[c]	500.0000	Anderson *et al.* (1990)

+, positive; (+), weakly positive; –, negative; 0, not tested
[a]In-vitro tests, μg/ml; in-vivo tests, mg/kg bw
[b]Positive in three of four laboratories
[c]Positive in one of two laboratories

5.2 Human carcinogenicity data

No data were available to the Working Group.

5.3 Animal carcinogenicity data

para-Chloroaniline was tested for carcinogenicity in mice and rats by administration in the diet and by gavage. It produced haemangiosarcomas in male and female mice in different organs after administration in the diet. It induced haemangiosarcomas of the spleen and liver and hepatocellular adenomas and carcinomas in male mice after administration by gavage. It induced sarcomas of the spleen and splenic capsule in male rats in both studies.

5.4 Other relevant data

para-Chloroaniline causes methaemoglobinaemia and is metabolized similarly in humans and experimental animals.

para-Chloroaniline induced DNA damage in bacteria, but conflicting results were obtained for gene mutation. Gene mutation but not mitotic recombination was induced in fungi. Gene mutation, sister chromatid exchange and chromosomal aberrations were induced in cultured mammalian cells, while conflicting data were obtained for cell transformation.

5.5 Evaluation[1]

There is *inadequate evidence* in humans for the carcinogenicity of *para*-chloroaniline.

There is *sufficient evidence* in experimental animals for the carcinogenicity of *para*-chloroaniline.

Overall evaluation

para-Chloroaniline is *possibly carcinogenic to humans (Group 2B).*

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[1]For definition of the italicized terms, see Preamble, pp. 26–30.

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