DICHLOROBENZENES

ortho- and *para*-Dichlorobenzenes were considered by previous working groups, in 1981 (IARC, 1982) and 1987 (IARC, 1987). Since that time, new data have become available, and these have been incorporated into the monograph and taken into consideration in the present evaluation.

1. Exposure Data

1.1 Chemical and physical data

1.1.1 *Nomenclature*

***ortho*-Dichlorobenzene**

Chem. Abstr. Serv. Reg. No.: 95-50-1
Chem. Abstr. Name: 1,2-Dichlorobenzene
IUPAC Systematic Name: *o*-Dichlorobenzene
Synonyms: *o*-Dichlorobenzol

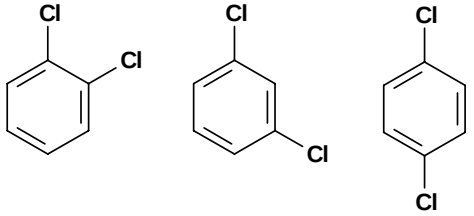
***meta*-Dichlorobenzene**

Chem. Abstr. Serv. Reg. No.: 541-73-1
Chem. Abstr. Name: 1,3-Dichlorobenzene
IUPAC Systematic Name: *m*-Dichlorobenzene
Synonyms: *m*-Dichlorobenzol; *m*-phenylene dichloride

***para*-Dichlorobenzene**

Chem. Abstr. Serv. Reg. No.: 106-46-7
Chem. Abstr. Name: 1,4-Dichlorobenzene
IUPAC Systematic Name: *p*-Dichlorobenzene
Synonyms: *p*-Chlorophenyl chloride; paradichlorobenzene; PDB

1.1.2 *Structural and molecular formulae and relative molecular mass*



ortho *meta* *para*

$C_6H_4Cl_2$ Relative molecular mass: 147.01

1.1.3 *Chemical and physical properties of the pure substance*

***ortho*-Dichlorobenzene**

(*a*) *Description*: Colourless liquid (Verschueren, 1996)
(*b*) *Boiling-point*: 180°C (Lide, 1997)
(*c*) *Melting-point*: –16.7°C (Lide, 1997)
(*d*) *Density*: 1.3059 g/cm^3 at 20°C (Lide, 1997)
(*e*) *Spectroscopy data*: Infrared (prism [1003], grating [201]), ultraviolet [303] and nuclear magnetic resonance (proton [746], C-13 [1844]) spectral data have been reported (Sadtler Research Laboratories, 1980).
(*f*) *Solubility*: Insoluble in water; soluble in ethanol and diethyl ether; miscible in acetone (Lide, 1997)
(*g*) *Volatility*: Vapour pressure, 200 Pa at 25°C; relative vapour density (air = 1), 5.07 (Verschueren, 1996)
(*h*) *Octanol/water partition coefficient (P)*: log P, 3.43 (Hansch *et al*., 1995)
(*i*) *Conversion factor*: mg/m^3 = 6.01 × ppm

***meta*-Dichlorobenzene**

(*a*) *Description*: Colourless liquid (National Toxicology Program, 1991a)
(*b*) *Boiling-point*: 173°C (Lide, 1997)
(*c*) *Melting-point*: –24.8ºC (Lide, 1997)
(*d*) *Density*: 1.2884 g/cm^3 at 20°C (Lide, 1997)
(*e*) *Spectroscopy data*: Infrared (prism [5934], grating [18109]), ultraviolet [1671] and nuclear magnetic resonance (proton [8596], C-13 [6235]) spectral data have been reported (Sadtler Research Laboratories, 1980).
(*f*) *Solubility*: Insoluble in water; soluble in ethanol and diethyl ether; miscible in acetone (Lide, 1997)
(*g*) *Volatility*: Vapour pressure, 665 Pa at 39°C; relative vapour density (air = 1), 5.08 (National Toxicology Program, 1991a)
(*h*) *Octanol/water partition coefficient (P)*: log P, 3.53 (Hansch *et al*., 1995)
(*i*) *Conversion factor*: mg/m^3 = 6.01 × ppm

***para*-Dichlorobenzene**

(*a*) *Description*: Volatile crystals with a characteristic penetrating odour (Budavari, 1996)
(*b*) *Boiling-point*: 174°C (Lide, 1997)
(*c*) *Melting-point*: 52.7°C (Lide, 1997)
(*d*) *Density*: 1.2475 g/cm^3 at 55°C (Lide, 1997)
(*e*) *Spectroscopy data*: Infrared (prism [146], grating [44]), ultraviolet [55] and nuclear magnetic resonance (proton [715], C-13 [37]) spectral data have been reported (Sadtler Research Laboratories, 1980).
(*f*) *Solubility*: Insoluble in water; soluble in diethyl ether; miscible in ethanol and acetone (Lide, 1997)

(*g*) *Volatility*: Vapour pressure, 80 Pa at 20°C; relative vapour density (air = 1), 5.07 (Verschueren, 1996)
(*h*) *Octanol/water partition coefficient (P)*: log P, 3.44 (Hansch *et al.*, 1995)
(*i*) *Conversion factor*: $mg/m^3 = 6.01 \times ppm$

1.1.4 *Technical products and impurities*

Industrial processes for the production of dichlorobenzenes give the *ortho*, *meta* and *para* isomers with varying amounts of the other isomers and of mono- and trichlorobenzenes. Technical-grade *ortho*-dichlorobenzene typically consists of 70–85% *ortho*-dichlorobenzene, < 0.05% chlorobenzene and < 0.5% trichlorobenzene, with the remainder as *meta*- and *para*-dichlorobenzene. Pure-grade *ortho*-dichlorobenzene consists of > 99.8% *ortho*-dichlorobenzene, < 0.05% chlorobenzene, < 0.1% trichlorobenzene and < 0.1% *para*-dichlorobenzene. Commercial-grade *meta*-dichlorobenzene typically consists of 85–99% *meta*-dichlorobenzene, < 0.01% chlorobenzene and < 0.1% *ortho*-dichlorobenzene, with the remainder as *para*-dichlorobenzene. Pure-grade *para*-dichlorobenzene consists of > 99.8% *para*-dichlorobenzene, < 0.05% chlorobenzene and trichlorobenzene and < 0.1% *ortho*- and *meta*-dichlorobenzene (Beck, 1986).

Trade names for *ortho*-dichlorobenzene include Cloroben, Dilatin DB and Dowtherm E. Trade names for *para*-dichlorobenzene include Di-chloricide, Dichlorocide, Evola, Paradi, Paradow, Paramoth, Persia-Perazol and Santochlor.

1.1.5 *Analysis*

Selected methods of analysis for dichlorobenzenes in various matrices are presented in Table 1.

1.2 Production and use

1.2.1 *Production*

Chlorobenzenes are prepared industrially by reaction of liquid benzene with gaseous chlorine in the presence of a catalyst at moderate temperature and atmospheric pressure. Hydrogen chloride is formed as a by-product. Generally, mixtures of isomers and compounds with varying degrees of chlorination are obtained. Lewis acids ($FeCl_3$, $AlCl_3$, $SbCl_3$, $MnCl_2$, $MoCl_3$, $SnCl_4$, $TiCl_4$) are the main catalysts used (Beck, 1986).

Dichlorobenzenes are formed in this process as isomeric mixtures with a low content of the 1,3-isomer. A maximum dichlorobenzene yield of 98% is obtainable in a batch process in which 2 mol of chlorine per mol of benzene are reacted in the presence of ferric chloride and sulfur monochloride at mild temperatures. The remainder of the product consists of mono- and trichlorobenzene. About 75% *para*-dichlorobenzene, 25% *ortho*-dichlorobenzene and only 0.2% *meta*-dichlorobenzene are obtained (Beck, 1986).

Only three chlorinated benzenes are currently produced in large volumes: monochlorobenzene, *ortho*-dichlorobenzene and *para*-dichlorobenzene. Total combined production of chlorobenzenes amounted to approximately 400 thousand tonnes in 1988, with 46% in the

Table 1. Selected methods for the analysis of dichlorobenzenes

Sample matrix	Sample preparation	Assay procedure	Limit of detection	Reference
Air	Adsorb on charcoal; desorb with carbon disulfide	GC/FID	0.01 mg/sample	Occupational Safety and Health Administration (1990) [Method 07]; Eller (1994) [Method 1003]
Air, water, soil, solid waste	Adsorb on particulate matter; filter; extract with dichloromethane; dry; concentrate (air); liquid–liquid or solid-phase extraction (water); Soxhlet, pressurized fluid, ultrasonic or supercritical fluid extraction (soil/sediment/waste)	GC/MS	10 µg/L (groundwater); 660 µg/kg (soil/sediment) [EQL]	Environmental Protection Agency (1996a) [Method 8270C]
Water	Extract (purge) with inert gas; trap on suitable sorbent; thermally desorb	GC/PID/ELCD GC/PID	0.01–0.02 µg/L (PID); 0.01–0.05 µg/L (ELCD) 0.006–0.02 µg/L (PID)	Environmental Protection Agency (1991, 1995a) [Methods 502.2 & 503.1]
	Extract (purge) with inert gas; trap on suitable sorbent; thermally desorb on capillary column	GC/MS	0.03–0.12 µg/L	Environmental Protection Agency (1995b) [Method 524.2]
Waste water, municipal, industrial	Extract (purge) with inert gas; trap on suitable sorbent; thermally desorb	GC/HSD GC/PID	0.15–0.32 µg/L 0.3–0.4 µg/L	Environmental Protection Agency (1997a,b) [Methods 601 & 602]
	Extract with dichloromethane; dry; exchange to hexane; concentrate	GC/ECD	1.14–1.34 µg/L	Environmental Protection Agency (1997c) [Method 612]
	Extract with dichloromethane; dry; concentrate	GC/MS	1.9–4.4 µg/L	Environmental Protection Agency (1997d) [Method 625]

Table 1 (contd)

Sample matrix	Sample preparation	Assay procedure	Limit of detection	Reference
Waste water, municipal, industrial (contd)	Add isotope-labelled analogue; extract with dichloromethane; dry over sodium sulfate; concentrate	GC/MS	10 µg/L	Environmental Protection Agency (1997e) [Method 1625B]
Solid waste matrices[a]	Extract (purge) with inert gas; trap on suitable sorbent; thermally desorb, sample headspace or inject directly	GC/PID/ELCD	0.007–0.05 µg/L (PID); 0.01–0.02 µg/L (ELCD)	Environmental Protection Agency (1996b,c) [Methods 8021B & 8260B]
		GC/MS	0.03–0.12 µg/L	
Water, soil, waste	Extract with dichloromethane or dichloromethane:acetone (1:1); exchange to hexane	GC/ECD	0.27–0.89 µg/L	Environmental Protection Agency (1994a) [Method 8121]
Waste water, soil, sediment, solid waste	Liquid–liquid extraction (water); Soxhlet or ultrasonic extraction (soil/ sediment/ waste)	GC/FT-IR	25 µg/L	Environmental Protection Agency (1994b) [Method 8410]

Abbreviations: GC, gas chromatography; FID, flame ionization detection; MS, mass spectrometry; PID; photoionization detection; ELCD, electrolytic conductivity detection; HSD, halide-specific detection; ECD, electron capture detection; FT-IR, Fourier transform-infrared detection

[a] Samples include groundwater, aqueous sludges, caustic liquors, acid liquors, waste solvents, oily wastes, mousses, tars, fibrous wastes, polymeric emulsions, filter cakes, spent carbons, spent catalysts, soils and sediments.

United States, 34% in western Europe and 20% in Japan; monochlorobenzene accounted for over 50% of the total production of chlorinated benzenes (Bryant, 1993).

Production of *ortho*-dichlorobenzene in the United States has decreased since the 1970s, from approximately 24 700 tonnes in 1975 to approximately 15 800 tonnes in 1993 (International Trade Commission, 1993; Environmental Protection Agency, 1998a). Production of *meta*-dichlorobenzene in the Federal Republic of Germany in 1987 was 3000–4000 tonnes (German Chemical Society, 1987), while that in the United States in 1983 was less than 500 tonnes. Production of *para*-dichlorobenzene in the United States has increased since the 1980s, from approximately 6800 tonnes in 1981 to approximately 32 600 tonnes in 1993 (International Trade Commission, 1993; Environmental Protection Agency, 1998b).

Information available in 1995 indicated that *ortho*-dichlorobenzene was produced in 19 countries, that *meta*-dichlorobenzene was produced in four countries and that *para*-dichlorobenzene was produced in 17 countries (Chemical Information Services, 1995).

1.2.2 *Use*

In western Europe and the United States, *ortho*-dichlorobenzene is used mainly in the production of 3,4-dichloroaniline, the base material for several herbicides; in Japan it is used for garbage treatment (Bryant, 1993). The estimated pattern of use of *ortho*-dichlorobenzene in the United States in 1987 was: organic synthesis (mainly for herbicides), 90%; toluene diisocyanate processing solvent, 5%; and miscellaneous uses, 5% (Environmental Protection Agency, 1998a). *ortho*-Dichlorobenzene is also used as a solvent for waxes, gums, resins, tars, rubbers, oils and asphalts; as an insecticide for termites and locust borers; as a degreasing agent for metals, leather, paper, dry-cleaning, bricks, upholstery and wool; as an ingredient of metal polishes; in motor oil additive formulations; and in paints (National Toxicology Program, 1991b; Budavari, 1996; Environmental Protection Agency, 1998b).

meta-Dichlorobenzene has been used in the production of various herbicides and insecticides; it has also been used in the production of pharmaceuticals and dyes (Beck, 1986; German Chemical Society, 1987; National Toxicology Program, 1991a).

In the United States and Canada, *para*-dichlorobenzene is used mainly as an air freshener and a moth repellent (e.g. as ‘moth balls’ or ‘moth crystals’) and in a range of pesticidal applications. It is also used in the manufacture of 2,5-dichloroaniline and pharmaceuticals; in the manufacture of polyphenylene sulfide resins used for surface coatings and moulding resins; and to control mildew. In Japan, the pattern of use of *para*-dichlorobenzene is about 81% for moth control, 11% for polyphenylene sulfide resins and 8% for dyestuffs (Beck, 1986; National Toxicology Program, 1991c; Bryant, 1993; Budavari, 1996; Government of Canada, 1993a; Environmental Protection Agency, 1998b).

1.3 Occurrence

1.3.1 *Natural occurrence*

Dichlorobenzenes are not known to occur naturally.

1.3.2 *Occupational exposure*

ortho-Dichlorobenzene

According to the 1981–83 United States National Occupational Exposure Survey (National Institute for Occupational Safety and Health, 1988), approximately 92 000 workers in the United States were potentially exposed to *ortho*-dichlorobenzene. Mechanics and persons working in textiles and dry-cleaning or laundering accounted for a large number of those potentially exposed. Occupational exposure to *ortho*-dichlorobenzene may occur by inhalation and eye or skin contact during its manufacture and its use as a chemical intermediate, as a deodorizing agent, as a fumigant, as a cleaner and degreaser, as a solvent for the application and removal of surface coatings, as a heat-transfer medium and in textile dyeing (National Institute for Occupational Safety and Health, 1978a).

In a study of three plants for the manufacture of chlorobenzene in the United States, personal concentrations of *ortho*-dichlorobenzene, a by-product, ranged from below the limit of detection to 13.7 mg/m^3 (Cohen *et al*., 1981). Concentrations in a dye manufacture factory in Germany in which *ortho*-dichlorobenzene was used as a solvent ranged from 0.3 to 14 mg/m^3 (German Chemical Society, 1990). Kumagai and Matsunaga (1997a,b) measured 8-h time-weighted personal exposure concentrations of 0.1–2.3 ppm for 10 workers employed in a plant synthesizing intermediate products for dyes. The concentrations of 2,3- and 3,4-dichlorophenols and 3,4- and 4,5-dichlorocatechol in urine samples collected at the end of a shift correlated with the level of exposure to *ortho*-dichlorobenzene (correlation coefficient, 0.8–0.9). According to Zenser *et al.* (1997), *N*-acetyl-*S*-(dichlorophenyl)cysteines (also known as dichlorophenylmercapturic acids) are also suitable biomarkers for monitoring occupational exposure to *ortho*-dichlorobenzene (study on volunteers). The determination of 2,3- and 2,4-dichlorophenylmercapturic acids in urine was considered to be more suitable for monitoring exposure to *ortho*-dichorobenzene than 2,3- and 3,4-dichlorophenols or 3,4- and 4,5-dichlorocathecols, which are excreted as glucurono and sulfo conjugates and may thus not be hydrolysed efficiently during the analytical procedure.

meta-Dichlorobenzene

No data were available to the Working Group.

para-Dichlorobenzene

According to the 1981–83 United States National Occupational Exposure Survey (National Institute for Occupational Safety and Health, 1998), approximately 34 000 workers in the United States were potentially exposed to *para*-dichlorobenzene; most of these were janitors and cleaners, mortuary employees and workers in pest control. Occupational exposure to *para*-dichlorobenzene may occur by inhalation and ocular or dermal contact during its manufacture, formulation and use as an insecticide, a moth control agent, a fumigant, a deodorant and in organic syntheses for preparation of dye intermediates (National Institute for Occupational Safety and Health, 1978b).

Few data are available, especially on recent occupational exposure (Table 2). Unmodified *para*-dichlorobenzene and its metabolite 2,5-dichlorophenol have been found in the urine of exposed workers at the end of their shift and have been suggested for use as biological indicators of exposure (Pagnotto & Walkley, 1965; Ghittori *et al*., 1985).

1.3.3 *Environmental occurrence*

Both *ortho*- and *para*-dichlorobenzenes are considered priority and/or hazardous pollutants in the United States by the Environmental Protection Agency (1979), in Canada (Meek *et al*., 1994a,b,c) and in the European Communities (1976a,b; Bro-Rasmussen, 1994) and have been reported, generally at low parts per thousand million levels, in air, surface, ground-, drinking- and seawater, sediments, sludges, fish, birds' eggs, foods and human tissues (Environmental Protection Agency, 1980, 1985, 1988; German Chemical Society, 1990; WHO, 1991; Government of Canada, 1993a,b; Agency for Toxic Substances and Disease Registry, 1997). The level of human exposure to *ortho*- and *para*-dichlorobenzenes has been estimated from daily intake via multiple pathways (WHO, 1991; Meek *et al*., 1994b,c).

The production and use of *ortho*-dichlorobenzene, primarily as a solvent and as an intermediate in organic synthesis, and the production and use of *para*-dichlorobenzene, primarily in a variety of consumer products (space deodorants, room fresheners, toilet deodorizer, general insecticide) and as an agricultural fumigant, are the main sources of their release to the environment from various waste streams. The *para* isomer is generally found at higher concentrations than the *ortho* isomer (Environmental Protection Agency, 1980, 1985, 1988; WHO, 1991; Agency for Toxic Substances Disease Registry, 1997).

(*a*) *Air*

According to the Toxic Release Inventory of the Environmental Protection Agency (1996d), emissions of *ortho*-dichlorobenzene to the air from 33 industrial facilities in the United States were 111 000 kg in 1994, and the estimated emissions of *para*-dichlorobenzene from 23 facilities were 117 000 kg.

The major sources of *ortho*-dichlorobenzene in the atmosphere have been reported to be solvent applications, which may account for 25% of annual releases to the atmosphere (Singh *et al*., 1981; Oliver & Nicol, 1982; Harkov *et al*., 1983; WHO, 1991; Agency for Toxic Subtances Disease Registry, 1997). *ortho*-Dichlorobenzene exists primarily in the vapour phase in the atmosphere.

The mean concentration of *ortho*-dichlorobenzene detected in air in Newark, NJ (United States), was 0.18 μg/m^3 in 29 of 38 samples; that in Elizabeth, NJ, was 0.12 μg/m^3 in 24 of 37 samples; and that in Camden, NJ, was 0.06 μg/m^3 in 27 of 35 samples during July–August 1981 (Harkov *et al*., 1983). Ambient mean air concentrations of 0.24–5.2 μg/m^3 *ortho*-dichlorobenzene were detected above six abandoned hazardous waste sites in New Jersey (Harkov *et al*., 1985). *ortho*-Dichlorobenzene was detected at concentrations of 0.09–0.66 μg/m^3 in ambient air in Bound Brook, NJ, during a one-day period in September 1978 (Krost *et al*., 1982). Mean concentrations of 75, 136 and 24 μg/m^3

Table 2. Occupational exposure to *para*-dichlorobenzene

Activity	Air concentration (mg/m^3)		Type and duration of sampling	No. of samples	Reference
	Mean	Range			
Manufacturing plant			NR	NR	Pagnotto & Walkley (1965)
Washing	204	42–288			
Shovelling and centrifuging	198	60–294			
Crushing and sizing	144	48–276			
Household product packaging plant					
Pulverizing					
Moth cake line	150	108–204			
Dumping crystals	55	48–72			
Crystal line	54	42–60			
Abrasive wheel manufacturing plant	66	48–108			
Mixing					
Wheel-forming	69	48–87			
	48	42–54			
Monochlorobenzene manufacturing plant		30.7–52.1	Area and personal	3	Albrecht (1980)
Drumming *para*-dichlorobenzene					
Chemical factory	44.7[a]	25–78	Personal, 8-h[b]	20	Ghittori *et al.* (1985)
Toilet-block manufacturing plants		30–487	Personal, 1–3.5-h	13	Fairhurst *et al.* (1994)
Hardwood bleaching plant	0.15×10^{-3} median[c]	$(0.06–0.8) \times 10^{-3}$	Area	34	Rosenberg *et al.* (1991)

NR, not reported
[a] Geometric mean
[b] Time-weighted average
[c] 24 samples below detection limit

ortho-dichlorobenzene were detected in the ambient air of Los Angeles, CA, Phoenix, AZ, and Oakland, CA (United States), respectively, during July–August 1981 (Singh *et al*., 1981).

The average 1-h concentrations of total isomeric dichlorobenzenes in 1980 were 0.36 μg/m^3 (maximum, 7.3 μg/m^3) in polluted parts of the Netherlands (Delft, Vlaardingen) and 0.18 μg/m^3 (maximum, 2.0 μg/m^3) on the island of Terschelling (Guicherit & Schulting, 1985).

The major sources of *para*-dichlorobenzene in the atmosphere are due to volatilization during its consumer or commercial use and from waste sites and emissions from waste incinerator facilities (Agency for Toxic Substances Disease Registry, 1997). In 1981, the mean ambient air concentrations of *para*-dichlorobenzene in three cities in New Jersey (United States) were 0.30 μg/m^3 (detected in 32 of 38 samples) in Newark, 0.42 μg/m^3 (30 of 37 samples) in Elizabeth and 0.24 μg/m^3 (34 of 35 samples) in Camden during July–August (Harkov *et al*., 1983).

Isomeric dichlorobenzenes have been found in emissions from municipal waste incinerator plants in Germany at concentrations of 0.02 μg/m^3 *ortho*-dichlorobenzene, 0.51 μg/m^3 *para*-dichlorobenzene and 0.21 μg/m^3 *meta*-dichlorobenzene (Jay & Stieglitz, 1995).

Because of its extensive indoor use (i.e. room deodorants, air fresheners, moth repellants), *para*-dichlorobenzene is often found at higher concentrations in indoor than ambient outdoor air (Barkley *et al*., 1980; Wallace *et al*., 1984; Pellizzari *et al*., 1986; Wallace *et al*., 1987; Wallace, 1991a; Fellin & Otson, 1994; Kostianinen, 1995). In a comparison of indoor and outdoor residential air concentrations of volatile organic chemicals in five areas in the United States (Greensboro, NC; Baton Rouge/Geismar, LA; Deer Park/Pasadena, TX; Elizabeth/Bayonne, NJ; Antioch/W. Pittsburg, CA), the medians and maximum indoor levels were generally higher than the corresponding outdoor concentrations for mixtures of *meta*- and *para*-dichlorobenzenes and *para*-dichlorobenzene alone and to a much lesser extent for *ortho*-dichlorobenzene. In some cases, the median indoor:outdoor ratios were greater than 10 (Pellizzari *et al*., 1986).

Moth crystals and room deodorizers are important sources of *para*-dichlorobenzene in homes. In the Total Exposure Assessment Methodology (TEAM) Study carried out by the Environmental Protection Agency between 1979 and 1985, personal exposures to toxic substances were estimated for 400 residents of the states of New Jersey, North Carolina and North Dakota (United States). The mean 24-h personal air and breath concentrations were consistently higher than the outdoor air concentrations for 10 compounds including *para*-dichlorobenzene (Wallace *et al*., 1987). In another comparison, the outdoor air concentration of 0.6 μg/m^3 found in the backyards of 175 homes in six urban areas in the United States was much lower than the mean 24-h average exposure (22 μg/m^3) of 750 persons living in these homes. In about one-third of the homes, *para*-dichlorobenzene was used for moth control or as a deodorizer (Wallace, 1991a).

Three large studies of volatile organic compounds, involving more than 100 homes each have been carried out in Germany, the Netherlands and the United States. The

arithmetic mean concentrations of *para*-dichlorobenzene in indoor air were 14 μg/m³ in Germany and 25 μg/m³ in the United States, and the median found in the Netherlands was 1 μg/m³; the maximum levels found were 1260 μg/m³ in Germany, 299 μg/m³ in the Netherlands and 1600 μg/m³ in the United States (Wallace, 1991b).

In a nationwide study of the indoor air concentrations of 26 volatile compounds in Canada in 1991, the mean *para*-dichlorobenzene concentrations were 36 μg/m³ in winter, 15 μg/m³ in spring, 11 μg/m³ in summer and 15 μg/m³ in autumn; the concentrations declined with increasing ambient air temperature. Indoor sources of *para*-dichlorobenzene (household products and moth-repellant crystal) were judged to have a greater influence on indoor air concentration than climatic variables (Fellin & Otson, 1994).

The concentration of total dichlorobenzenes in the ambient air of household basements near industrial and chemical waste disposal sites in the Love Canal area of New York State (United States) were 2.3–190 μg/m³ (Pellizzari, 1982). The concentrations of dichlorobenzenes in ambient air outside this area ranged from traces to 0.44 μg/m³ (Barkley *et al.*, 1980).

(*b*) *Water and sediments*

(i) *Surface water*

The isomeric dichlorobenzenes are generally considered to persist in the aquatic environment, since they are not readily biodegraded, hydrolysed or photodegraded (WHO, 1991; Agency for Toxic Substances Disease Registry, 1997). According to the National Library of Medicine (1998) Toxic Chemicals Release Inventory, in 1994 1277 kg of *ortho*-dichlorobenzene were released to surface waters from 33 facilities in the United States and 723 kg of *para*-dichlorobenzene were released from 23 facilities.

ortho-Dichlorobenzene was detected in 15 of 463 bodies of surface water in New Jersey, United States, during 1977–79, 8.2 μg/L being the highest concentration found (Page, 1981). In 1980, mean concentrations of 5 ng/L (range, 2–7 ng/L) and 45 ng/L (range, 33–64 ng/L) *ortho*- and *para*-dichlorobenzenes, respectively, were found in open waters at five locations in Lake Ontario, Canada. Mean concentrations of 4 ng/L (range, 3–6 ng/L) *para*-dichlorobenzene were found at five open water locations in Lake Huron. Ten monitoring stations on Grand River, Canada (the largest tributary of the Canadian Great Lakes), registered mean concentrations of 6 ng/L (range, not detected–31 ng/L) *ortho*-dichlorobenzene and 10 ng/L (range, not detected–42 ng/L) *para*-dichlorobenzene. These concentrations were highest below cities from which treated sewage was discharged into the River, and dissipated further downstream (Oliver & Nicol, 1982).

The concentrations of dichlorobenzene in the Niagara River at four sites near Niagara Falls, New York (United States), ranged from not detected to 56 ng/L for *ortho*-dichlorobenzene and from 1 to 94 ng/L for *para*-dichlorobenzene. The effluents and raw sewage of four activated sludge waste-water treatment plants in Canada, two discharging into Lake Ontario and two into the Grand River, contained mean concentrations of 13 ng/L (range, 6–22 ng/L) *ortho*-dichlorobenzene and 600 ng/L (range, 484–920 ng/L) *para*-dichlorobenzene (Oliver & Nicol, 1982).

The approximate input from the Niagara River to Lake Ontario (North America) was estimated to be 2000 kg each of *ortho*- and *para*-dichlorobenzenes on the basis of measurements between September 1981 and September 1983 (Oliver & Nicol, 1984).

ortho-Dichlorobenzene was detected in industrial effluents from 2.5% of 1311 sites and in 0.6% of ambient water samples at 1077 sites in the United States, in both cases at a median concentration < 10 g/L. *para*-Dichlorobenzene was found in industrial effluents from 1.7% of 1306 sites and in 3% of ambient water samples from 8575 sites, at a median concentration < 0.1 μg/L (Staples et al., 1985).

Sewage effluents are believed to be the most important source of *para*-dichlorobenzene in Lake Zurich, Switzerland, and the total annual amount discharged to the central basin from treatment plants was estimated to be 62 kg (Schwarzenbach *et al*., 1979). Volatilization was found to be the predominant mechanism of elimination of *para*-dichlorobenzene from Lake Zurich in one-year monitoring studies, and the average residence time for this isomer was approximately five months.

(ii) *Drinking-water*

para-Dichlorobenzene is the main dichlorobenzene found in drinking-water, probably resulting from its release into surface waters after its extensive use in urinal deodorant blocks (Oliver & Nicol, 1982; WHO, 1991).

In a survey of the groundwater supply in the United States in 1980, *ortho*-dichlorobenzene was found at concentrations of 2.2 and 2.7 μg/L in two of 945 finished water supplies (Westrick *et al*., 1984), and *para*-dichlorobenzene was found at mean concentrations of 0.60–0.74 μg/L in nine of these supplies (Westrick, 1990).

para-Dichlorobenzene was detected in five of 29 raw and treated (day 1) potable water supplies of Canadian municipalities at concentrations < 1 μg/L but was not detected after the second day of treatment during August-September 1979 and was not detected in raw or treated potable water during November–December 1979 (Otson *et al*., 1982a,b).

Drinking-water samples collected from three cities in the Lake Ontario, Canada, area in 1980 contained mean concentrations of 3 μg/L (range, not detected–7 μg/L) *ortho*-dichlorobenzene and 13 μg/L (range, 8–20 μg/L) *para*-dichlorobenzene (Oliver & Nicol, 1982).

(iii) *Leachates and sediments*

The isomeric dichlorobenzenes were monitored in wetland-treated leachate water at a municipal solid-waste landfill site in central Florida (United States) in 1989–90 and 1992–93. During the first sampling period, *para*-dichlorobenzene was detected in surface water samples at 0.04–0.13 μg/L and in groundwater samples at 0.08–11 μg/L. During the second sampling period, *para*-dichlorobenzene was not detected in surface water and was found at concentrations of 0.45 and 3.7 μg/L in two of the four groundwater samples (Chen & Zoltek, 1995).

In Canada, the mean *ortho*-dichlorobenzene concentrations found in surface sediments in 1980 were 1 μg/mL from 13 sites at Lake Superior, 8 μg/L from 42 sites at Lake Huron,

2 µg/L from five sites at Lake Erie and 11 µg/L from 11 sites at Lake Ontario. The mean *para*-dichlorobenzene concentrations at these sites were 5 µg/L at Lake Superior, 16 µg/L at Lake Huron, 9 µg/L at Lake Erie and 94 µg/L at Lake Ontario. The major source of the chlorobenzenes appeared to be leachates from chemical waste dumps and direct chemical manufacturing effluents. *ortho*- and *para*-Dichlorobenzene were found at mean concentrations of 2–19 µg/kg and 17–230 µg/kg, respectively, in seven Lake Ontario sediment cores (0–7 cm in depth) from the Niagara Basin between 1932–41 and 1976–80, indicating that contamination of the Lake had begun over 40 years earlier (Oliver & Nicol, 1982).

(*c*) *Soil and sludges*

The concentrations of dichlorobenzenes in contemporary sewage sludges vary significantly according to waste-water source, sludge type and treatment technique as well as temporally and spatially (Rogers *et al*., 1989; Wang *et al*., 1992). Municipal sludge is often applied to agricultural land in Canada, the United Kingdom and the United States (Jacobs & Zabik, 1983; Webber & Lesage, 1989; Wang *et al*., 1992; Rogers, 1996). In an analysis of 12 industrial sludges in the United Kingdom, *ortho*-dichlorobenzene was found at concentrations (dry weight) of not detected to 14 mg/kg (median, 7.9 mg/kg) and *para*-dichlorobenzene at not detected to 34 mg/kg (median, 9.8 mg/kg) (Rogers *et al*., 1989).

In a survey of 215 sewage sludges in the United States, the concentration ranges (dry weight) were 0.02–810 mg/kg *ortho*-dichlorobenzene and 0.04–630 mg/kg *para*-dichlorobenzene (Jacobs & Zabik, 1983; Rogers, 1996).

ortho-Dichlorobenzene was found in nine Canadian municipal sludges and sludge composts at levels ranging from 0.03 to 0.32 mg/kg between September 1993 and February 1994. During the same period, *para*-dichlorobenzene was found in 11 Canadian sludge samples at levels ranging from 0.26 to 2.6 mg/kg dry weight (Webber *et al*., 1996).

The principal sources of *para*-dichlorobenzene on land are disposal of industrial waste in landfills, application of sewage sludge containing *para*-dichlorobenzene to agricultural land and atmospheric deposition (Webber & Lesage, 1989; Wang *et al*., 1992, 1995; Webber *et al*., 1996). In the United Kingdom, *para*-dichlorobenzene was found at increasing concentrations in sewage sludge samples stored from 1942 to 1961. It was detected in 100% of the sludge samples at concentrations of 7.8–72 µg/kg (median, 26 µg/kg; mean, 30 µg/kg) (Wang *et al*., 1995).

In 1994, industrial releases of *ortho*-dichlorobenzene to the land from 33 facilities in the United States amounted to 11 000 kg, and those of *para*-dichlorobenzene were 500 kg (National Library of Medicine, 1998).

(*d*) *Food*

Dichlorobenzenes may be present as contaminants in foods, although little information is available. *para*-Dichlorobenzene has been found in a variety of Canadian foods, including some samples of soft drinks (0.1 µg/kg), butter (1.3–2.7 µg/kg), margarine (12.2–14.5 µg/kg), peanut butter (1.2–8.8 µg/kg), flour (7.3 µg/kg) and pastry mix (22 µg/kg) (Page & Lacroix, 1995).

para-Dichlorobenzene was detected at a concentration of 0.55 ng/kg in cows' milk from Ontario, Canada, but not in four other composites analysed, i.e. leafy vegetables, fruits, root vegetables and eggs/meat. *ortho*-Dichlorobenzene was detected at a level of 1.8 ng/kg in food composites containing eggs or meat but was not found (limit of detection, 0.1 ng/kg) in leafy vegetables, fruits, root vegetables (including potatoes) or milk (Davies, 1988).

ortho-Dichlorobenzene was found at concentrations of 0.3, 1, 1 and 1 μg/kg in trout taken from Lakes Superior, Huron, Erie and Ontario (Canada), respectively, during 1980 (Oliver & Nicol, 1982).

The mean concentrations of *ortho*-dichlorobenzene found in samples of cows' milk and beef from markets in Yugoslavia were 2.6 and 1.0 μg/kg, respectively, and the mean concentrations of *para*-dichlorobenzene were 5.3 and 5.0 μg/kg, respectively (Jan, 1983a).

In an isolated incident in England, tainted pork (lean and fat meat) contained 5–20 mg/kg *para*-dichlorobenzene. This isomer was also present in other batches of pork from the same source. Other meat products from various commercial sources contained concentrations of < 10 μg/kg during the period 1979–81 (Watson & Patterson, 1982).

para-Dichlorobenzene was detected in Yugoslavia in the oils of seeds from corn, soya bean, rape, sunflower, peanut, sesame, walnut, hazelnut and poppy, the highest level (0.90 μg/kg) being found in corn (Jan, 1980).

(*e*) *Human tissues and secretions*

In a national Canadian survey, *ortho*-dichlorobenzene was found at a maximum concentration of 29 μg/kg (mean, 3 μg/kg) in breast milk (three to four weeks after parturition) and 890 μg/kg in milk fat (mean, 84 μg/kg). The mean concentration of *meta*- and *para*-dichlorobenzenes (combined) in whole breast milk was 6.0 μg/kg, and that in milk fat was 160 μg/kg (Mes *et al*., 1986).

ortho-Dichlorobenzene was found at an average concentration of 9 μg/kg (range, 5–12 μg/kg) in 12 samples of human whole milk in Yugoslavia. The corresponding average concentration of *para*-dichlorobenzene was 25 μg/kg (range, 5–35 μg/kg). Mean concentrations of 13 μg/kg *ortho*-dichlorobenzene and 140 μg/kg *para*-dichlorobenzene were found in 15 samples of human adipose tissue in Yugoslavia (Jan, 1983b).

ortho-Dichlorobenzene (1–4 μg/L), *meta*-dichlorobenzene (3–8 μg/L) and *para*-dichlorobenzene (26 μg/L) were found in samples of blood from residents of the Love Canal area in Niagara Falls, New York (United States) (Bristol *et al*., 1982).

Median *para*-dichlorobenzene concentrations of 1.3, 1.3 and 1.2 μg/m^3 were found in the autumn of 1981, the summer of 1982 and the winter of 1983, respectively, in 344 breath samples from individuals in New Jersey (United States) who were participating in the United States Environmental Protection Agency TEAM Study in 1979–85. Median *para*-dichlorobenzene levels of 1.2 μg/m^3 and 0.82 μg/m^3 were found in 33 and 23 breath samples from individuals from Greensboro, NC, and Devils Lake, ND, respectively (Wallace *et al.*, 1987).

In a study of 1000 adults in the United States, 96% had detectable concentrations of *para*-dichlorobenzene in their blood (≤ 49 µg/L; median, 0.33 µg/L; mean, 2.1 µg/L). Additionally, 98% of these adults had detectable levels of 2,5-dichlorophenol, a metabolite of *para*-dichlorobenzene, in their urine (Hill *et al*., 1995).

1.4 Regulations and guidelines

Occupational exposure limits and guidelines for dichlorobenzenes in a number of countries are presented in Table 3.

WHO (1993) has established international drinking-water guidelines of 1 mg/L for *ortho*-dichlorobenzene and 300 mg/L for *para*-dichlorobenzene. Canada has recommended a maximum acceptable concentration (MAC) for *ortho*-dichlorobenzene in drinking-water of 0.2 mg/L (0.005 mg/L for *para*-dichlorobenzene) and an odour/taste threshold concentration of ≤ 0.003 mg/L (0.001 mg/L for *para*-dichlorobenzene). The Czech Republic has set MACs for dichlorobenzenes combined of 300 ng/L in drinking-water and 0.001 mg/L in surface water. Germany has set an air emission standard maximum for *ortho*-dichlorobenzene of 20 mg/m^3 at a mass flow ≥ 0.1 kg/h (100 mg/m^3 at a mass flow ≥ 2 kg/h for *para*-dichlorobenzene). The maximum residue limit of *para*-dichlorobenzene in all food products in Germany is 0.01 mg/kg. The Russian Federation has set a preliminary exposure standard for *ortho*-dichlorobenzene in ambient air of 0.03 mg/m^3 (0.035 mg/m^3 for *meta*- and *para*-dichlorobenzene) and a MAC in surface water of 0.002 mg/L [all isomers] (United Nations Environment Programme, 1998). The Environmental Protection Agency (1998a,b) in the United States has set maximum contaminant levels of 0.6 mg/L for *ortho*-dichlorobenzene and 0.075 mg/L for *para*-dichlorobenzene in primary drinking-water. The European Union has set a standard of 12 mg/kg for the concentration of *para*-dichlorobenzene that can migrate from plastics and articles intended to come in contact with foodstuffs. Sweden has banned the use and handling of *para*-dichlorobenzene as a pesticide on the basis of its suspected carcinogenicity (United Nations Environment Programme, 1998).

Separate regulations and guidelines have not been established for *meta*-dichlorobenzene (WHO, 1993; United Nations Environment Programme, 1998).

2. Studies of Cancer in Humans

2.1 Case reports

One report of a series of five cases suggested an association between leukaemia and exposure to dichlorobenzenes (IARC, 1982).

2.2 Cohort study

Mortality from cancer was studied among 14 457 workers exposed to a large number of organic solvents and other chemicals, including *ortho*-dichlorobenzene, during employment in one aircraft maintenance facility in the United States (Spirtas *et al*., 1991). In

Table 3. Occupational exposure limits for dichlorobenzenes

Country	Year	Concentration (mg/m^3)		Interpretation
		ortho isomer	*para* isomer	
Argentina	1991	300	450	TWA
Australia	1993	300	450	TWA
			675	STEL
Austria	1993	300		TWA
Belgium	1993		451	TWA
		301 (skin)	661	STEL
Canada	1994	300 (ceiling)	450	TWA
			675	STEL
Denmark	1993		450	TWA
		300		STEL
Finland	1998	300 (skin)	450 (skin)	TWA
		450	690	STEL
France	1993		450	TWA
		300	675	STEL
Germany	1997	300 (skin)	300 (skin)	TWA
Hungary	1993	50 (skin)		TWA
		100		STEL
Ireland	1997		150	TWA
		300	300	STEL
Japan	1996	150	300 (Ca)	TWA
Netherlands	1997	150	150	TWA
		300	300	STEL
Philippines	1993	300	450	TWA
Poland	1993	20	20	TWA
Russian Federation	1993		300	TWA
		50		STEL
Sweden	1993		450	TWA
		300	700	STEL
Switzerland	1993	300	450	TWA
		600	900	STEL
Thailand	1993	300		TWA
Turkey	1993	300	450	TWA
United Kingdom	1997		153	TWA
		300	306	STEL

Table 3 (contd)

Country	Year	Concentration (mg/m^3)		Interpretation
		ortho isomer	*para* isomer	
United States				
OSHA (PEL)	1997	300	450	Ceiling
NIOSH (REL)	1994	300	lfc	Ceiling
ACGIH (TLV)[a]	1997	150 (A4)	60 (A3)	TWA
		301 (A4)		STEL

From International Labour Office (1991); American Conference of Governmental Industrial Hygienists (1997, 1998); National Library of Medicine (1998); United Nations Environment Programme (1998)

TWA, time-weighted average; STEL, short-term exposure limit; A3, animal carcinogen; A4, not classifiable as a human carcinogen; Ca, carcinogen designation; lfc, lowest feasible concentration; PEL, permissible exposure limit; REL, recommended exposure limit; skin, potential dermal absorption; TLV, threshold limit value

[a] The following countries follow the exposure limits suggested by the ACGIH: Bulgaria, Colombia, Jordan, Republic of Korea, New Zealand, Singapore and Viet Nam.

comparison with the general male population, the rate of mortality from any cancer in the cohort was slightly reduced (standardized mortality ratio, 0.90; 95% confidence interval, 0.8–1.0). The only cancers evaluated in a subgroup of workers with estimated exposure to *ortho*-dichlorobenzene [size of the subgroup not given] were multiple myeloma, from which no deaths occurred, and non-Hodgkin lymphoma, from which one death occurred among men and one among women with 1.4 and 0.5 expected, respectively.

3. Studies of Cancer in Experimental Animals

3.1 Oral administration

3.1.1 ortho-*Dichlorobenzene*

Mouse: Groups of 50 male and 50 female B6C3F$_1$ mice, seven weeks of age, were given *ortho*-dichlorobenzene (purity, > 99%) by oral gavage in corn oil at doses of 0, 60 or 120 mg/kg bw on five days per week for 103 weeks. The body-weight gain of treated mice was not decreased when compared with controls. No significant difference in survival was observed between groups or between sexes; the rates ranged from 52% in control males to 70% in those at the high dose and from 66% in control females to 80% in those at the low dose. *ortho*-Dichlorobenzene did not increase the incidence of tumours in mice of either sex (National Toxicology Program, 1985).

Rat: Groups of 50 male and 50 female Fischer 344/N rats, seven weeks of age, were given *ortho*-dichlorobenzene by oral gavage in corn oil at doses of 0, 60 or 120 mg/kg bw

on five days per week for 103 weeks. The body-weight gain of treated males was reduced in comparison with controls. The survival of males at the high dose (38%) was significantly reduced when compared with controls (84%; $p < 0.001$) and those at the low dose (72%; $p = 0.014$). The survival rates of female rats ranged from 62% in controls to 66% at the low dose. *ortho*-Dichlorobenzene did not increase the incidence of tumours in either male or female rats (National Toxicology Program, 1985).

3.1.2 meta-*Dichlorobenzene*

No data were available to the Working Group.

3.1.3 para-*Dichlorobenzene*

Mouse: Groups of 50 male and 50 female B6C3F$_1$ mice, eight weeks of age, were given *para*-dichlorobenzene (purity, > 99%) by oral gavage in corn oil at doses of 0, 300 or 600 mg/kg bw on five days per week for 103 weeks. There was no significant difference in survival between groups or sexes; the survival rates at termination ranged from 56 to 64% in male groups and 70 to 72% in female groups. As shown in Table 4, *para*-dichlorobenzene increased the incidences of hepatocellular tumours (adenomas and carcinomas) in both male and female mice. The incidence rates of liver tumours, adjusted for survival, were 43% in controls, 58% at 300 mg/kg bw and 100% at 600 mg/kg bw in males and 39, 26 and 90% in females, respectively. A marginal increase in the incidence of phaeochromocytomas of the adrenal gland was seen in male mice, but the incidence was within the historical control range for that laboratory (National Toxicology Program, 1987).

Rat: Groups of 50 male and 50 female Fischer 344/N rats, seven weeks of age, were given *para*-dichlorobenzene (purity, > 99%) by oral gavage in corn oil at doses of 0, 150 or 300 mg/kg bw for male rats and 0, 300 or 600 mg/kg bw for female rats on five days per week for 103 weeks. The survival rate of the high-dose males was significantly lower

Table 4. Incidences of primary hepatocellular tumours in B6C3F$_1$ mice exposed by oral administration to *para*-dichlorobenzene

Tumour	Animals with tumours					
	Males			Females		
	Control	300 mg/kg bw	600 mg/kg bw	Control	300 mg/kg bw	600 mg/kg bw
Adenoma	5/50	13/49 ($p = 0.035$)	16/50 ($p = 0.015$)	10/50	6/48	21/50 ($p = 0.012$)
Carcinoma	14/50	11/49	32/50 ($p < 0.001$)	5/50	5/48	19/50 ($p < 0.001$)

From National Toxicology Program (1987)

(40%) than that of the control males (64%) at study termination, but no significant difference in survival was observed between female groups, the rates ranging from 58% at the high dose to 70% in controls and 78% at the low dose. *para*-Dichlorobenzene increased the incidence of renal tubular carcinoma in males at the high dose (control, 1/50; low-dose, 3/50; high-dose, 7/50; $p = 0.03$, Fisher's exact test) but not in females. The incidence rates of kidney carcinomas in male rats (adjusted for survival) were 3.1% in controls, 9.2% at 150 mg/kg bw and 26% at 300 mg/kg bw (National Toxicology Program, 1987).

3.2 Inhalation

Mouse: Groups of 75 male and 75 female Alderley Park SPF mice [age unspecified] were exposed by inhalation to *para*-dichlorobenzene vapour at concentrations of 0, 75 or 500 ppm [0, 45 and 3000 mg/m^3] in air for 57 weeks. The male mice were killed after week 57 since their mortality rate due to fighting and respiratory infection approached 80%. The surviving females were killed at weeks 75–76, i.e. 18–19 weeks after cessation of exposure. The tumour incidence was thus based on 64, 63 and 67% surviving females at 0, 75 and 500 ppm, respectively. Under these conditions, *para*-dichlorobenzene did not increase the tumour incidence (Loeser & Litchfield, 1983). [The Working Group noted the inadequacy of the study due to the short duration and the poor survival.]

Rat: Groups of 76–79 male and female Alderley Park Wistar-derived SPF rats [age unspecified] were exposed by inhalation to *para*-dichlorobenzene vapour at concentrations of 0, 75 or 500 ppm [0, 45 and 3000 mg/m^3] in air for 5 h per day, on five days per week for 76 weeks. Surviving rats were given control air for up to 36 weeks after cessation of exposure. Under these conditions *para*-dichlorobenzene did not increase the tumour incidence (Loeser & Litchfield, 1983). [The Working Group noted the inadequacy of the study due to the short duration of exposure.]

3.3 Administration with known carcinogens

Rat: In a model of liver carcinogenesis, groups of 12 (vehicle control) or 18 male Fischer 344 rats, 10 weeks of age, received a single intraperitoneal injection of either 200 mg/kg bw *N*-nitrosodiethylamine (NDEA) dissolved in 0.9% saline or saline alone. Two weeks after the NDEA or saline injection, *para*-dichlorobenzene [purity unspecified] was administered by gavage at doses of 0.1 or 0.4 mmol/kg bw per day in corn oil for six weeks; control groups received only corn oil or NDEA in corn oil. One week after the start of *para*-dichlorobenzene treatment (i.e. week 3), all animals underwent a partial hepatectomy. The study was terminated at the end of week 8. Hepatic foci were identified by immunohistochemical staining for the placental form of glutathione *S*-transferase. The incidence of hepatic foci was not increased, and the authors concluded that *para*-dichlorobenzene is not a liver tumour promoter (Gustafson *et al.*, 1998).

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

4.1 Absorption, distribution, metabolism and excretion

4.1.1 *Humans*

2,5-Dichlorophenol has been detected in the urine of persons exposed to *para*-dichlorobenzene (Hill *et al*., 1995). Studies of the occurrence of dichlorobenzenes in human tissues and secretions are described on pp. 236–237.

4.1.2 *Experimental systems*

(*a*) ortho-*Dichlorobenzene*

After oral administration to rabbits (500 mg/kg bw), *ortho*-dichlorobenzene is metabolized mainly to 3,4-dichlorophenol, but 2,3-dichlorophenol, 3,4-dichlorophenylmercapturic acid and 3,4- and 4,5-dichlorocatechol are also formed (Azouz *et al*., 1955).

The relationship between the metabolism and the toxicity of *ortho*-dichlorobenzene was investigated by evaluating its biotransformation, tissue distribution, blood kinetics and excretion after oral administration of 5, 50 or 250 mg/kg bw to male Wistar rats. The dose of 250 mg/kg bw had been demonstrated to be toxic in previous studies. The major route of elimination of *ortho*-dichlorobenzene (75–85%) was via the kidneys; excretion in the faeces represented 19% of the low dose and 7% of the high dose. Excretion was nearly complete within 24 h after the low and intermediate doses and within 48 h after the high dose. Pretreatment with phenobarbital accelerated excretion of the high dose and resulted in an overall higher proportion of urinary excretion. Biliary excretion constituted 50–60% of the dose, indicating significant enterohepatic recirculation. The highest concentrations of radiolabel after a low dose were found in fat, liver and kidney 6 h after administration; these then declined rapidly. The maximal concentration in blood was reached 6–8 h after administration of the low and intermediate doses and 24 h after the high dose. *ortho*-Dichlorobenzene was detected in blood only during the first 2 h after administration of 5 mg/kg bw. The major route of biotransformation was via the glutathione pathway, 60% of the urinary metabolites being mercapturic acids; the major metabolites in bile were also conjugates of glutathione. Other major metabolites in urine were the sulfate conjugates of 2,3- and 3,4-dichlorophenol. No significant differences in metabolic profiles were observed with dose. Induction with phenobarbital increased excretion of sulfate conjugates (30% in induced rats, 20% in control rats), the main one being the conjugate of 3,4-dichlorophenol. The mercapturic acids in urine and the glutathione conjugates in bile were epoxide-derived metabolites, and no quinone- or hydroquinone-derived metabolites were observed. A high dose of *ortho*-dichlorobenzene results in depletion of glutathione, followed by oxidative stress and possibly binding to macromolecules (Hissink *et al.*, 1996a).

The oxidative biotransformation of *ortho*-dichlorobenzene was investigated in hepatic microsomes from male Wistar, Fischer 344 and Sprague-Dawley rats, phenobarbital- and isoniazid-treated male Wistar rats and humans; in addition, microsomes from cell lines

that selectively express cytochrome P450 (CYP) 2E1, 1A1, 1A2, 2B6, 2C9, 2D6, 2A6 or 3A4 were used. The rate of conversion was 0.09 nmol/min per mg protein in both Wistar and Fischer 344 rat microsomes, 0.04 in Sprague-Dawley microsomes and 0.14 in human microsomes. Induction of Wistar rats with isoniazid, a CYP 2E1 inducer, or phenobarbital, a CYP 2B1/2 inducer, resulted in increased conversion rates of 0.20 and 0.42 nmol/min per mg protein, respectively. Covalent binding of radiolabel to microsomal proteins was similar in Wistar, Fischer and isoniazid-treated Wistar rats (16–17% of total metabolites), whereas induction with phenobarbital resulted in a slightly increased covalent binding rate of 23% of total metabolites. The covalent binding rate was 31% in Sprague-Dawley microsomes but only 4.6% in human microsomes. Ascorbic acid reduced covalent binding only in Sprague-Dawley microsomes, indicating that quinones are probably major contributors to macromolecular binding in these microsomes. Conjugation of epoxides with glutathione inhibited most covalent binding in all microsomes. In the absence of glutathione, the epoxides were hydrolysed by epoxide hydrolase to dihydrodiols, and inhibition of epoxide hydrolase increased the covalent binding for all microsomes tested, indicating a role of epoxides in the covalent binding. The finding that Fischer 344 rat liver microsomes had less epoxide hydrolase activity than microsomes from Wistar and Sprague-Dawley rats may explain the greater sensitivity of rats of this strain to the hepatotoxicity of *ortho*-dichlorobenzene *in vivo*. Conjugation of the epoxides with glutathione was predominantly non-enzymatic in rats, whereas in humans conjugation was catalysed almost exclusively by glutathione *S*-transferases. This difference may be due to formation of a 'non-reactive' 3,4-epoxide by CYP 2E1 in human microsomes: incubation with microsomes that selectively express human CYP 2E1 or with human liver microsomes resulted in the formation of similar amounts of 2,3- and 3,4-dichlorophenol and two glutathione–epoxides in equal amounts. In rat microsomes, one major glutathione–epoxide conjugate was found, with a much higher covalent binding index, particularly for the phenobarbital-induced microsomes. The authors suggested that rat CYP 2B1/2 preferentially oxidizes the 4,5 site of *ortho*-dichlorobenzene, while human CYP 2E1 forms predominantly the 'non-reactive' 3,4-epoxide. They concluded that the risk for liver toxicity due to exposure to 1,2-dichlorobenzene will be overestimated when it is based solely on toxicity in rats (Hissink *et al.*, 1996b).

2,3- and 3,4-Dichlorophenyl methyl sulfoxides (2,3- and 3,4-sulfoxides) and 2,3- and 3,4-dichlorophenyl methyl sulfones (2,3- and 3,4-sulfones) were detected in the urine of rats given *ortho*-dichlorobenzene. After administration, swift decreases were observed in the concentrations of *ortho*-dichlorobenzene in blood, liver and kidneys, whereas 3,4-sulfone appeared in blood, liver, kidneys and adipose tissue. The concentrations of 3,4-sulfone in the blood and three tissues reached maxima at 24 h. The activities of aminopyrine *N*-demethylase and aniline hydroxylase and the cytochrome P450 content of hepatic microsomes decreased 24 h after administration of *ortho*-dichlorobenzene. In contrast, the 3,4-sulfone increased the activities of these enzymes and the cytochrome P450 and b_5 contents of rat liver microsomes. The concentrations of 2,3- and 3,4-sulfones in blood, liver, kidneys and adipose tissue were dramatically reduced in

both antibiotic-pretreated and bile duct-cannulated rats dosed with *ortho*-dichlorobenzene, suggesting that the process of formation of methylsulfonyl metabolites of *ortho*-dichlorobenzene involves biliary secretion of the sulfones and/or their precursors, which are subjected to metabolism by intestinal microflora. In antibiotic-pretreated rats, the inhibitory effects of administration of *ortho*-dichlorobenzene on the activities of aminopyrine- and aniline-metabolizing enzymes and the contents of cytochromes P450 and b_5 in hepatic microsomes were greater than those observed in the intact rats. In bile duct-cannulated rats, the decrease in aminopyrine *N*-demethylase activity after administration of *ortho*-dichlorobenzene was greater than that observed in the intact rats. Hence, metabolites other than the sulfones dominate the effects of the parent compound on liver enzymes (Kato & Kimura, 1997).

(*b*) meta-*Dichlorobenzene*

No data were available to the Working Group.

(*c*) para-*Dichlorobenzene*

Following repeated whole-body exposure of female CFY (Sprague-Dawley-derived strain) rats to atmospheres containing [^{14}C]*para*-dichlorobenzene (1000 ppm) for 3 h per day for up to 10 days or administration of oral or subcutaneous doses of 250 mg/kg bw per day for up to 10 days, ^{14}C was measured in tissues 24 h after the last dose. After the atmospheric or oral doses, the highest concentrations of radiolabel were measured in fat, followed by kidneys, liver and lungs. The concentration declined rapidly in plasma and tissues five days after the last dose. During the five days after repeated dosing, 91–97% of the excreted radiolabel was found in the urine, indicating biotransformation to polar metabolites. Excretion was more prolonged after subcutaneous administration. After single doses to bile duct-cannulated animals, 46–63% of the excreted radiolabel was found in the bile over 24 h, indicating extensive enterohepatic circulation. The pattern of metabolites in urine and bile was similar after each type of administration, although there were quantitative differences. Urine extracts contained two major ^{14}C components, namely a sulfate and a glucuronide of 2,5-dichlorophenol, representing 46–54% and 31–34% of the urinary radiolabel, respectively. Two minor components were identified by mass spectrometry as a dihydroxydichlorobenzene and the mercapturic acid of *para*-dichlorobenzene. The glucuronide of 2,5-dichlorophenol was the major (30–42%) component of radiolabel in bile (Hawkins *et al.*, 1980).

Male and female Fischer 344 rats were given 900 mg/kg bw [^{14}C]*para*-dichlorobenzene by gavage, housed for 72 h in metabolic cages for collection of urine and then killed. Selected organs were excised to determine total and protein-bound radiolabel. In liver, kidney, lung and spleen, the radiolabel bound to proteins was below the limit of detection. Approximately 38–42% of the dose was recovered in urine, where both sulfate and glucuronide conjugates of 2,5-dichlorophenol were identified. These results confirm those of other studies that 2,5-dichlorophenol is a major metabolite of *para*-dichlorobenzene. 2,5-Dichlorohydroquinone was identified in urine as a minor metabolite only after

acid hydrolysis. The authors note that hydroquinones are relatively inert chemically and may be conjugated to glucuronides and excreted without resulting in covalent binding or toxicity (Klos & Dekant, 1994).

The distribution of *para*-dichlorobenzene in organs was compared in male and female Fischer 344/DuCrj rats after they had inhaled 500 ppm for 24 h in a whole-body chamber. The concentrations of *para*-dichlorobenzene in serum, liver, kidney and fatty tissues were measured by gas chromatography at intervals up to 24 h after treatment. Although no significant differences in serum concentrations were observed between male and female rats, those in the livers of female rats were significantly higher than in male rats. Conversely, significantly higher levels of *para*-dichlorobenzene were found in the kidneys of male than female rats. The authors concluded that the distribution correlates with the finding of nephrotoxic changes only in male rats and of minor hepatotoxic changes only in females (Umemura *et al*., 1990).

The biotransformation and kinetics of *para*-dichlorobenzene were studied in male Wistar rats given doses of 10, 50 or 250 mg/kg bw orally. At all doses, excretion was predominantly via the urine (78–85%) with only a small amount via the faeces (2–5%); excretion in the bile represented < 5% of the low dose and 30% of the high dose. The major biliary metabolite was the glucuronide of 2,5-dichlorophenol. The time at which the plasma concentrations of the parent compound and the metabolites were maximal and the maximal concentrations increased with dose. Induction of CYP 2E1 by isoniazid resulted in faster urinary elimination, whereas the time at which the plasma concentrations of the parent compound and the metabolites were maximal and the maximal concentrations were lower. At 50 mg/kg bw, the integrated area under the curve of time–concentration in blood was smaller (148 versus 244 μmol × h/L) and total clearance was higher (33 versus 24 mL/min per kg bw) in induced rats. At this dose, the plasma half-life was approximately 7 h in uninduced rats and 4.5 h in induced rats; these values were similar at the high dose. *para*-Dichlorobenzene was metabolized mainly to 2,5-dichlorophenol (~90%), which was detected in urine as its sulfate (50–60%), glucuronide (20–30%) and the free form (5–10%). Minor metabolites were *N*-acetyl-cysteine-*S*-dihydro-hydroxy-1,4-dichlorobenzene and the corresponding dehydrated *N*-acetyl-cysteine-*S*-1,4-dichlorobenzene, which comprised about 10% of total metabolites. No hydroquinones were observed, even under conditions of induced oxidative metabolism (Hissink *et al.*, 1997a).

Conversion of *para*-dichlorobenzene to oxidized metabolites, glutathione conjugates and covalently bound metabolites was investigated in hepatic microsomes from humans, male B6C3F_1 mice and male Fischer 344, Sprague-Dawley and Wistar rats to determine possible species and strain differences. *para*-Dichlorobenzene is hepatocarcinogenic in B6C3F_1 mice but not in Wistar or Fischer rats, and is nephrotoxic and nephrocarcinogenic in male Fischer rats. The species rank order for total conversion of *para*-dichlorobenzene *in vitro* was mouse > rat >> human. Microsomes from Fischer and Wistar rats showed similar conversion, whereas those from Sprague-Dawley rats converted less of the compound. Liver microsomes prepared from mice produced most of the reactive

metabolites, as indicated by covalent binding to macromolecules: > 20% of total metabolites were formed, whereas the amounts formed by rat and human microsomes were not detectable to 13%. Covalent binding by mouse microsomes was extensively inhibited by ascorbic acid, with a concomitant increase in hydroquinone formation, suggesting that benzoquinones are the reactive metabolites. Phenobarbital pretreatment of rats enhanced the conversion of *para*-dichlorobenzene *in vitro* and the amount of covalent binding. Covalent binding by all rat microsomes was partly (33–79%) inhibited by ascorbic acid. Addition of glutathione and ascorbic acid further diminished the covalent binding, with a concomitant increase in the formation of the glutathione-conjugated epoxide. Human microsomes produced the least reactive metabolites, > 70% of the covalent binding being prevented by the addition of glutathione (Hissink *et al.*, 1997b).

(*d*) *Comparative studies of* ortho-, para- *and* meta-*dichlorobenzenes*

The oxidation of [^{14}C]*ortho*- and *para*-dichlorobenzene was investigated in liver microsomes from male Wistar rats. The major metabolites of both isomers were dichlorophenols (2,5-dichlorophenol for *para*-dichlorobenzene and 2,3- and 3,4-dichlorophenol for *ortho*-dichlorobenzene) and dichlorohydroquinones. Formation of polar dihydrodiols appeared to be a major route for *ortho*- but not for *para*-dichlorobenzene. Both the hepatotoxic *ortho*-dichlorobenzene and the non-hepatotoxic *para*-dichlorobenzene were oxidized to metabolites that interacted covalently with protein and to only a small extent with DNA. Protein binding could be inhibited by the addition of ascorbic acid, with a concomitant increase in the formation of hydroquinones and catechols, indicating involvement of reactive benzoquinone metabolites in protein binding. In the presence of ascorbic acid, a substantial amount of protein-bound metabolites of *ortho*-dichlorobenzene was still observed, while protein binding of *para*-dichlorobenzene metabolites was nearly completely inhibited. This effect was ascribed to the direct formation of reactive benzoquinone metabolites in a single cytochrome P450-mediated oxidation of the primary oxidation product, a dichlorophenol. The presence of a chlorine *para* to the phenolic group (such as in 3,4-dichlorophenol, which is produced from *ortho*-dichlorobenzene) results in direct formation of a reactive benzoquinone and elimination of the chlorine as an anion. In contrast, 2,5-dichlorophenol, the major phenol isomer derived from *para*-dichlorobenzene is oxidized to its hydroquinone derivative, which requires prior oxidation in order to generate the reactive benzoquinone species. Reactive intermediates in the secondary metabolism of *ortho*-dichlorobenzene lead to more covalent binding than those derived from *para*-dichlorobenzene, and this finding correlates very well with their reported hepatotoxic potency (den Besten *et al.*, 1992). [The Working Group noted that after administration of *ortho*-dichlorobenzene to rats *in vivo*, the glutathione conjugates in bile and the mercapturic acids in urine were epoxide-derived and quinone- or hydroquinone-derived *S*-conjugates were not observed.]

4.2 Toxic effects

4.2.1 *Humans*

(*a*) ortho-*Dichlorobenzene*

Occupational exposure to *ortho*-dichlorobenzene at a concentration of 100 ppm caused some irritation of the eyes and upper respiratory tract (American Conference of Governmental Industrial Hygienists, 1991).

(*b*) meta-*Dichlorobenzene*

No data were available to the Working Group.

(*c*) para-*Dichlorobenzene*

A case of acute haemolytic anaemia was described in a three-year-old boy whose mother had seen him playing with moth crystals containing *para*-dichlorobenzene. Traces of 2,5-dichloroquinol and two other phenols where identified in urine collected six days later, but 2,5-dichlorophenol, the major metabolite of *para*-dichlorobenzene, could not be identified (Hallowell, 1959).

A case of aplastic anaemia was reported in a 68-year-old female employee of a clothing resale store who had handled a total of 5.5 kg *para*-dichlorobenzene and 7 kg naphthalene over a period of one month in a poorly ventilated storage area (Harden & Baetjer, 1978).

[The Working Group noted that neither report provides proof of a causal involvement of *para*-dichlorobenzene in the observed anaemia.]

4.2.2 *Experimental systems*

(*a*) ortho-*Dichlorobenzene*

Rats treated by gavage on five days a week with 188 or 376 mg/kg bw *ortho*-dichlorobenzene for 27 weeks had increased liver and kidney weights. Exposure by inhalation to 539 ppm (3200 mg/m^3) *ortho*-dichlorobenzene for one to three days for 3–6.5 h per day resulted in marked centrilobular necrosis of the liver and swelling of the kidney tubular epithelium (Hollingsworth *et al*., 1958).

Liver damage resulting from acute 4-h exposure to 246, 369, 610 or 739 ppm (1500, 2200, 3700 or 4400 mg/m^3) *ortho*-dichlorobenzene was found in male Sprague-Dawley rats. An inverse linear relationship was established between the logarithmic values of serum glutamate dehydrogenase and sorbitol dehydrogenase activities and decreased centrilobular liver-cell glucose-6-phosphatase staining intensity; the levels of exposure were linearly related to the same two parameters (Brondeau *et al*., 1986).

The ability of acetone and three other ketone vapours to affect the hepatotoxicity of inhaled *ortho*-dichlorobenzene was examined in male Sprague-Dawley rats and OF1 mice. Methylethylketone, methylisobutylketone or cyclohexanone increased liver cytochrome P-450 content and glutathione *S*-transferase activity but did not affect serum glutamate dehydrogenase activity in rats. Pre-exposure to these ketones enhanced the *ortho*-dichlorobenzene-induced increase in serum glutamate dehydrogenase activity by

8–63-fold, while the increases in cytochrome P450 content (33–86%) and glutathione *S*-transferase activity (42–64%) were identical to those resulting from exposure to the ketones alone. Acetone elicited cytochrome P450 and glutathione *S*-transferase responses comparable to those caused by the other ketones; however, pre-exposure to acetone potentiated (at 4785 ppm), reduced (at 10 670 ppm) or suppressed (at 14 790 ppm) *ortho*-dichlorobenzene-induced liver toxicity. The authors suggested that the concentration-dependent effects of acetone were due to induction of different microsomal enzymes: a toxifying isozyme at the lower concentration and a detoxifying isozyme at the higher concentration, as has been observed with 1,1-dichloroethylene (Brondeau *et al.*, 1989).

ortho-Dichlorobenzene was administered to male and female Sprague-Dawley rats at doses of 37.5, 75, 150 or 300 mg/kg bw per day for 10 days or at 25, 100 or 400 mg/kg bw per day for 90 days in corn oil by gavage; control animals received corn oil. In the 10-day study, male rats treated with 300 mg/kg bw had significantly decreased final body weights; heart, kidney, spleen, testis and thymus weights; and relative spleen and thymus weights. These animals also had significantly increased absolute and relative liver weights. Males also displayed significant increases in water consumption (at 300 mg/kg bw), alanine aminotransferase activity (at 300 mg/kg bw) and number of leukocytes (at 150 and 300 mg/kg bw). A significant increase in the incidence of hepatocellular necrosis was seen in males at 300 mg/kg bw when compared with controls. In the 90-day study, male rats exposed to 400 mg/kg bw *ortho*-dichlorobenzene had significantly decreased body weights and absolute and relative spleen weights and significantly increased absolute weights of kidney and liver and relative weights of heart, kidney, liver, lung, brain and testis. Females at this dose had increased absolute and relative weights of both kidney and liver. The only effects on clinical chemical parameters were increased alanine aminotransferase activity at 100 and 400 mg/kg bw, increased blood urea nitrogen and total bilirubin concentrations in males at 400 mg/kg bw and increased total bilirubin content in females at this dose. Histopathological evaluation showed hepatocellular lesions associated with treatment, which included centrilobular degeneration and hypertrophy and single-cell necrosis in males and females receiving 400 mg/kg bw *ortho*-dichlorobenzene. No adverse effect was observed at 25 mg/kg bw per day (Robinson *et al.*, 1991).

The hepatic toxicity of *ortho*-dichlorobenzene was studied in Fischer 344 rats given methyl palmitate in order to inhibit Kupffer-cell function or superoxide dismutase (conjugated to polyethylene glycol) to scavenge superoxide anions. Administration of either compound dramatically reduced the severity of *ortho*-dichlorobenzene-induced liver injury, and both agents reduced the increase in plasma alanine aminotransferase activity by 80%; light microscopic examination confirmed that the reductions in enzyme activity reflected protection from hepatocellular injury. Interestingly, methyl palmitate did not protect against *ortho*-dichlorobenzene-induced hepatotoxicity in phenobarbital-pretreated rats, and the degree of inhibition of hepatotoxicity by polyethylene glycol–superoxide dismutase was not significantly different from that in normal rats. The lack of significant inhibition of phenobarbital-potentiated hepatotoxicity by both polyethylene glycol–

superoxide dismutase and methyl palmitate suggests that reactive oxygen species released from a non-parenchymal source are not as crucial to the hepatotoxicity of *ortho*-dichlorobenzene in phenobarbital-pretreated as in the normal rats. The results suggest that reactive oxygen species released from Kupffer cells play a major role in the progression of *ortho*-dichlorobenzene hepatotoxicity (Gunawardhana *et al.*, 1993).

Twenty-two hours after intraperitoneal injection of [^{14}C]*ortho*-dichlorobenzene (127 μCi/kg bw, 42 μCi/μmol) to male Wistar rats and BALB/c mice, covalent binding of radiolabel was detected in the DNA, RNA and proteins of liver, kidney, lung and stomach. The authors stated that the covalent binding index to liver DNA (17 in rats, 50 in mice) was typical of that of carcinogens classified as weak initiators. The enzyme-mediated interaction of *ortho*-dichlorobenzene with calf thymus DNA of synthetic polyribonucleotides *in vitro* was mediated by a microsomal mixed-function oxidase system and microsomal glutathione transferases, which seemed to be effective only in liver and lung of rats and mice. Cytosolic glutathione transferases played a minor role in the bioactivation of *ortho*-dichlorobenzene (Colacci *et al.*, 1990). [The Working Group noted that DNA adducts were not identified.]

(*b*) meta-*Dichlorobenzene*

See the section on comparative studies of the toxicity of *ortho*-, *para*- and *meta*-dichlorobenzene, below.

(*c*) para-*Dichlorobenzene*

Daily oral administration of 0–200 mg/kg bw *para*-dichlorobenzene to female rats [strain unspecified] did not increase their liver weights or the concentrations of liver or urinary porphyrins (Carlson, 1977).

Groups of male and female Wistar rats and female Alderley Park mice were exposed for 5 h per day on five days a week to *para*-dichlorobenzene at concentrations of 0, 75 or 500 ppm (0, 450 or 3000 mg/m^3) for 76 weeks (rats) or 57 weeks (female mice), followed by 36 weeks (rats) or 19 weeks (female mice) without exposure. No clinical signs of toxicity were apparent at 75 ppm, nor were there any treatment-related effects on blood or urinary clinical chemistry. Slightly elevated urinary coproporphyrin excretion and increased liver and kidney weights were considered to be treatment-related effects in rats exposed to 500 ppm *para*-dichlorobenzene. [The Working Group noted that no quantitative data were included in the report]. Histopathological evaluation of non-neoplastic lesions did not indicate any treatment-related effects in either species (Loeser & Litchfield, 1983).

Fischer 344 rats were given 37.5–1500 mg/kg bw *para*-dichlorobenzene by gavage on five days per week for 13 weeks. Body-weight gain was decreased at doses ≥ 600 mg/kg bw, and the mortality rate was increased at doses ≥ 900 mg/kg bw. At doses ≥ 300 mg/kg bw, male rats developed kidney damage characterized by tubular degeneration and necrosis, while females had no adverse renal effects at doses ≤ 1500 mg/kg bw. Hepatotoxicity was observed in rats at doses ≥ 600 mg/kg bw, and the urinary concentration of

coproporhyrins was increased at 1200 mg/kg bw. In the animals treated with 1200 or 1500 mg/kg bw, additional adverse effects were seen, consisting of bone-marrow hypoplasia, lymphoid depletion of the spleen and thymus and necrosis in the nasal turbinates and intestinal mucosa. In the same study, $B6C3F_1$ mice were treated with daily oral doses of 84–1800 mg/kg bw. Body-weight gain was affected at doses > 1000 mg/kg bw; deaths were seen only at 1800 mg/kg bw. Histological and clinical hepatotoxicity was induced at 600 mg/kg bw but not at 338 mg/kg bw. Mice treated with 1500 mg/kg bw or 1800 mg/kg bw developed lymphoid necrosis in the thymus, lymphoid depletion in the spleen and haematopoietic hypoplasia of the spleen and bone marrow. No effect on the kidney was observed (National Toxicology Program, 1987).

Groups of 10 male and 10 female Fischer 344 rats were dosed by gavage with 0, 75, 150, 300 or 600 mg/kg bw per day of *para*-dichlorobenzene in corn oil. Half of the animals were killed after four weeks and the remainder after 13 weeks. Increased urinary lactate dehydrogenase activity, increased epithelial cell excretion and exacerbation of hyaline droplet accumulation in the cytoplasm of renal cortical cells were observed in male rats over the entire dose range investigated. Tubular single-cell necrosis and dilated tubules with granular cast formation in the outer zone of the medulla were evident in male rats after 4 and 13 weeks of treatment with doses of 150–600 mg/kg bw per day. Female rats showed no indication of nephrotoxicity. The authors concluded that the morphological characteristics of the sex-specific effects on the kidney corresponded to the light hydrocarbon nephropathy observed after short-term treatment with a number of aliphatic and cyclic hydrocarbons (Bomhard *et al.*, 1988).

Male Fischer 344 rats were given a single dose of 300 or 500 mg/kg bw [^{14}C]*para*-dichlorobenzene or [^{14}C]*ortho*-dichlorobenzene by gavage, placed in metabolism cages for collection of urine and killed 24 h later. Gel filtration chromatography of soluble renal proteins from *para*-dichlorobenzene-treated rats showed that the radiolabel co-eluted with α_{2u}-globulin in a single sharp peak, and *para*-dichlorobenzene and its metabolite, 2,5-dichlorophenol, were found to be reversibly bound to this globulin. *ortho*-Dichlorobenzene-derived radiolabel, but not that from *para*-dichlorobenzene, was found to bind covalently to liver and high-molecular-mass plasma proteins. *para*-Dichlorobenzene increased protein droplet formation in male rat kidneys, whereas equimolar doses of *ortho*-dichlorobenzene had no effect. Renal-cell proliferation, measured by [^{3}H]thymidine incorporation into renal DNA, was increased after treatment with *para*- but not *ortho*-dichlorobenzene (Charbonneau *et al*., 1989).

Male NCI-Black-Reiter rats are the only animals known not to synthesize α_{2u}-globulin in the liver. Under conditions of exposure that clearly induced α_{2u}-globulin nephropathy in male Fischer 344 rats (500 mg/kg bw per day on four consecutive days), *para*-dichlorobenzene did not induce α_{2u}-globulin accumulation, hyaline (protein) droplet formation or renal lesions in these animals (Dietrich & Swenberg, 1991).

Increases in the amount of kidney-type α_{2u}-globulin (16 kDa), which result from renal processing of the 19 kDa native-type α_{2u}-globulin produced in the liver, were detected in the urine of male rats treated with 220 mg/kg bw per day *para*-dichlorobenzene for seven

consecutive days. The increase correlated directly with increased concentrations of kidney-type α_{2u}-globulin in renal tissue and with accumulation of hyaline droplets in the proximal convoluted tubules. Similar changes were not observed with the nephrotoxic chemicals puromycin aminonucleoside and hexachlorobutadiene, but a marked increase in kidney-type α_{2u}-globulin was detected after administration of 2,2,4-trimethylpentane, *d*-limonene, decalin or isophorone (Saito *et al.*, 1996).

B6C3F$_1$ mice were exposed to *para*-dichlorobenzene in corn oil by gavage for up to five days at a dose of 600 mg/kg bw per day, and male Fischer 344 rats were exposed to 300 mg/kg bw per day on five days per week for up to three weeks. The percentage of cells in S-phase (labelling index) was compared in tissues of animals given either 5-bromo-2′-deoxyuridine (BrDU) or [^{3}H]thymidine as a single intraperitoneal injection 2 h before being killed or continuously via a subcutaneously implanted osmotic pump for three or six days. Cell proliferation was increased in the livers of animals of both species treated with *para*-dichlorobenzene when compared with controls. After four days of treatment with the chemical and continuous administration of a DNA precursor label during the last three days of treatment, the labelling indices in control and *para*-dichlorobenzene-treated mouse livers were 0.7 and 19% for BrDU and 0.9 and 15% for [^{3}H]thymidine, respectively. The labelling indices for BrDU- and [^{3}H]thymidine-labelled renal proximal tubular cells were 7.7 and 8.0%, respectively, in male rats receiving *para*-dichlorobenzene for four days, while those in controls were 4.3 and 3.7%, respectively. The renal proximal tubular cell labelling index increased to 11% in male BrDU-labelled rats treated with *para*-dichlorobenzene for three weeks (Eldridge *et al.*, 1990).

A sharp increase in labelling index was seen in female B6C3F$_1$ mice and Fischer 344 rats 24 h after a single treatment with 600 mg/kg bw *para*-dichlorobenzene, and after 48 h in male mice. No increase in the activity of liver-associated plasma enzymes was seen at doses up to 1200 mg/kg bw. In mice treated for 13 weeks with *para*-dichlorobenzene by gavage at 300 or 600 mg/kg bw per day, a statistically significant, transient peak of hepatocellular proliferation was observed during week 1 at 600 mg/kg bw per day. Hepatocellular proliferation was also observed in female rats, which had no increase in liver tumour incidence when compared with controls. The relative liver weights (percentage of body weight) in comparison with controls were increased in male and female mice and female rats at the high dose, but not in male rats. No significant increases in the activities of liver-associated plasma enzymes were found at any time, indicating a lack of overt hepatotoxicity. Histopathological evaluation revealed no evidence of hepatocellular necrosis in any group. The authors considered that their data indicated early mitogenic stimulation of cell proliferation rather than regeneration secondary to cytotoxicity in the livers of *para*-dichlorobenzene-treated mice, which correlates with the observed tumour formation in a dose-dependent manner. The induction of cell proliferation by *para*-dichlorobenzene in rat liver in the absence of a tumorigenic response was suggested by the authors to imply important species differences in the relationship between cell proliferation and carcinogenesis (Eldridge *et al.*, 1992).

Cell proliferation in the kidneys and livers of Fischer 344 rats and $B6C3F_1$ mice treated by gavage with *para*-dichlorobenzene at 0, 150, 300 or 600 mg/kg bw per day for four days was evaluated by measuring BrDU incorporation into nuclei of DNA-synthesizing cells. The cumulative fraction of proliferating cells was increased in the proximal tubular epithelial cells of male rats at the high dose but not at the lower doses or in females at either dose, when the γ-glutamyl transferase reaction was used to identify tubular cells. No increase in cell proliferation was found in mouse kidney. The fractions of proliferating cells in the livers of rats and mice of each sex were also increased at the two higher doses. Although the increased cell proliferation in male rat kidney and in the livers of mice of each sex correlates with the reported carcinogenic effects of *para*-dichlorobenzene in those tissues, cell proliferation was also induced in the livers of rats of each sex and in female mice at the low dose in the absence of an increased incidence of liver tumours, indicating that acute induction of cell proliferation is not sufficient to lead to or explain tumour formation (Umemura *et al.*, 1992).

A single administration of 300 mg/kg bw *para*-dichlorobenzene or 950 mg/kg bw diethylhexyl phthalate to male Fischer 344 rats by gavage induced an increase in the hepatic labelling index and in the expression of the immediate early genes c-*fos*, c-*myc* and c-*jun* in the liver similar to that in untreated controls (Hasmall *et al.*, 1997). The authors concluded that neither the labelling index nor the expression of immediate early genes can distinguish between hepatocarcinogenic (diethylhexyl phthalate) and non-hepatocarcinogenic (*para*-dichlorobenzene) liver mitogens. [The Working Group noted that the experimental design, involving a single administration, is not suitable for evaluating mechanisms of carcinogenicity and that *para*-dichlorobenzene is hepatocarcinogenic at doses that concomitantly induce liver injury.]

$B6C3F_1$ mice and Fischer 344 rats were treated by gavage for four weeks with *para*-dichlorobenzene in corn oil. The doses for mice were 150, 300 or 600 mg/kg bw (the maximal tolerated dose, which also increased liver tumour formation), and those for rats were 75, 150 or 300 mg/kg bw. In mice at the high dose, the incidence of hepatic cell proliferation was increased by 16-fold at one week and by fourfold at four weeks; at 300 mg/kg bw, the increase was seen only at one week and had subsided by four weeks. In rats at doses of 150 and 300 mg/kg bw, the incidence of hepatic cell proliferation was increased after one week but had returned to normal after four weeks. The authors concluded that sustained cell proliferation occurs only in susceptible species at a carcinogenic dose (Umemura *et al.*, 1998).

Male Fischer 344 rats and male $B6C3F_1$ mice were given 0, 25, 75, 150, 300 or 600 mg/kg bw per day *para*-dichlorobenzene by gavage on five days a week for 1, 4 or 13 weeks. *para*-Dichlorobenzene produced significant, dose-related increases in relative liver weights in both rats and mice, which was associated with mild and marked centrilobular hypertrophy, respectively. Dose-related increases in cytochrome P450 content and 7-pentoxyresorufin-*O*-depentylase activity were observed throughout the 13-week treatment period in animals of each sex. CYP 2B isoenzymes were induced by *para*-dichlorobenzene in both rat and mouse liver microsomes. The hepatic labelling index was

increased in rats treated for one week with 300 mg/kg bw *para*-dichlorobenzene, whereas in mice the hepatic labelling index was increased by treatment with 300 or 600 mg/kg bw *para*-dichlorobenzene for one and four weeks. The labelling index in the kidney proximal tubular cells of rats was increased at 1, 4 and 13 weeks of *para*-dichlorobenzene administration, while little effect was seen in mouse kidney (Lake *et al*., 1997).

(*d*) *Comparative studies of the toxicity of* ortho-, para- *and* meta-*dichlorobenzenes*

The flow of bile duct and pancreatic fluid was increased and the protein concentration of the fluid was decreased 24 h after intraperitoneal administration of 5 mmol/kg bw *ortho*-dichlorobenzene to male Holtzman rats, while *para*-dichlorobenzene had no such action. This effect did not involve secretin or cholinergic stimulation of the pancreas and was not associated with hepatotoxicity, as shown by the absence of an increase in serum glutamate pyruvate transaminase activity (Yang *et al*., 1979).

Tenfold more covalent binding was observed in the livers of male C57BL/6J mice treated with 0.5 mmol/kg bw *ortho*- compared with *para*-dichlorobenzene. The amount of covalent binding was increased by pretreatment with phenobarbital, and this increase was prevented by concomitant pretreatment with SKF 525-A (Reid & Krishina, 1973).

The acute hepatotoxicity of the three isomers of dichlorobenzene was evaluated in male Fischer 344 rats at various times after intraperitoneal administration. Plasma alanine aminotransferase activity, measured 24 h after treatment with 1.8–5.4 mmol/kg bw *ortho*-dichlorobenzene, was dramatically elevated. In contrast, equimolar doses of *para*-dichlorobenzene had no effect, and *meta*-dichlorobenzene had a clearly weaker effect on enzyme activity at doses ≥ 2.7 mmol/kg bw. Histopathological changes in the livers of treated animals correlated with the alterations in enzyme activities. Phenobarbital pretreatment potentiated the acute hepatotoxicity of *ortho*- and *meta*-dichlorobenzene but did not affect the toxicity of *para*-dichlorobenzene. Similarly, SKF-525A pretreatment inhibited the hepatotoxicity of *ortho*-dichlorobenzene. Equimolar doses of *ortho*- and *meta*-dichlorobenzene produced approximately equivalent depletion of intrahepatic glutathione, while *para*-dichlorobenzene had no effect on this parameter. Prior depletion of hepatic glutathione by pretreatment with phorone markedly potentiated the hepatotoxicity of *ortho*- and *meta*-dichlorobenzene but only slightly increased the toxicity of *para*-dichlorobenzene. These quantitative and qualitative differences could not be explained by differences in hepatic distribution or covalent binding to hepatic proteins. Interestingly, male Fischer rats are 75 times more sensitive than Sprague-Dawley rats to the acute hepatotoxicity of *ortho*-dichlorobenzene, and this is one of the most dramatic strain differences in toxicity (Gunawardhana & Sipes, 1991; Stine *et al*., 1991).

Toxic effects on the liver, kidneys and thyroid were monitored after a single intraperitoneal administration of 1, 2 or 4 mmol/kg bw *ortho*- or *para*-dichlorobenzene to male Wistar rats. *ortho*-Dichlorobenzene was the most potent hepatotoxicant, as determined by plasma alanine aminotransferase activity and histopathological appearance after 72 h. Protein droplets were observed in tubular epithelial cells 72 h after administration of *para*-

dichlorobenzene, but not after administration of *ortho*-dichlorobenzene. Both chlorinated benzenes reduced the plasma thyroxine concentration (den Besten *et al.*, 1991).

Male Fischer 344 rats were injected intraperitoneally with 2, 3 or 4 mmol/kg bw *ortho*-, *meta*- or *para*-dichlorobenzene, and pair-fed control animals were injected intraperitoneally with corn oil (1 mL/kg bw). After 24 h, plasma alanine aminotransferase activity was found to be increased by *ortho*-dichlorobenzene in a dose-dependent manner. Centrilobular necrosis was observed in rats treated with *ortho*-dichlorobenzene, while the morphological appearance was relatively normal in rats treated with *meta*- or *para*-dichlorobenzene. Kidney weights and blood urea nitrogen concentration were not altered by treatment with *meta*- or *para*-dichlorobenzene. Accumulation of *para*-aminohippurate in renal cortical slices was decreased by *meta*- (2 and 4 mmol/kg bw) and *ortho*-dichlorobenzene (3 and 4 mmol/kg bw), while accumulation of the cation tetraethylammonium was decreased by 4 mmol/kg bw *para*-dichlorobenzene. The results demonstrate that *ortho* substitution enhances hepatic toxicity and that the liver is more sensitive than the kidney to the toxic effects of dichlorobenzenes (Valentovic *et al.*, 1993).

Although Fischer 344 rats are many times more sensitive to the hepatotoxic effect of *ortho*-dichlorobenzene than Sprague-Dawley rats, the LD_{50} values (1.7 mL/kg bw in male Fischer 344 and 1.8 mL/kg bw in Sprague-Dawley rats) were similar. In age-matched male Sprague-Dawley and Fischer 344 rats given *ortho*-dichlorobenzene intraperitoneally (0.2, 0.6 or 1.2 mL/kg bw), liver injury over time was assessed by measuring plasma alanine aminotransferase and sorbitol dehydrogenase activities and histopathology. Fischer 344 rats showed larger increases in plasma alanine aminotransferase activity after administration of 0.2 or 0.6 mL/kg bw *ortho*-dichlorobenzene than Sprague-Dawley rats. When sorbitol dehydrogenase was used as a marker of liver injury, the strain difference was seen only at 0.2 mL/kg bw. Liver regeneration was estimated from [^{3}H]thymidine incorporation into liver DNA and an assay for proliferating cell nuclear antigen. These markers indicated that Fischer 344 rats had up to fourfold more hepatocellular regeneration than Sprague-Dawley rats. The significantly greater depletion of hepatic glycogen observed in Fischer 344 rats after administration of 0.2 or 0.6 mL/kg bw *ortho*-dichlorobenzene was not accompanied by significant changes in plasma glucose concentration and was consistent with the stimulated tissue repair seen in these rats at the corresponding doses (Kulkarni *et al.*, 1996).

The acute hepatotoxicity of the dichlorobenzene isomers was compared in the livers of male $B6C3F_1$ mice at different times after a single intragastric administration of *ortho*-, *meta*- or *para*-dichlorobenzene at 300, 300 or 1800 mg/kg bw, respectively. Acute hepatic injury was assessed from serum alanine aminotransferase activity, histopathological appearance and hepatocyte replication (BrDU labelling). Both *ortho*- and *meta*-dichlorobenzene significantly increased liver weights and serum alanine aminotransferase activity and caused extensive liver-cell necrosis. In contrast, *para*-dichlorobenzene induced slight hepatocyte injury only at the sixfold higher dose of 1800 mg/kg bw; however, it induced hepatocyte proliferation at 1000 mg/kg bw, in the absence of any signs of hepatotoxicity while increased cell proliferation due to *ortho*- or *meta*-dichlorobenzene occurred only at doses that caused hepatic injury. These data suggest that the hepatocyte proliferation

induced by *ortho*- or *meta*-dichlorobenzene is compensatory regeneration, while that induced by *para*-dichlorobenzene is a response to mitogenic stimulation (Umemura *et al.*, 1996).

4.3 Reproductive and developmental effects

4.3.1 *Humans*

No data were available to the Working Group.

4.3.2 *Experimental systems*

The developmental effects of *para*-dichlorobenzene in experimental systems have been reviewed (Loeser & Litchfield, 1983). In rats exposed by inhalation to 0, 75, 200 or 500 ppm (0, 450, 1200 or 3000 mg/m^3) for 6 h per day on days 6–15 of gestation, isolated malformations were seen at all doses, but the authors concluded that these did not constitute evidence of embryo- or fetotoxicity or teratogenicity.

Groups of 30–32 Fischer 344 rats were exposed to *ortho*-dichlorobenzene (purity, 98.81%) by inhalation on days 6–15 of gestation, and groups of 28–30 New Zealand rabbits were exposed on days 6–18 of gestation to 0, 100, 200 or 400 ppm (0, 600, 1200 or 2400 mg/m^3). Further groups of rabbits were exposed to 0, 100, 300 or 800 ppm (0, 600, 1800 or 4800 mg/m^3) *para*-dichlorobenzene (purity, 99.9%) on days 6–18 of gestation. In rats, maternal toxicity, evident as decreased weight gain and increased relative liver weights, was seen in all treated groups, but there was no indication of an effect on the developing organism. In rabbits, decreased maternal body weights were noted in all exposed groups, but the effect was largely limited to changes manifest within the first three days of exposure; again, there were no effects on the developing offspring attributable to *ortho*-dichlorobenzene. With *para*-dichlorobenzene, maternal body-weight gain was reduced at the high dose at several periods during gestation, but no other dose-related effects were seen in the does or fetuses (Hayes *et al*., 1985).

The developmental effects of *para*-dichlorobenzene (99% pure) in groups of 13–17 CD rats were evaluated after exposure to 0, 250, 500, 750 or 1000 mg/kg bw per day by oral gavage in corn oil. Decreased food consumption was seen in all treated groups, and females at the highest dose had decreased body-weight gain during treatment. There were no effects on fetal viability, but fetal body weights were decreased at the highest dose, and the incidence of extra ribs was increased at all doses above 250 mg/kg bw per day (Giavini *et al*., 1986).

4.4 Genetic and related effects

4.4.1 *Humans*

A study of 26 individuals accidentally exposed to *ortho*-dichlorobenzene (presumably > 100 ppm) for four days revealed a statistically significant (4.4-fold) increase in the frequency of chromosomal aberrations in peripheral blood lymphocytes as compared with a control group; six months later, chromosomal aberrations were still more frequent than in the control group (Zapata-Gayon *et al*., 1982).

4.4.2 *Experimental systems* (see Table 5 for references)

ortho-Dichlorobenzene did not induce point mutations in eight histidine-requiring mutants of *Salmonella typhimurium*, which involve the *C*, *D* and *G* genes of the *histidine* operon, and was not mutagenic to *S. typhimurium* strains TA100, TA1535, TA1537, TA1538 or TA98 with and without metabolic activation. It induced mitotic gene conversion and reverse mutation in the D7 strain of *Saccharomyces cerevisiae* in the presence of an exogenous metabolic system from the livers of induced mice and was very weakly mutagenic in a methionine-requiring auxotroph of *Aspergillus nidulans*. A dose-dependent increase in the frequency of micronucleated polychromatic erythrocytes was detected in the bone marrow of male mice after intraperitoneal injection of two equal doses of *ortho*-dichlorobenzene. DNA damage was not induced in the livers of female rats given two oral doses of *ortho*-dichlorobenzene. Covalent binding of [^{14}C]*ortho*-dichlorobenzene to calf thymus DNA was detected *in vitro* after incubation with various subcellular preparations of liver from induced mice. Weak covalent binding of *ortho*-dichlorobenzene to the DNA of various organs in male rats and mice was also reported *in vivo* after a single intraperitoneal treatment.

meta-Dichlorobenzene did not induce mutation in *S. typhimurium* strains TA100, TA1535, TA1537, TA1538 or TA98 or in *Escherichia coli* WP2 *uvr*A with and without metabolic activation; it had contrasting effects in differential toxicity assays with *E. coli* and *Bacillus subtilis* and caused gene conversion in *Saccharomyces cerevisiae*. A dose-dependent increase in the frequency of micronucleated polychromatic erythrocytes was detected in the bone marrow of male mice after intraperitoneal injection of two equal doses of *meta*-dichlorobenzene.

para-Dichlorobenzene was not mutagenic to *S. typhimurium* strains TA100, TA1535, TA1537, TA1538 or TA98 with and without metabolic activation; in only one study, a more than twofold increase in the number of revertant colonies was observed in the presence of metabolic activation in one of two experiments carried out in strain TA1535. *para*-Dichlorobenzene induced mitotic gene conversion and reverse mutation in the D7 strain of *Saccharomyces cerevisiae* in the presence of a metabolic activation system from liver of induced mice. It was reported to induce reverse mutations of a methionine-requiring auxotroph of *Aspergillus nidulans* and to induce chromosomal abnormalities and breakage in the root tips of two *Vicia* species. *para*-Dichlorobenzene did not induce DNA fragmentation in primary cultures of either rat or human hepatocytes. It did not significantly increase the frequency of mutants in mouse lymphoma L5178Y *tk*$^{+/-}$ cells and did not induce sister chromatid exchange in Chinese hamster ovary cells either in the absence or in the presence of liver preparations from Aroclor 1254-induced rats. *para*-Dichlorobenzene significantly increased the frequency of micronucleated cells in primary cultures of rat hepatocytes, but not in primary cultures of human hepatocytes under the same experimental conditions. It did not increase the frequency of chromosomal aberrations in Chinese hamster ovary cells in the absence or in the presence of a metabolic system from the liver of Aroclor 1254-induced rats. *para*-Dichlorobenzene increased the frequency of sister chromatid exchange in human

Table 5. Genetic and related effects of dichlorobenzenes

Test system	Results[a]		Dose[b] (LED or HID)	Reference
	Without exogenous metabolic activation	With exogenous metabolic activation		
***ortho*-Dichlorobenzene**				
Salmonella typhimurium TA100, TA98, TA1535, TA1537, reverse mutation	–	–	100 µg/plate	Haworth *et al.* (1983)
Salmonella typhimurium TA100, TA98, TA1535, TA1537, TA1538, reverse mutation	–	–	832 µg/plate	Shimizu *et al*. (1983)
Salmonella typhimurium (eight unidentified strains), reverse mutation	–	NT	NR	Andersen *et al*. (1972)
Aspergillus nidulans, reverse mutation	(+)	NT	200	Prasad (1970)
Saccharomyces cerevisiae, homozygosis by mitotic recombination or gene conversion	–	+	74	Paolini *et al*. (1998)
Saccharomyces cerevisiae, reverse mutation	–	+	74	Paolini *et al*. (1998)
DNA strand breaks, cross-links or related damage, female rat liver cells *in vivo*	–		300 po × 2	Kitchin *et al*. (1993)
Micronucleus formation, male mouse bone-marrow cells *in vivo*	+		93.5 ip × 2	Mohtashamipur *et al*. (1987)
Binding (covalent) to calf thymus DNA *in vitro*	–	+	15	Paolini *et al*. (1998)
Binding (covalent) to DNA, male rat liver, lung, kidney and stomach *in vivo*	+		0.4 ip × 1	Colacci *et al.* (1990)
Binding (covalent) to DNA, male mouse liver, lung, kidney and stomach *in vivo*	+		0.4 ip × 1	Colacci *et al.* (1990)
***meta*-Dichlorobenzene**				
Escherichia coli pol A/W3110-P3478, differential toxicity (spot test)	+	NT	13000	Environmental Protection Agency (1984)
Bacillus subtilis rec strains, differential toxicity	–	NT	13000	Environmental Protection Agency (1984)
Salmonella typhimurium TA100, TA98, TA1535, TA1537, TA1538, reverse mutation	–	–	820 µg/plate	Shimizu *et al*. (1983)

Table 5 (contd)

Test system	Results[a]		Dose[b] (LED or HID)	Reference
	Without exogenous metabolic activation	With exogenous metabolic activation		
***meta*-Dichlorobenzene (contd)**				
Salmonella typhimurium TA100, TA98, TA1535, TA1537, TA1538, reverse mutation	–	–	325	Environmental Protection Agency (1984)
Escherichia coli WP2 *uvr*A, reverse mutation	–	–	325	Environmental Protection Agency (1984)
Saccharomyces cerevisiae, gene conversion	+	+	30	Environmental Protection Agency (1984)
Micronucleus formation, male mouse bone-marrow cells *in vivo*	+		87.5 ip × 2	Mohtashamipur *et al*. (1987)
***para*-Dichlorobenzene**				
Salmonella typhimurium TA100, TA98, TA1535, TA1537, reverse mutation	–	–	100 µg/plate	Haworth *et al*. (1983)
Salmonella typhimurium TA100, TA98, TA1538, reverse mutation	–	–	2500 µg/plate	Loeser & Litchfield (1983)
Salmonella typhimurium TA1535, reverse mutation	–	?	500 µg/plate	Loeser & Litchfield (1983)
Salmonella typhimurium TA100, TA98, TA1535, TA1537, TA1538, reverse mutation	–	–	6552 µg/plate	Shimizu *et al*. (1983)
Saccharomyces cerevisiae, homozygosis by mitotic recombination or gene conversion	–	+	74	Paolini *et al*. (1998)
Saccharomyces cerevisiae, reverse mutation	–	+	147	Paolini *et al*. (1998)
Aspergillus nidulans, reverse mutation	(+)	NT	200	Prasad (1970)
Vicia sativa, chromosomal aberrations	+	NT	NR	Sharma & Bhattacharyya (1956)
Vicia faba, chromosomal aberrations	+	NT	NR	Srivastava (1966)

Table 5 (contd)

Test system	Results[a]		Dose[b] (LED or HID)	Reference
	Without exogenous metabolic activation	With exogenous metabolic activation		
***para*-Dichlorobenzene (contd)**				
DNA strand breaks, cross-links or related damage, rat hepatocytes *in vitro*	–	NT	470	Canonero *et al*. (1997)
Gene mutation, mouse lymphoma L5178Y cells, *tk* locus *in vitro*	–	–	100	US National Toxicology Program (1987)
Sister chromatid exchange, Chinese hamster ovary cells *in vitro*	–	–	150	Galloway *et al.* (1987)
Micronucleus formation, rat hepatocytes *in vitro*	+	NT	150	Canonero *et al*. (1997)
Chromosomal aberrations, Chinese hamster ovary cells *in vitro*	–	–	150	Galloway *et al.* (1987)
DNA strand breaks, cross-links or related damage, human hepatocytes *in vitro*	–	NT	470	Canonero *et al*. (1997)
Micronucleus formation, human hepatocytes *in vitro*	–	NT	470	Canonero *et al*. (1997)
Sister chromatid exchange, human lymphocytes *in vitro*	(+)	NT	0.1000	Carbonell *et al*. (1991)
DNA strand breaks, cross-links or related damage, mouse liver and spleen cells *in vivo*	+		2000 ip × 1	Sasaki *et al*. (1997)
DNA strand breaks, cross-links or related damage, mouse kidney, lung and bone-marrow cells *in vivo*	–		2000 ip × 1	Sasaki *et al.* (1997)
Unscheduled DNA synthesis, male and female mouse hepatocytes *in vivo*	–		1000 po × 1	Sherman *et al.* (1998)
Unscheduled DNA synthesis, male and female rat kidney *in vivo*	–		1000 po × 1	Sherman *et al.* (1998)
Micronucleus formation, male mouse bone-marrow cells *in vivo*	+		177.5 ip × 2	Mohtashamipur *et al*. (1987)
Micronucleus formation, male mouse erythrocytes in *vivo*	–		1800 po × 13 wk	National Toxicology Program (1987)
Micronucleus formation, male and female mouse bone-marrow cells *in vivo*	–		1600 ip × 2	Morita *et al*. (1997)
Micronucleus formation, mouse bone-marrow cells *in vivo*	–		2000 po × 2	Morita *et al*. (1997)
Chromosomal aberrations, rat bone-marrow cells *in vivo*	–		682 ppm in air 2 h × 1	Loeser & Litchfield (1983)

Table 5 (contd)

Test system	Results[a]		Dose[b] (LED or HID)	Reference
	Without exogenous metabolic activation	With exogenous metabolic activation		
***para*-Dichlorobenzene (contd)**				
Chromosomal aberrations, rat bone-marrow cells *in vivo*	–		500 ppm in air 5 h/d × 3 mo	Loeser & Litchfield (1983)
Dominant lethal mutation, mice	–		450 ppm in air 6 h/d × 5	Loeser & Litchfield (1983)
Binding (covalent) to calf thymus DNA *in vitro*	–	+	0.003	Lattanzi *et al.* (1989)
Binding (covalent) to calf thymus DNA *in vitro*	–	+	15	Paolini *et al.* (1998)
Binding (covalent) to DNA, male mouse liver, lung, kidney and stomach *in vivo*	+		0.4 ip × 1	Lattanzi *et al.* (1989)
Binding (covalent) to DNA, male rat liver, lung, kidney and stomach *in vivo*	–		0.4 ip × 1	Lattanzi *et al.* (1989)
Binding (covalent) to RNA or protein, male mouse liver, lung, kidney and stomach *in vivo*	+		0.4 ip × 1	Lattanzi *et al.* (1989)
Binding (covalent) to RNA or protein, male rat liver, lung, kidney and stomach *in vivo*	–		0.4 ip × 1	Lattanzi *et al.* (1989)

[a] +, positive; (+), weak positive; –, negative; NT, not tested; ?, inconclusive

[b] LED, lowest effective dose; HID, highest ineffective dose; unless otherwise stated, in-vitro tests, μg/mL; in-vivo tests, mg/kg bw per day; NR, not reported; po, oral; ip, intraperitoneal; wk, week; mo, month; d, day

peripheral blood lymphocytes to a modest but significant extent in the absence of metabolic activation.

A significant increase in the frequency of alkali-labile DNA lesions was detected by means of the comet assay in liver and spleen, but not in kidney, lung or bone marrow, of mice given a single intraperitoneal dose of *para*-dichlorobenzene. A dose-dependent increase in the frequency of micronucleated polychromatic erythrocytes was detected in the bone marrow of male mice after intraperitoneal injection of two equal doses of *para*-dichlorobenzene, but no response was found in another study in mice of each sex; moreover, no significant increase in the frequency of micronucleated peripheral blood reticulocytes was seen in male mice given oral or intraperitoneal doses, and no increase in the frequency of chromosomal abnormalities was detected in bone-marrow cells of rats after single or multiple exposures to *para*-dichlorobenzene by inhalation.

para-Dichlorobenzene did not induce unscheduled DNA synthesis in mouse hepatocytes or rat kidney cells after single oral doses comparable to the daily doses given in carcinogenicity assays conducted with this chemical (see section 3).

para-Dichlorobenzene did not induce dominant lethal mutations at any maturation stage of the eight-week spermatogenic cycle of mice.

Covalent binding of [^{14}C]*para*-dichlorobenzene to calf thymus DNA was detected *in vitro* after incubation with various subcellular fractions of liver from induced mice. After intraperitoneal injection of [^{14}C]*para*-dichlorobenzene, DNA, RNA and protein adducts were detected in liver, lung, kidney and stomach of male mice but not male rats. Studies of the interaction of *para*-dichlorobenzene with calf thymus DNA *in vitro* indicated that microsomal mixed-function oxidases and microsomal glutathione tranferases are involved in its metabolic activation.

4.5 Mechanistic considerations

4.5.1 *Renal tumours in male rats*

The criteria for establishing that an agent causes renal tumours in male rats through a response associated with α_{2u}-globulin (Capen *et al*., 1999) are as follows:

- lack of genotoxic activity (the agent and/or a metabolite) on the basis of an overall evaluation of results obtained *in vitro* and *in vivo*;
- nephropathy and renal tumorigenicity seen only in male rats;
- induction in shorter studies of the characteristic sequence of histopathological changes, of which protein droplet accumulation is obligatory;
- identification of the protein that accumulates in tubular cells as α_{2u}-globulin;
- reversible binding of the chemical metabolite to α_{2u}-globulin;
- induction of a sustained increase in cell proliferation in the renal cortex; and
- similarities between the dose–response relationship for tumour outcome with those for histopathological end-points (protein droplets, α_{2u}-globulin accumulation, cell proliferation).

The results of several 13-week studies in male and female rats showed that *para*-dichlorobenzene causes renal damage characterized by tubular degeneration and necrosis

in male rats but no adverse effects in female rats. Necrosis in single tubular cells and dilated tubules with granular cast formation were seen in the outer zone of the medulla in male rats. In male Fischer 344 rats, *para*-dichlorobenzene increased the number of protein droplets that stained for α_{2u}-globulin. In contrast, in NCI-Black Reiter rats, which do not synthesize α_{2u}-globulin, *para*-dichlorobenzene did not increase the number of protein droplets.

para-Dichlorobenzene and its metabolite 2,5-dichlorophenol bound to α_{2u}-globulin isolated from *para*-dichlorobenzene-treated male rats; the binding was found to be reversible. *In vitro*, *para*-dichlorobenzene and 2,5-dichlorophenol competed with 2,4,4-trimethyl-2-pentanol for binding to α_{2u}-globulin (Borghoff *et al*., 1991). Binding of 2,5-dichlorophenol, but not *para*-dichlorobenzene, to α_{2u}-globulin *in vitro* reduced the rate of lysosomal degradation relative to the native protein (Lehman-McKeeman *et al*., 1990).

A number of studies showed that *para*-dichlorobenzene increases cell proliferation in the renal cortex of male, but not female, rats. This increased cell proliferation is sustained during up to 13 weeks of administration of the chemical. Increased protein droplet accumulation and renal-cell proliferation were observed at a concentration that causes renal tumours in male rats.

para-Dichlorobenzene, but not *ortho*-dichlorobenzene, induces renal tumours specifically in male rats. There is substantial evidence that *para*-dichlorobenzene induces these tumours through an α_{2u}-globulin-associated response. Although *para*-dichlorobenzene does not bind to DNA in the male rat kidney, there is weak evidence that it binds to DNA in several tissues in treated mice. Both *ortho*- and *para*-dichlorobenzene have been reported to bind to proteins and DNA in the same mouse tissues. No attempt was made to isolate any DNA adducts. The data available on the genotoxicity of *para*-dichlorobenzene and *ortho*-dichlorobenzene also do not allow any distinction to be made between these two compounds, which differ significantly in their tumorigenicity: *ortho*-dichlorobenzene does not cause tumours, whereas *para*-dichlorobenzene causes liver tumours in mice and kidney tumours in male rats. Overall, the data on genotoxicity do not support a mechanism for renal-cell tumour induction in rats involving direct interaction of *para*-dichlorobenzene with DNA. Therefore, the overall data, including those on genotoxicity, indicate that *para*-dichlorobenzene causes renal tumours in male rats through an α_{2u}-globulin associated response.

4.5.2 *Hepatic tumours in mice*

para-Dichlorobenzene produces liver tumours in mice, and there is some evidence that it is genotoxic in mouse liver. *para*-Dichlorobenzene bound to purified calf thymus DNA when microsomal and cytosolic activating enzymes from mouse liver were present. *In vivo*, *para*-dichlorobenzene bound covalently to DNA fractions purified from the livers of mice that had been treated by intraperitoneal injection; however, the amount of binding was low (covalent binding index, 14). DNA adducts were not identified in other tests, such as ^{32}P-postlabelling. DNA damage was seen in mouse liver in two further assays. Overall, the data preclude a determination that a DNA-reactive mechanism is operative in the

formation of liver tumours in mice. There is evidence of enhanced cell proliferation in mouse liver, but this proliferative response was also present in rats.

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Dichlorobenzenes are chemical intermediates used widely in the manufacture of dyes, pesticides and various industrial products. *ortho*-Dichlorobenzene is further used as a solvent and an insecticide. *para*-Dichlorobenzene is used widely as a moth repellent and an air deodorizer and also as a pesticide.

Occupational exposure to dichlorobenzenes may occur during their manufacture and use, at levels reaching up to a few hundred milligrams per cubic meter in the case of *para*-dichlorobenzene. *ortho*-Dichlorobenzene and *para*-dichlorobenzene are found in ambient air at levels usually below 1 μg/m^3; in indoor air, *para*-dichlorobenzene is typically found at a level an order of magnitude higher. These two isomers have been detected in some drinking-water supplies at levels usually below 1 μg/L and in some foods at levels up to 10 μg/kg. Concentrations of 5–30 μg/kg *ortho*- and *para*-dichlorobenzene have been reported in human milk.

meta-Dichlorobenzene is produced in smaller quantities than the *ortho* and *para* isomers and is used primarily as a chemical intermediate. The data on exposure to this chemical are limited.

5.2 Human carcinogenicity data

In a cohort study from the United States, no association was observed between occupational exposure to *ortho*-dichlorobenzene and mortality from multiple myeloma or non-Hodgkin lymphoma; however, the risk estimates were based on exceedingly few observations.

5.3 Animal carcinogenicity data

ortho-Dichlorobenzene was tested by oral administration in one well-conducted study in mice and one well-conducted study in rats. No increased incidence of tumours was observed.

meta-Dichlorobenzene has not been adequately tested for potential carcinogenicity in laboratory animals.

para-Dichlorobenzene was tested by oral administration and inhalation in mice and rats. After oral administration, it increased the incidence of adenomas and carcinomas of the liver in male and female mice and of renal tubular carcinomas in male rats. Studies in mice and rats exposed by inhalation were judged to be inadequate. *para*-Dichlorobenzene did not promote hepatic foci in a two-stage model of carcinogenesis in rats.

5.4 Other relevant data

No data were available on the absorption, distribution, metabolism or excretion of *ortho*-, *meta*- or *para*-dichlorobenzene in humans.

The major route of biotransformation of *ortho*-dichlorobenzene in male rats was via the glutathione pathway; most of the urinary metabolites were mercapturic acids. Other metabolites were conjugates of 2,3- and 3,4-dichlorophenol. A high dose of *ortho*-dichlorobenzene results in depletion of glutathione. The major metabolite of *para*-dichlorobenzene is 2,5-dichlorophenol. After administration of a high oral dose of *para*-dichlorobenzene to male rats, dichlorohydroquinone was identified in the urine only after acid hydrolysis.

No data were available to evaluate the toxicity of *meta*-dichlorobenzene in humans. Occupational exposure to *ortho*- and *para*-dichlorobenzene caused ocular irritation; *ortho*-dichlorobenzene also caused irritation in the upper respiratory tract.

para-Dichlorobenzene was reported to be hepatotoxic at doses of 600 mg/kg bw and higher in rats. *ortho*-Dichlorobenzene was found to be a more potent hepatotoxicant in rats than *para*-dichlorobenzene. *para*-Dichlorobenzene was reported to cause a mitogenic response in both mouse and rat liver under the dosing conditions used in the cancer bioassay.

para-Dichlorobenzene causes male rat-specific nephrotoxicity resulting from accumulation of the male rat-specific protein α_{2u}-globulin. Both *para*-dichlorobenzene and its major metabolite, 2,5-dichlorophenol, bind reversibly to α_{2u}-globulin. *para*-Dichlorobenzene causes sustained cell proliferation in proximal renal tubular cells, and the dose–response relationships for tumour outcome, enhanced cell proliferation and other histopathological end-points typical of α_{2u}-globulin nephropathy are similar. Female rats, male rats of strains that do not express this protein and mice are not susceptible to the nephrotoxic action of *para*-dichlorobenzene.

ortho-Dichlorobenzene did not cause developmental toxicity in rats or rabbits exposed by inhalation during gestation. After administration by gavage to rats during gestation, decreased fetal growth and an increased incidence of extra ribs were observed. *para*-Dichlorobenzene did not cause developmental toxicity in rabbits exposed during gestation.

A statistically significant, fourfold increase in the frequency of persistent chromosomal aberrations was observed in peripheral blood lymphocytes of individuals accidentally exposed to *ortho*-dichlorobenzene. No data were available on the genetic and related effects of *meta*-dichlorobenzene or *para*-dichlorobenzene in humans.

ortho-Dichlorobenzene induced micronuclei in the bone marrow of mice treated *in vivo*. Radiolabelled *ortho*-dichlorobenzene was found to bind covalently to DNA, RNA and proteins of the liver, kidney, lung and stomach of treated rats and mice. It bound to DNA *in vitro* in the presence but not in the absence of metabolic activation. It was mutagenic to yeast and fungi but not to bacteria.

meta-Dichlorobenzene increased the frequency of micronuclei in the bone marrow of mice treated *in vivo*. It caused gene conversion in yeast. It was not mutagenic to bacteria but gave contradictory results with respect to DNA damage.

para-Dichlorobenzene bound to DNA in liver, lung and kidney of mice but not of male rats. It induced DNA damage in liver and spleen but not in kidney, lung or bone marrow of mice. No conclusion can be drawn from the few data on genotoxicity *in vivo*. There is weak evidence for the genotoxicity of *para*-dichlorobenzene in mammalian cells *in vitro*. It was not mutagenic to bacteria. Overall, the results of tests for genotoxicity do not support a mechanism for renal-cell tumour induction in male rats that involves a direct interaction between *para*-dichlorobenzene or its metabolites and DNA.

5.5 Evaluation

There is *inadequate evidence* in humans for the carcinogenicity of dichlorobenzenes.

There is *evidence suggesting lack of carcinogenicity* in experimental animals of *ortho*-dichlorobenzene.

There is *inadequate evidence* in experimental animals for the carcinogenicity of *meta*-dichlorobenzene.

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

Overall evaluation

In making its overall evaluation of the carcinogenicity of *para*-dichlorobenzene to humans, the Working Group concluded that *para*-dichlorobenzene produces renal tubular tumours in male rats by a non-DNA-reactive mechanism, through an α_{2u}-globulin-associated response. Therefore, the mechanism by which *para*-dichlorobenzene increases the incidence of renal tubular tumours in male rats is not relevant to humans.

para-Dichlorobenzene caused a high incidence of liver tumours in male and female mice. Supporting evidence that its mechanism of carcinogenesis may be relevant for humans includes evidence that it causes DNA damage in liver and spleen of mice and weakly binds to DNA in mouse liver.

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

meta-Dichlorobenzene is *not classifiable as to its carcinogenicity to humans (Group 3).*

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

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