PENTACHLOROPHENOL

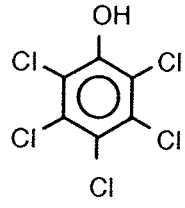
This substance was considered by previous Working Groups, in 1978 (IARC, 1979), 1986 (IARC, 1986) and 1987 (IARC, 1987a). Since that time, new data have become available, and these have been incorporated into the monograph and taken into consideration in the present evaluation.

1. Exposure Data

1.1 Chemical and physical data

1.1.1 *Synonyms, structural and molecular data*

Chem. Abstr. Serv. Reg. No.: 87-86-5
Chem. Abstr. Name: Pentachlorophenol
IUPAC Systematic Name: Pentachlorophenol
Synonyms: Chlorophen; 1-hydroxypentachlorobenzene; PCP; penchlorol; penta; 2,3,4,5,6-pentachlorophenol



C_6HCl_5O Mol. wt: 266.34

1.1.2 *Chemical and physical properties*

(*a*) *Description*: Colourless to light-brown flakes or crystals with characteristic phenolic odour (Royal Society of Chemistry, 1989; WHO, 1989)
(*b*) *Boiling-point*: 309-310°C (decomposes) at 754 mm Hg [100.5 kPa] (Weast, 1989)
(*c*) *Melting-point*: 174°C (monohydrate); 191°C (anhydrous) (Weast, 1989)
(*d*) *Spectroscopy data:* Infrared (prism [279]; grating [96]), ultraviolet [112] and nuclear magnetic resonance (proton [39667]; C-13 [26001]) spectral data have been reported (Sadtler Research Laboratories, 1980, 1990).
(*e*) *Solubility*: Almost insoluble in water (8 mg/100 ml); soluble in acetone (215 g/l at 20°C), diethyl ether (150 g/l), benzene (150 g/l), ethanol (1200 g/l), methanol (1800 g/l), isopropanol (850 g/l), ethylene glycol (110 g/l); slightly soluble in cold petroleum ether, carbon tetrachloride and paraffins (WHO, 1987; Budavari, 1989; Royal Society of Chemistry, 1989)

(*f*) *Vapour pressure*: 1.5×10^{-5} mm Hg [0.2×10^{-5} kPa] at 20°C (WHO, 1989)
(*g*) *Stability*: Relatively stable and non-hygroscopic (Royal Society of Chemistry, 1989); decomposes on heating in the presence of water, forming corrosive fumes (hydrochloric acid); thermal degradation (at 600°C) products of technical pentachlorophenol include pentachlorobenzene, hexachlorobenzene, octachlorostyrene, octachloronaphthalene, decachlorobiphenyl, hexachlorodibenzofuran, octachlorodibenzofuran and octachlorodibenzodioxin (WHO, 1987). Sodium pentachlorophenate is degraded in water photolytically (Hiatt *et al.*, 1960). At pH 7.3, pentachlorophenol disappeared completely within 20 h (half-time, 3.5 h) but was more persistent at pH 3.3 (half-time, ~ 100 h) (Wong & Crosby, 1981).
(*h*) *Octanol/water partition coefficient* (P): log P = 3.32 at pH 7.2 (WHO, 1987)
(*i*) *Conversion factor for airborne concentrations*[1]: $mg/m^3 = 10.89 \times ppm$

1.1.3 *Trade names, technical products and impurities*

Some examples of trade names are: Dowicide 7; Dowicide EC-7; Durotox; EP 30; Fungifen; Grundier Arbezol; Lauxtol; Liroprem; Permasan; Santophen 20; Witophen P; Weedone

Pentachlorophenol in aqueous solution can exist in ionized (phenate) or nonionized forms depending on pH. At pH 2.7, pentachlorophenol is only 1% ionized; at pH 6.7, it is 99% ionized. Technical-grade pentachlorophenol consists of brownish flakes, in some cases coated with a mixture of benzoin polyisopropyl and pine oil to suppress dust. Technical-grade sodium pentachlorophenate consists of cream-coloured beads (WHO, 1987). The formulated product is available as granules, wettable powder and oil-miscible liquid (Royal Society of Chemistry, 1989). Pentachlorophenol is also formulated as blocks, pellets, prills and concentrates (Meister, 1990). It is available as a liquid formulation in Finland and as granules in the Netherlands (Royal Society of Chemistry, 1986). In the USSR, it is manufactured as a 20% mineral oil concentrate (Izmerov, 1984).

Technical-grade pentachlorophenol has been shown to contain a large number of impurities, depending on the manufacturing method. Reported levels of impurities in commercial pentachlorophenol preparations are as follows: tetrachlorophenol (see IARC, 1987a), 4.4-10.2%; trichlorophenol (see IARC, 1987a), $\leq$ 1%; chlorinated phenoxyphenols, 5-6.2%; octachlorodibenzodioxin (see IARC, 1987b), 5.5-3600 mg/kg; heptachlorodibenzodioxin (see IARC, 1987b), 0.6-520 mg/kg; hexachlorodibenzodioxin (see IARC, 1987b), < 0.03-100 mg/kg; octachlorodibenzofuran, < 0.1-260 mg/kg; heptachlorodibenzofuran, < 0.1-400 mg/kg; hexachlorodibenzofuran, < 0.03-90 mg/kg; pentachlorodibenzofuran, < 0.03-40 mg/kg; and tetrachlorodibenzofuran < 0.02-0.45 mg/kg (Scow *et al.*, 1980; WHO, 1987). In addition, chlorinated cyclohexenones and cyclohexadienones, hexachlorobenzene (see IARC, 1987c) and polychlorinated biphenyls (see IARC, 1987d) are found (WHO, 1987).

The presence of the highly toxic 2,3,7,8-tetrachlorodibenzo-*para*-dioxin (see IARC, 1987e) has been confirmed only once in commercial pentachlorophenol samples. In the

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

course of a collaborative survey, one of five laboratories detected this dioxin in technical pentachlorophenol and sodium pentachlorophenate samples at concentrations of 0.25-0.26 and 0.89-1.10 μg/kg, respectively. Detectable amounts of tetrachlorodibenzo-*para*-dioxin (0.05-0.23 mg/kg) were reported in some samples of different technical pentachlorophenol products, but the identity of the compound could not be confirmed on re-analysis. In other cases, tetrachlorodibenzo-*para*-dioxin has not been identified, at detection limits of 0.001-0.2 mg/kg (WHO, 1987).

The higher polychlorinated dibenzodioxins and dibenzofurans are more characteristic of pentachlorophenol formulations. The 1,2,3,6,7,9-, 1,2,3,6,8,9-, 1,2,3,6,7,8- and 1,2,3,7,8,9-isomers of hexachlorodibenzo-*para*-dioxin have been detected in technical-grade pentachlorophenol. The 1,2,3,6,7,8- and 1,2,3,7,8,9-hexachlorodibenzo-*para*-dioxins predominated in commercial samples of technical-grade pentachlorophenol (Dowicide 7) and sodium pentachlorophenate. Octachlorodibenzo-*para*-dioxin is present in relatively high amounts in unpurified technical-grade products (WHO, 1987).

Suppliers of pentachlorophenol in the USA and Canada are now required to limit the hexachlorodibenzo-*para*-dioxin and 2,3,7,8-tetrachlorodibenzo-*para*-dioxin content to less than 4 ppm (mg/kg) and none detectable (< 0.001 ppm [mg/kg]), respectively (Agricultural Canadian Plant Research Centre, 1990).

The presence of 2-bromo-3,4,5,6-tetrachlorophenol as a major contaminant in three commercial pentachlorophenol samples (~ 0.1%) has been reported. This manufacturing by-product has probably not been detected in other analyses because it is not resolved from the pentachlorophenol peak by traditional chromatographic methods (WHO, 1987).

For the treatment of wood in the USA, pentachlorophenol is usually administered as a 5% solution in a mineral spirit solvent, such as No. 2 fuel oil (see IARC, 1989) or kerosene (see IARC, 1989), or in dichloromethane (see IARC, 1987f), isopropyl alcohol (see IARC, 1987g) or methanol. Since pentachlorophenol is not very soluble in hydrocarbon solvents and tends to migrate to, and crystallize on, treated wood surfaces (a phenomenon known as 'blooming'), formulations may also contain co-solvents and anti-blooming agents. An aqueous solution of sodium pentachlorophenate is used commercially to control sapstain (WHO, 1987).

Chlorophenols may be combined with other active components, such as methylene bisthiocyanate and copper naphthenate, in the formulation of pentachlorophenol pesticides. Conversely, pentachlorophenol is added to biocides, the primary active ingredient of which is another compound; for example, sodium fluoride formulations for wooden poles and posts may contain up to 10% technical pentachlorophenol (WHO, 1987).

1.1.4 *Analysis*

Most of the analytical methods used today involve acidification of the sample to convert pentachlorophenol to its nonionized form, extraction into an organic solvent, possible cleaning by back-extraction into a basic solution, and determination by gas chromatography with electron-capture detector or other chromatographic methods as ester or ether derivatives (e.g., acetyl-pentachlorophenol). Depending on sampling procedures and matrices, detection limits as low as 0.05 μg/m^3 in air and 0.01 μg/l in water can be achieved (WHO, 1987).

Selected methods for the analysis of pentachlorophenol in various matrices are given in Table 1.

Table 1. Methods for the analysis of pentachlorophenol

Sample matrix	Sample preparation	Assay procedure[a]	Limit of detection[b]	Reference
Air	Collect sample in bubble containing ethylene glycol; add methanol	HPLC/UV	8 μg per sample	Eller (1984a)
Drinking-water	Extract by passing sample through liquid-solid extractor; elute with dichloromethane; concentrate by evaporation	GC/MS	0.3 μg/l (I) 3.0 μg/l (M)	US Environmental Protection Agency (1988)
	Adjust to pH 12; wash with dichloromethane; acidify; extract with ethyl ether; derivatize with diazomethane	GC/ECD	0.076 μg/l	US Environmental Protection Agency (1989a)
Formulation	Dissolve sample in dioxane; inject aliquot	HPLC/UV	Not reported	Lawrence (1982)
Urine	Add concentrated hydrochloric acid and sodium bisulfite; boil; extract with benzene; concentrate; derivatize with diazomethane; add hexane and evaporate; clean up on alumina column	GC/ECD	1 μg/l	Eller (1984b)
Water	Adjust pH to > 11; extract sample with dichloromethane to remove base/neutral fraction; acidify to pH < 2; extract with dichloromethane to obtain acid fraction; dry; concentrate; analyse	GC/MS	3.6 μg/l	US Environmental Protection Agency (1989b)
Industrial municipal sludge	Acidify; extract with dichloromethane; dry extract; exchange solvent to 2-propanol during concentration of volume	GC/FID	0.59 μg/l	US Environmental Protection Agency (1989c)
Blood	Add 6 M sulfuric acid; add hexane and boil; extract with hexane; concentrate; derivatize with diazomethane; add hexane; evaporate; clean-up on alumina column	GC/ECD	1 μg/l	Eller (1984b)

[a]Abbreviations: GC/ECD, gas chromatography/electron capture detection; GC/FID, gas chromatography/flame ionization detection; GC/MS, gas chromatography/mass spectrometry; HPLC/UV, high-performance liquid chromatography/ultraviolet detection

[b]Abbreviations: (I), ion trap mass spectrometer; (M), magnetic sector mass spectrometer

1.2 Production and use

1.2.1 *Production*

Pentachlorophenol is prepared either by catalytic chlorination of phenol or by alkaline hydrolysis of hexachlorobenzene (see IARC, 1987g) (WHO, 1987).

World production of pentachlorophenol is estimated to be of the order of 30 000 tonnes per year (WHO, 1987). Four manufacturers in the USA produced a total of 18 000-23 000 tonnes of pentachlorophenol annually from 1945 to 1978. Less than 14 000 tonnes were produced in 1980 by two manufacturers. In 1987, about 12 000 tonnes were produced by the sole US producer; and in 1988, about 6000 tonnes were produced by the sole European producer. In 1985, about 3000 tonnes of sodium pentachlorophenate were produced by two European producers (Gjøs & Haegh, 1990).

1.2.2 *Use*

The main commercial use of pentachlorophenol is as a wood preservative; this use began in the late 1930s (WHO, 1987). It is used as a fungicide to protect wood from fungal decay and wood-boring insects. It is also used as a pre-harvest defoliant in cotton and as a general pre-emergence, non-selective contact herbicide (Worthing & Walker, 1987). It has been used as a bactericide in drilling fluids, as a fungicide in adhesives and textiles and for slime control in pulp and paper manufacture (WHO, 1987). Pentachlorophenol has also been used to control the snails that are the hosts of schistosomiasis (Meister, 1990).

Other reported applications of pentachlorophenol are in bactericidal soaps, laundry products, dental care products, leather tanning, mushroom culture, and as disinfectants for use in houses, farms and hospitals (WHO, 1987).

In the USA, it was estimated that 97% of the pentachlorophenol usage was as a wood preservative, 1% as a general herbicide and the remainder for miscellaneous smaller applications (Eckerman, 1986).

1.3 Occurrence

Pentachlorophenol is a ubiquitous environmental contaminant. Its widespread occurrence has been reviewed (WHO, 1987).

1.3.1 *Water*

Evaporation is commonly used for disposing of pentachlorophenol in wastewater at wood-preserving plants (WHO, 1987). Both temperature and pH influence the loss, since the phenate is non-volatile. At pH 5, the half-time is 328 h (30°C), whereas at pH 6 it increases to 3120 h (Klöpffer *et al.*, 1982). Wood-treatment factories contribute significantly to the pentachlorophenol load in surface water, which ranges from non-detectable to 10 500 µg/l. The majority of water samples analysed contained less than 10 µg/l, and most contained less than 1 µg/l. Extreme levels of up to 10 500 µg/l were reported in a polluted stream near an industrial area in the vicinity of Philadelphia (USA) (Fountaine *et al.*, 1976) .

Levels of pentachlorophenol in a man-made lake in Mississipi, USA, increased from a background of 0.3 µg/l to 16-81 µg/l immediately after an accidental overflow from a pole-treatment plant and to 29-147 a month after the accident. After four months, levels had returned to 5-16 µg/l (Pierce & Victor, 1978). Pignatello *et al.* (1983) showed that aquatic microflora can adapt to pentachlorophenol and become the most important factor for clearing pentachlorophenol from contaminated surface water.

Municipal sewage contains only low concentrations of pentachlorophenol, as opposed to industrial wastewater from wood-treatment factories (see Table 2). Levels of penta-

chlorophenol in industrial and municipal discharges in different countries ranged from 0.1 to 75 000 μg/l (WHO, 1987).

The pentachlorophenol input into the German Bight near the River Weser was calculated to be about 1000 kg per year, assuming an average level of pentachlorophenol of 0.1 μg/l per year and a water flow of 300 m^3/sec. The total load in all surface water in western Germany was estimated to be 60 tonnes per year, with 30-40 tonnes transported by the Rhine (as reported by WHO, 1987).

In general, sediments contain much higher levels of pentachlorophenol than the overlying waters. At several freshwater and marine sites in British Columbia, Canada, receiving effluents from the wood-treatment industry, average pentachlorophenol levels in the sediments ranged from not detectable to 590 μg/kg, while the corresponding range for the overlying waters was from not detectable to 7.3 μg/l (as reported by WHO, 1987).

Pentachlorophenol levels in surface water in various countries are given in Table 2.

Table 2. Concentrations of pentachlorophenol (PCP) in surface waters of different countries[a]

Country	Surface water and location	PCP (μg/l)	
		Range	Mean
Germany	Weser River and estuary	0.05-0.5	
	German Bight	< 0.002-0.026	
	Ruhr River	< 0.1-0.2	0.1
	River Rhine, Cologne	0.1	
Japan	Tama River, Tokyo	0.1-0.9	
		0.01-0.09	
	Sumida River, Tokyo	1-9	
	River water, Tokyo area	0.18 ± 0.14	
Netherlands	River Rhine 1976	Max 2.4	0.7
	River Rhine 1977	Max 11.0	1.1
	River Meuse 1976	Max 1.4	0.3
	River Meuse 1977	Max 10.0	0.8
South Africa	124 sampling points	ND-0.85	
Sweden	River water downstream from a pulp mill	9	
	Lake receiving discharges	3	
USA	Willamette River	0.1-0.7	
	Estuary in Galveston Bay, Texas	ND-0.01	
	Pond in Mississippi contaminated by waste from pole-treatment plant	< 1-82	

[a]From WHO (1987)
ND, not detectable

1.3.2 *Soil*

Soil samples from four sites near a Swiss pentachlorophenol-producing facility contained 25-140 μg/kg (dry weight) at depths of 0-10 cm and 33-184 μg/kg at 20-30 cm.

These levels were greater than those at a reference site (< 35 μg/kg for both depths) (as reported by WHO, 1987).

Soil surrounding Finnish sawmills was heavily contaminated, with up to 45.6 mg/kg at 0-5 cm depth near the treatment basin and up to 0.14 mg/kg in the area for storing treated wood. The background level was 0.012 mg/kg (Valo *et al.*, 1984). Average pentachlorophenol levels in soil samples at 2.5, 30.5 and 152.5 cm from poles treated with pentachlorophenol were 658, 3.4 and 0.26 mg/kg, respectively (Arsenault, 1976). The background level (0.26 mg/kg) was considered to be high and could have resulted from contamination of the soil or of analytical samples (WHO, 1987).

Both pentachlorophenol and sodium pentachlorophenate are readily leached from soils. Substantial quantities of pentachlorophenol were found in waters leaching from contaminated soil, and residues ranging from 3.0 to 23 μg/l were detected in groundwater within saw-mill areas. A level as high as 3.35 mg/l was found in groundwater near a wood-preserving plant (WHO, 1987), and levels of pentachlorophenol of < 1 μg/l were detected in water seeping from a landfill site (Kotzias *et al.*, 1975).

1.3.3 *Food*

In Canada, a total of 881 pork liver tissue samples revealed a gradual decline of pentachlorophenol levels in 1988-89 from those in previous years. Some 6.6% of the samples contained levels in excess of 0.1 mg/kg, the highest level being 0.72 mg/kg. Of 51 beef liver samples, 2.0 % had levels in excess of 0.1 mg/kg, the maximal level being 0.35 mg/kg. Examination of 214 chicken and 68 turkey liver samples showed only one with a level above 0.1 mg/kg; this incident was traced to the use of wood shavings as bedding (Agriculture Canada, 1989).

The amount of pentachlorophenol that enters the food chain and the long-term average daily intake of pentachlorophenol by the general population in the USA was estimated using six-compartment environmental partitioning models. Pentachlorophenol partitions mainly into soil (96.5%), and food chains, especially fruits, vegetables and grains, account for 99.9% of human exposure to pentachlorophenol. The long-term, average daily intake of pentachlorophenol is estimated to be 16 μg/day (Hattemer-Frey & Travis, 1989).

1.3.4 *Humans*

The mean levels of pentachlorophenol in samples collected from the general population in Barcelona, Spain, in 1982-83 were 25 ng/ml (50 samples) in urine and 21.9 ng/ml (100 samples) in serum (Gómez-Catalán *et al.*, 1987).

A family living in a wooden house in Germany was subjected to continual minor illnesses following the application of wood protection agents. These included nearly 12 kg pentachlorophenol and 3 kg lindane. While the air concentrations were low, the textiles in the house, comprising mostly clothing and bed linen, were highly contaminated, and extensive contact with these materials resulted in high dermal absorption (Gebefügi, 1989).

1.3.5 *Occupational exposure*

Aerial spraying of farm crops gave rise to levels of pentachlorophenol of 0.9 mg/m^3 in the cockpit of the spray plane, 38 mg/m^3 in the vicinity of the signal man and 1-4 mg/m^3 outside the treated field (Demidenko, 1969).

In general, studies of pentachlorophenol in human tissues and body fluids are discussed in section 4.1.1 of this monograph. Table 6 shows the concentrations of pentachlorophenol found in workers involved in the production of pentachlorophenol and treatment of wood with pentachlorophenol. In pressure treatment of wood, workers are exposed to pentachlorophenol when opening the door of pressure vessels. In non-pressure treatment, there is continuous evaporation of pentachlorophenol into the air, and consequently the residues in the urine of these workers are higher. People using the treated timber, such as carpenters and boat builders, have lower exposures.

1.4 Regulations and guidelines

In the USSR, the maximum allowable single concentration of pentachlorophenol in the air of communities is 0.005 mg/m^3, and the median daily concentration is 0.001 mg/m^3 (Izmerov, 1984).

The maximum allowable concentration of pentachlorophenol in drinking-water is 0.06 mg/l in Canada (Ritter & Wood, 1989) and 0.3 mg/l in the USSR (Izmerov, 1984). WHO (1984) recommended a drinking-water quality guideline value of 10 μg/l for pentachlorophenol based on 10% of the acceptable daily intake of 3 μg/kg bw.

In the USA, the acceptable daily intake of pentachlorophenol from food is 3 μg/kg bw per day (WHO, 1987).

National pesticide residue limits for pentachlorophenol in foods are presented in Table 3.

Table 3. National pesticide residue limits for pentachlorophenol in foods[a]

Country	Residue limit (mg/kg)	Commodities
Australia	0.01[b]	Citrus, grapes, mushrooms, pineapples, potatoes
Austria	0.05	Foods of vegetable origin
Belgium	0.05[c]	Mushrooms
	0 (0.01)[d]	Other foodstuffs of vegetable origin
Germany	0.01	All foods of plant origin
Israel	0.05	Mushrooms, other foods
Netherlands	0.05	Mushrooms
	0 (0.01)[d]	Other crops and foods
Switzerland	0.05[e]	Milk
USSR	Not permitted	
Yugoslavia	0.01	Crops and food

[a]From Health and Welfare Canada (1990)
[b]Including the sodium salt
[c]Including salts
[d]Residues shall be absent while value in parentheses indicates highest concentration at which requirement has been met.
[e]Includes 'TCP' as an impurity; upper limit value beyond which food is unfit for human consumption

Occupational exposure limits for pentachlorophenol in some countries and regions are given in Table 4. Each limit has a notation indicating a hazard for absorption through skin.

Table 4. Occupational exposure limits to pentachlorophenol[a]

Country	Year	Concentration	Interpretation[b]
Austria	1987	0.5	TWA
Belgium	1987	0.5	TWA
Denmark	1987	0.5	TWA
Finland	1987	0.5	TWA
	1987	1.5	STEL (15 min)
Germany	1989	0.05	TWA
Hungary	1987	0.2	TWA
	1987	0.4	STEL
Indonesia	1987	0.5	TWA
Italy	1987	0.5	TWA
Mexico	1987	0.5	TWA
Netherlands	1987	0.5	TWA
Poland	1987	0.5	TWA
Romania	1987	0.5	TWA
	1987	1	STEL
Sweden	1987	0.5	TWA
	1987	1.5	STEL
Switzerland	1987	0.5	TWA
Taiwan	1987	0.5	TWA
United Kingdom	1987	0.5	TWA
	1987	1.5	STEL (10 min)
USA			
ACGIH	1989	0.5	TWA
OSHA	1989	0.5	TWA
USSR	1987	0.1	TWA
Venezuela	1987	0.5	TWA
	1987	1.5	Ceiling
Yugoslavia	1987	0.5	TWA

[a]From Cook (1987); American Conference of Governmental Industrial Hygienists (ACGIH) (1989); Deutsche Forschungsgemeinschaft (1989); US Occupational Safety and Heath Administration (OSHA) (1989)
[b]TWA, time weighted average; STEL, short-term exposure limit

Some countries have restricted the use of pentachlorophenol. Sweden banned all use of pentachlorophenol in 1977, and Germany banned all uses in 1987. The USA cancelled its registration for herbicidal and anti-microbial use and for the preservation of wood in contact with food, feed, domestic animals and livestock; the sale and use of pentachlorophenol is restricted to certified applicators. The agricultural use of pentachlorophenol has also been suspended or restricted in other countries, including Canada and Japan. Canada and the Netherlands have suspended its use for indoor wood treatment (WHO, 1987).

2. Studies of Cancer in Humans

Exposure to pentachlorophenol usually occurs concomitantly with exposure to other chlorophenols. The effects of exposure to chlorophenols as a group were evaluated in Volume 41 of the *Monographs* (IARC, 1986). In this monograph, only those studies in which exposure to pentachlorophenol was reported specifically are reviewed.

2.1 Case reports

Bishop and Jones (1981) reported two cases of non-Hodgkin's lymphoma of the scalp in a cohort of 158 workers handling pentachlorophenol.

Greene *et al.* (1978) reported the occurrence of Hodgkin's disease in three siblings and a first cousin. Two of the brothers had been employed by a fence installation company for 12 and 15 years, respectively, and had worked primarily with wood products immersed in pentachlorophenol. They had prepared the preservative by hand without protective clothing, and the one sibling still employed at the time of the study had high levels of pentachlorophenol in his serum and urine. There were no similar exposures in the remaining two familial cases.

2.2 Case-control studies

Risk from exposure to chlorophenols in farming was estimated in three population-based case-control studies based on data from the New Zealand Cancer Registry (Smith *et al.*, 1984; Pearce *et al.*, 1986a, 1987). The authors reported that sodium pentachlorophenate is used for treating sawn timber and, to a lesser extent, fencing materials against sap stain. Vacuum-pressure impregnation with copper chrome arsenate is the principal method for preserving fencing timber in New Zealand, but, in the past, pentachlorophenol was also used (on less than 1% of posts) (Pearce *et al.*, 1986b). Thus, sawmill workers who reported handling treated timber were considered potentially to have been exposed to sodium pentachlorophenate, whereas fencing workers were considered to be exposed predominantly to copper chrome arsenate rather than chlorophenols.

In the case-control study on soft-tissue sarcomas, 82 male patients registered during 1976-80 (or their next of kin) were interviewed regarding their occupational history, and the findings were compared with those for 92 age-matched male controls with other types of cancer selected from the National Cancer Registry. The response rate was 84% for cases and 83% for controls. Work in a sawmill or timber company was reported for 12 cases and 11 controls (odds ratio, 1.3; 90% confidence interval [CI], 0.6-2.9). Of these, three cases and five controls were considered potentially to have been exposed to chlorophenols [presumably sodium pentachlorophenate (see above)] (odds ratio, 0.7; 90% CI, 0.1-2.7). Work as a fencing contractor was reported for five cases and three controls (1.9; 0.5-8.6), whereas 20 cases and 26 controls were farmers who had carried out fencing work (0.8; 0.4-1.5). These results were not affected by stratification on year of birth, year of registration or whether the patient or next-of-kin was interviewed (Smith *et al.*, 1984).

The second study included 183 cases of non-Hodgkin's lymphoma registered in 1977-81 and 338 cancer registry controls (other than soft-tissue sarcoma, Hodgkin's disease and

multiple myeloma) (Pearce *et al.*, 1985), with response rates of 85 and 81%, respectively. All analyses were adjusted for age and whether the patient or next-of-kin had been interviewed. The odds ratio for work in a sawmill or timber company was 0.9 (24 exposed cases, 45 exposed cancer controls; 90% CI, 0.6-1.5), and that for potential exposure to chlorophenols [presumably sodium pentachlorophenate (see above)] in these occupations was 1.0 (11 exposed cases, 18 exposed controls; 90% CI, 0.5-2.0). The odds ratio for fencing work was 1.4 (68 exposed cases, 93 exposed controls; 90% CI, 1.0-2.0) (Pearce *et al.*, 1987).

The third study involved interviews with 76 patients with multiple myeloma registered in 1977-81 (or their next-of-kin) and 315 controls with cancers other than soft-tissue sarcoma, Hodgkin's disease and non-Hodgkin's lymphoma, who were also included in the control group for the study on non-Hodgkin's lymphoma of Pearce *et al.* (1987). Response rates were 82 and 81%, respectively, for cases and controls. All analyses were adjusted for age and whether the patient or next-of-kin had been interviewed. Work in a sawmill or timber company was reported for 11 cases and 42 controls (odds ratio, 1.1; 95% CI, 0.5-2.3), and potential exposure to chlorophenols [presumably sodium pentachlorophenate (see above)] was reported for five of the cases and 16 of the controls (odds ratio, 1.4; 95% CI, 0.5-3.9). Fencing work was reported for 29 cases and 87 controls (1.6; 0.9-2.7) (Pearce *et al.*, 1986a).

A population-based case-control study in central Sweden comprised 237 cases of soft-tissue sarcoma and 237 controls matched for age, gender and county of residence. The design is described in detail in the monograph on occupational exposure in spraying and application of insecticides (p. 70). Exposure to pentachlorophenol more than five years before the date of diagnosis for one week or more continuously or at least one month in total was reported from interviews with patients or next-of-kin for 11 cases and three controls (odds ratio, 3.9; 95% CI, 1.2-12.9). This analysis excluded cases and controls for whom exposure to phenoxyacetic herbicides was reported (Eriksson *et al.*, 1990).

2.3 Cohort studies

A cohort study of workers in the sawmill industry in the province of Kymi in Finland (Jäppinen *et al.*, 1989) comprised 721 men and 502 women who had been employed for at least one year during 1945-61. Cancer incidence during the period 1953-80 was identified through the cancer registries of Finland, Sweden and Norway, but the incidence figures for Kymi were used as reference. There were 90 cases of cancer in men (standardized incidence ratio (SIR), 1.1; 95% CI, 0.87-1.3) and 55 cases in women (SIR, 1.2; 95% CI, 0.93-1.6). Several cancer types occurred in excess in both men and women, including skin cancer (ICD, 173) (8 cases [SIR, 2.7; 95% CI, 1.2-5.3]), cancer of the lip, mouth and pharynx (7 cases [1.6; 0.7-3.4]) and leukaemia (7 cases [2.3; 0.9-4.8]). One case of soft-tissue sarcoma was observed (0.6 expected). The chlorophenols used for wood treatment in this industry, however, contained predominantly 2,3,4,6-tetrachlorophenol and only 5-9% pentachlorophenol by weight.

3. Studies of Cancer in Experimental Animals

The Working Group was aware of a study in mice by the US National Technical Information Service (1968) and Innes *et al.* (1969) and a study in rats by Schwetz *et al.* (1978), which were considered in the previous monograph (IARC, 1979). Because of deficiencies in design, performance and/or reporting, the present Working Group did not consider these studies informative for an evaluation.

Oral administration

Mouse: Groups of 50 male and 50 female B6C3F$_1$ mice, nine weeks old, were fed technical-grade pentachlorophenol (90.4% pure; tetrachlorophenol, 3.8%; nonachlorohydroxydiphenyl ether, 3.56%; octachlorohydroxydiphenyl ether, 1.91%; heptachlorohydroxydibenzofuran, 0.47%; trichlorophenol, 0.01%) at 100 or 200 mg/kg of diet or Dowicide EC-7 (a technical-grade formulation: 91% pure; tetrachlorophenol, 9.4%) at 100, 200 or 600 mg/kg of diet for two years. Two groups of 35 male and 35 female mice were fed control diets. Animals were killed at the age of 112 weeks. Survival was similar in treated and control groups, except that the survival of low-dose females was significantly reduced after 628 days with the EC-7 formulation. A significant, dose-related increase in the incidence of hepatocellular adenomas and carcinomas was observed in male mice treated with either formulation of pentachlorophenol; and a significant, dose-related increase in the incidence of hepatocellular adenomas was seen in females treated with EC-7 (Table 5). There was also a dose-related increase in the incidence of adrenal phaeochromocytomas in male mice exposed to either formulation and in females exposed to the high dose of EC-7. Female mice exposed to high doses of either formulation had a significantly higher incidence of haemangiosarcomas of the spleen and/or liver (US National Toxicology Program, 1989).

Table 5. Study of the carcinogenicity of two grades of pentachlorophenol fed in the diet for 103 weeks in B6C3F$_1$ mice[a]

Material	Sex	Experimental parameter/ observation	Group				Statistical conclusion (trend test)[b]
			0	1	2	3	
Technical-grade	M	Dose (mg/kg of diet)	0	100	200		
		Liver adenomas	5/32	20/47	33/48***		$p < 0.001$
		Liver carcinomas	2/32	10/47	12/48		
		Phaeochromocytomas	0/31	10/45*	23/45***		$p < 0.001$
	F	Dose (mg/kg of diet)	0	100	200		
		Liver adenomas	3/33	8/49	8/50		NS
		Liver carcinomas	0/33	1/49	1/50		NS
		Haemangiosarcomas	0/35	3/50	6/50*		$p < 0.05$
EC-7	M	Dose (mg/kg of diet)	0	100	200	600	
		Liver adenomas	5/35	13/48	17/48**	32/49***	$p < 0.001$
		Liver carcinomas	1/35	7/48*	7/48*	9/49*	
		Phaeochromocytomas	0/34	4/48	21/48***	44/49***	$p < 0.001$

Table 5 (contd)

Material	Sex	Experimental parameter/ observation	Group				Statistical conclusion (trend test)[b]
			0	1	2	3	
EC-7 (contd)	F	Dose (mg/kg of diet)	0	100	200	600	
		Liver adenomas	1/34	3/50	6/49	30/48***	$p < 0.001$
		Liver carcinomas	0/34	1/50	0/49	2/48	ND
		Haemangiosarcomas	0/35	1/50	3/50	8/49*	$p < 0.01$

[a]From US National Toxicology Program (1989)
[b]Incidental tumour test (adjusted for survival)
*$p < 0.05$
**$p < 0.01$
***$p < 0.001$
NS, not signifiicant

4. Other Relevant Data

4.1 Absorption, distribution, metabolism and excretion

The pharmacokinetics of pentachlorophenol has been reviewed (Ahlborg & Thunberg, 1980; Exon, 1984; WHO, 1987) and shows great variation between studies and across species. Data are available for humans, monkeys, rats and, to a lesser extent, mice.

4.1.1 *Humans*

Dermal and pulmonary absorption of pentachlorophenol may occur during occupational exposure (Truhaut *et al.*, 1952; Menon, 1958; Robson *et al.*, 1969; Kauppinen & Lindroos, 1985).

The half-time for absorption of orally administered sodium pentachlorophenate (0.1 mg/kg bw) to healthy volunteers was found to be 1.3 ± 0.4 h. The decrease in the plasma concentration (maximum plasma concentration occurring 4 h after ingestion) fitted a first-order, one-compartment model with a half-time of 30.2 ± 4.0 h. Maximal urinary excretion occurred 40 h after ingestion, with a half-time of excretion of 33.1 ± 5.4 h (Braun *et al.*, 1979). These results were challenged in another study in which the blood half-time of orally administered pentachlorophenol (0.98 mg ^{13}C-labelled compound) to a presumably healthy volunteer was found to be 16 ± 2.5 days. In the same subject, the urine half-time was 18 ± 2.4 days, whereas in another subject given 18.8 mg/kg bw pentachlorophenol orally it was 20 ± 3.4 days (Uhl *et al.*, 1986). These authors calculated similar figures for comparable data obtained from the literature: a urinary half-time of 16 days could be calculated from the urinary concentrations measured after accidental skin exposure (Bevenue *et al.*, 1967), and half-times for both plasma and urine of 12 days were calculated from measurements before and after holidays in workers occupationally exposed to pentachlorophenol (Begley *et al.*, 1977). Finally, in a case of intentional ingestion (Haley, 1977), an elimination half-time of about 10 days could be calculated (WHO, 1987). Uhl *et al.* (1986) concluded that elimination

behaviour does not depend on the extent of the exposure. The long elimination half-time of pentachlorophenol cannot be explained by enterohepatic circulation (biliary levels of pentachlorophenol were in the same range as those in plasma and urine in patients with biliary drainage) but rather by the extensive plasma protein binding of the compound (> 96%) and by its very effective tubular reabsorption, as shown *in vivo* by changing urinary pH. From these results, it can be calculated that urinary levels in humans will reach a steady state within approximately three months.

Data on tissue distribution in humans have been derived from examination of autopsy samples from unexposed and poisoned subjects (WHO, 1987). Decreasing tissue concentrations of pentachlorophenol have been found in liver, kidney and brain of people with no known exposure. Data from cases of poisoning resulting in death show large variations among different organs.

Pentachlorophenol is metabolized *in vitro* by human liver microsomes to tetrachlorohydroquinone (Juhl *et al.*, 1985), which has been found in the urine of workers exposed to pentachlorophenol (Ahlborg *et al.*, 1974). Pentachlorophenol glucuronide is also formed *in vitro* by human liver microsomes (Lilienblum, 1985), but its concentration in urine as compared with that of the parent compound may vary and is probably underestimated owing to the instability of the conjugate at urinary pH.

Many data are available on blood and urinary levels of pentachlorophenol in occupationally exposed workers, nonoccupationally exposed subjects, including residents of log homes treated with pentachlorophenol, and subjects with no known exposure; these were summarized (WHO, 1987). Studies in which levels of pentachlorophenol were measured both in air and in the serum, plasma or urine of exposed people are summarized in Tables 6 and 7. Studies in which levels were measured in the serum or plasma of people with no known exposure are summarized in Table 8.

4.1.2 *Experimental systems*

The absorption rate constants of ^{14}C-labelled pentachlorophenol after oral administration to male and female rats (10 mg/kg bw) were found to be 1.95 and 1.52/h, respectively. Maximal plasma concentrations were reached 4-6 h after administration (Braun *et al.*, 1977). The average half-times of absorption in male and female rhesus monkeys were 3.6 and 1.8 h, respectively, with a plasma peak concentration within 12-24 h after administration (Braun & Sauerhoff, 1976). Rapid absorption of pentachlorophenol also occurred in rats after inhalation (Hoben *et al.*, 1976).

Conflicting results have been reported on elimination kinetics (*via* urine or urine and faeces) in mammals after administration of single oral doses of pentachlorophenol (WHO, 1987). Besides interspecies variation, there also appeared to be sex differences. Monophasic elimination was reported in male rats after inhalation of 5.7 mg/kg bw (Hoben *et al.*, 1976) and in female rats after an oral dose of 100 mg/kg bw (Braun *et al.*, 1977). Biphasic elimination was reported in female rats after oral doses of 37-41 mg/kg bw and 10 mg/kg bw (Larsen *et al.*, 1972; Braun *et al.*, 1977) and in male rats after oral doses of 10 or 100 mg/kg bw pentachlorophenol (Braun *et al.*, 1977). The half-times for the single and the rapid phase were between 10 and 27 h, whereas for the slow phase they were between 33 h and 102 days.

Table 6. Levels of pentachlorophenol in the air and in the serum or plasma and urine of individuals exposed occupationally[a]

Exposure	No. of subjects	Length of exposure (years)	Air (μg/m³)		Serum (mg/l)		Urine (mg/l)	
			Mean	Range	Mean	Range	Mean	Range
Lumber, dipping	NS	NS	19	3-63	NA		2.83	0.12-9.68
Lumber dipping, spraying or brushing	18	NS	NA		5.14	0.43-14	1.31	0.09-3.3
6th day of vacation								
20th day of vacation	18	NS	NA		4.92	0.50-13	1.36	0.18-3.5
51st day of renewed work	18	NS	NA		2.19	0.32-5.3	0.59	0.05-1.4
	13	NS	NA		2.61	0.19-8.1	0.95	0.03-3.6
Lumber, general	3	5 (2-11)	1[b]	< 1-15	1.11[b]	0.35-3	0.15[b]	0.044-0.47
Lumber, office	1	10	2[b]	< 1-3	0.65[b]	0.42-0.75	0.06[b]	0.04-0.11
Lumber, pressure treatment	1	5	6[b]	< 1-15	2.29[b]	1.51-3.55	0.30[b]	0.09-0.76
	NS	NS	14[c]	4-1000	NA		1.24	0.17-5.57
Airborne and dermal	10	5-10	55.6	± 89	0.71	± 0.38	0.11	± 0.02
Airborne	8	5-10	66.7	± 100	0.24	± 0.23	0.05	± 0.02
Lumber, spraying	NS	NS	6[c]	3-69	NA		0.98	0.13-2.58
Pentachlorophenol application	23	3[d] (0.5-12)	2.4	0.3-8	1[d,e]	0.2-2..4	NS	
Pentachlorophenol processing[f]	18	10[d] (0.2-31)	17.5	2-50	0.25[d,e]	0.02-1.5	NS	
Pentachlorophenol processing factory[f]	18	12 (0.3-31)	NS	2.2-55.5	0.25[d]	0.02-1.5	0.112[d]	0.013-1.224
Pentachlorophenol production	8	NS	< 100- > 500[g]		4.73 ± 3.41		2.38 ± 1.91	
	18	NS	270-4000		NA		0.72 ± 0.55	
Sodium pentachlorophenol production	14	NS	< 100-> 500[h]		2.23 ± 1.51		0.84 ± 0.65	
	50	NS	0-50		NA		0.35 ± 0.30	

[a]Selected from WHO (1987)
[b]Calculated from sampling data collected over 5 months
[c]Air at 'maximum exposure' sites, next to sources, contained 26 μg/m³ (lumber spraying site) and 297 μg/m³ (pressure treatment site).
[d]Median
[e]Plasma
[f]Overlapping studies
[g]Of 67 samples, 18 were < 100 and 10 > 500 μg/m³
[h]Of 55 samples, 7 were < 100 and 8 > 500 μg/m³
NA, not analysed
NS, not specified

Table 7. Levels of pentachlorophenol in the air and in the serum or plasma and urine of individuals exposed non-occupationally[a]

Exposure	No. of subjects	Length of exposure (years)	Air (μg/m³)		Serum (mg/l)		Urine (mg/l)	
			Mean	Range	Mean	Range	Mean	Range
Indoor application of pentachlorophenol solutions	16	NS	NS	1-10	NA		NS	0.030-0.150
Residence in log homes treated with pentachlorophenol solutions	5	NS	0.29[b]	0.20-0.38	1.126	0.580-1.750	0.084	0.047-0.216
Indoor application of an average of 40 litres pentachlorophenol solution	989	NS (< 9 years)	6.1[c] 4.9[d]	ND-25 2.5-0.5	NA		0.044 0.029[d]	0.013-0.071
Men < 18 years	16	NS	≤ 5		NA		0.047[d]	0.017-0.107
Men ≥ 18 years	39	NS	≤ 5		NA		0.023[d]	0.011-0.052
Women < 18 years	22	NS	≤ 5		NA		0.033[d]	0.016-0.066
Women ≥ 18 years	39	NS	≤ 5		NA		0.026[d]	0.015-0.059
Men < 18 years	23	NS	> 5		NA		0.079[d]	0.014-0.125
Men ≥ 18 years	31	NS	> 5		NA		0.043[d]	0.011-0.146
Women < 18 years	25	NS	> 5		NA		0.059[d]	0.011-0.103
Women ≥ 18 years	43	NS	> 5		NA		0.039[d]	0.021-0.125
Indoor application of about 70 litres pentachlorophenol solution								
Before ventilation	6	6	0.60	0.14-1.20	NA		0.032	0.0007-0.0078
After ventilation	6	–	0.08	ND-0.24	0.080[e]	0.025-0.190	0.0033	0.0018-0.0080
Indoor application of about 75 litres pentachlorophenol solution	2	0.5	0.15	ND-0.40	0.033[e]	0.031-0.034	NA	
Indoor application of about 100 litres pentachlorophenol solution	2	1	0.67	0.44-0.95	0.565[e]	0.47-0.66	NA	

[a]Selected from WHO (1987)

[b]Samples taken on 1st and 2nd floors of a two-storey log house; a sample of interior surface wood contained 1132 mg/kg pentachlorophenol (0.11%)

[c]104 indoor air samples taken

[d]Median (2/3 range)

[e]Plasma

NA, not analysed; ND, not detectable; NS, not specified

Table 8. Levels of pentachlorophenol (PCP) in the serum or urine of individuals with no known exposure[a]

Exposure	No. of subjects	Serum (mg/l)		Urine (mg/l)	
		Mean	Range	Mean	Range
US National Human Monitoring Program for Pesticides	418	NA		0.0063	ND-0.193
Control group for non-occupational exposure (indoor application of PCP solutions)	12	NA		0.0135	0.006-0.023
Control group for non-occupational exposure (residents of log homes treated with PCP solutions)					
January 1980 'conventional' homes	42	NS	0.004-0.068	NS	0.0007-0.011
March 1980 untreated log homes	2	0.051	0.034-0.075	0.0014	0.001-0.002
March 1980 'conventional' homes	11	0.048	0.015-0.055	0.025	0.001-0.007
Control group for non-occupational indoor air levels below detection limit of 0.1 $\mu g/m^3$ (indoor application of 40 litres PCP solution)	207	NA		0.0127 0.0102[c]	0.0038-0.0214
Control group for non-occupational exposure (indoor application of PCP solution, 70-100 litres)	99	0.129 0.088[b]	<0.05-1.10	NA	
Non-specifically exposed persons	12 30	0.025	0.019-0.036	0.014	0.007-0.034[c]

[a]Selected from WHO (1987)
[b]Median (2/3 range)
[c]Assuming a daily urine volume of 1.4 litres
NA, not analysed; ND, not detectable; NS, not specified

The half-time value for clearance of pentachlorophenol from plasma was 83.5 h for female and 72 h for male rhesus monkeys given 10 mg/kg bw of a ^{14}C-labelled compound orally. The half-times for urinary excretion were 92.4 h for females and 40.8 h for males. Slow, steady elimination of the compound in the faeces of monkeys suggests a role of enterohepatic circulation (Braun & Sauerhoff, 1976).

Pentachlorophenol was shown to be 99% bound to plasma protein in rats (Braun *et al.*, 1977).

Concentrations of pentachlorophenol in tissues account for only a small fraction of the administered dose, because it is usually rapidly excreted in urine. Total-body recovery of radiolabel from rats nine days after a single oral dose of 10 mg/kg bw of ^{14}C-labelled compound was less than 0.5%, most of which was concentrated in the liver (Braun *et al.*, 1977). Similar results were obtained in mice after subcutaneous and intraperitoneal injection of ^{14}C-labelled compound (15-37 mg/kg bw) (Jakobson & Yllner, 1971) and in lactating dairy cows after oral administration (Kinzell *et al.*, 1985). The total tissue concentration of radiolabel recovered from monkeys 360 h after administration was about 11% of a dose of 10 mg/kg bw ^{14}C-pentachlorophenol (Braun & Sauerhoff, 1976).

Very little pentachlorophenol crosses the placenta in rats. When ^{14}C-pentachlorophenol was administered orally on day 15 of pregnancy (60 mg/kg bw), the maximal amount of specific radiolabel in maternal blood was 1.1% of the dose, while it never exceeded 0.3% in the placenta and 0.1% in the fetuses (Larsen *et al.*, 1975).

Biotransformation of pentachlorophenol in rats involves its urinary excretion as the glucuronic acid conjugate and its hydrolytic dechlorination to tetrachlorohydroquinone, which is excreted free or conjugated with glucuronic acid in the urine (Ahlborg *et al.*, 1978). Trichlorohydroquinone is also formed in rats by reductive dechlorination of tetrachlorohydroquinone and excreted as the glucuronate in urine (Ahlborg & Thunberg, 1978, 1980). Free and conjugated pentachlorophenol and free tetrachlorohydroquinone have been identified in the urine of mice administered pentachlorophenol (Jakobson & Yllner, 1971). In contrast to rodents, rhesus monkeys eliminate pentachlorophenol in urine unchanged (Braun & Sauerhoff, 1976). A number of drugs that affect liver microsomal enzymes have also been shown to influence the biotransformation of pentachlorophenol selectively (Ahlborg & Thunberg, 1978; Ahlborg *et al.*, 1978; Van Ommen *et al.*, 1986).

4.2 Toxic effects

The toxicology of pentachlorophenol has been reviewed (Ahlborg & Thunberg, 1980; Williams, 1982; Exon, 1984; WHO, 1987).

4.2.1 *Humans*

Several cases of acute accidental, suicidal and occupational poisoning have been reported and reviewed (WHO, 1987). Symptoms of acute poisoning include central nervous system disorders, dyspnoea and hyperpyrexia; the cause of death is cardiac arrest, and poison victims usually show marked rigor mortis. Examination *post mortem* shows nonspecific organ damage. One case of fatal poisoning was associated with higher pentachlorophenol concentrations in bile and kidney (Wood *et al.*, 1983). The minimal lethal dose of pentachlorophenol in man has been estimated to be 29 mg/kg bw. Occupational exposures to technical-grade pentachlorophenol resulted in various disorders of the skin and mucous membranes (WHO, 1987). The incidence of chloracne was highest in people who had had confirmed direct skin contact (O'Malley *et al.*, 1990). Several health and biomonitoring surveys of workers with plasma pentachlorophenol concentrations ranging from nanograms to milligrams per litre showed some minor and often transitory changes in various biochemical, haematological and electrophysiological parameters, but no clinical effect was seen (Klemmer *et al.*, 1980; Triebig *et al.*, 1981; Zober *et al.*, 1981). Anecdotal exposure to pentachlorophenol has been associated with aplastic anaemia and/or red-cell aplasia (Roberts, 1983).

4.2.2 *Experimental systems*

Data on the acute toxicity in experimental animals of pentachlorophenol given by various routes have been summarized (WHO, 1987).

The oral LD_{50} was 36-177 mg/kg bw in mice (Ahlborg & Larsson, 1978; Borzelleca *et al.*, 1985), 27-175 mg/kg bw in rats (Deichmann *et al.*, 1942; Gaines, 1969) and 168 mg/kg bw in hamsters (Cabral *et al.*, 1979, abstract). Cutaneous minimal lethal doses ranged from

39-170 mg/kg bw in rabbits (Kehoe *et al.*, 1939; Deichmann *et al.*, 1942) to 300 mg/kg bw in rats (Gaines, 1969). The acute toxicities of some known and possible metabolites of pentachlorophenol have also been reported (Borzelleca *et al.*, 1985; Renner *et al.*, 1986).

Symptoms of acute toxicity are similar to those in humans, including hyperpyrexia and neurological and respiratory dysfunction (WHO, 1987). Furthermore, palmitoylpentachlorophenol, which has been isolated from human fat (Ansari *et al.*, 1985), causes selective pancreatic toxicity in rats after single oral doses of 100 mg/kg bw (Ansari *et al.*, 1987).

A number of toxic effects described in acute and short-term toxicity studies have been attributed to impurities present in technical-grade pentachlorophenol preparations. The toxicity of impurities became clear when comparative studies with pure and technical-grade pentachlorophenol products were reported (Johnson *et al.*, 1973; Goldstein *et al.*, 1977; Kimbrough & Linder, 1978). Rats receiving 500 ppm [mg/kg] technical-grade pentachlorophenol in the diet for eight months had slow growth rates, liver enlargement, porphyria and increased activities of some liver microsomal enzymes (Goldstein *et al.*, 1977); rats fed purified pentachlorophenol at the same dose and for the same period of time showed only a reduction of growth rate and increased liver glucuronyl transferase activity. Analogous results were reported in a similar study (Kimbrough & Linder, 1978). Technical-grade pentachlorophenol, but not the pure compound, caused a porphyria similar to that due to hexachlorobenzene when given orally to rats for several months at increasing doses (Wainstok de Calmanovici & San Martin de Viale, 1980).

Several toxic effects of pentachlorophenol have been explained by the uncoupling effect of pentachlorophenol on oxidative phosphorylation (Ahlborg & Thunberg, 1980). Studies of structure–activity relationships among a series of chlorinated phenols showed that the effect increases with increasing chlorination of the phenol ring (Farquharson *et al.*, 1958). Pentachlorophenol and other chlorophenols inhibited some liver microsomal enzymes (Arrhenius *et al.*, 1977a,b), and pentachlorophenol strongly inhibited sulfotransferase activity in rat and mouse liver cytosol (Boberg *et al.*, 1983).

Reduced humoral immunity was observed in mice exposed to technical-grade pentachlorophenol, as well as impairment of T-cell cytolytic activity *in vitro* (Kerkvliet *et al.*, 1982a,b). In rats exposed to technical-grade pentachlorophenol, decreased cell-mediated and humoral immunity was demonstrated, while phagocytosis by macrophages and numbers of induced peritoneal macrophages were increased (Exon & Koller, 1983). Dioxin and furan contaminants are thought to be the chemical species responsible for the immunotoxicity of technical-grade pentachlorophenol (Kerkvliet *et al.*, 1985).

4.3 Reproductive and developmental effects

4.3.1 *Humans*

No data were available to the Working Group.

4.3.2 *Experimental systems*

Purified and commercial grades of pentachlorophenol were administered orally to rats at doses ranging from 5 to 50 mg/kg bw per day at various intervals during days 6-15 of pregnancy. A dose-related increase in the incidence of resorptions, subcutaneous oedema, dilated ureters and anomalies of the skull, ribs, vertebrae and sternebrae was observed. Early

organogenesis was the most sensitive period. The no-effect dose level of the commercial grade was 5 mg/kg bw per day; purified pentachlorophenol given at the same dose level caused a statistically significant increase in the incidence of delayed ossification of the skull bones but had no other effect on embryonal or fetal development (Schwetz *et al.*, 1974). Ingestion of 3 mg/kg bw per day of a commercially available purified grade of pentachlorophenol had no effect on reproduction, neonatal growth, survival or development (Schwetz *et al.*, 1978).

In Charles River CD rats given a single oral dose of 60 mg/kg bw pentachlorophenol (purity, > 99%) at various times on one of days 8-13 of gestation, the incidence of resorptions was not significantly greater than that in controls. Malformations were observed (5.8% of 51 fetuses examined after exposure on day 9 *versus* 0% in controls), including, for example, exencephaly and lack of tail, but the number was considered minimal, and the authors suggested that the effect could have been due to indirect toxic effects of the compound on the dams. No maternal mortality was reported (Larsen *et al.*, 1975).

Two later studies (Exon & Koller, 1982; Welsh *et al.*, 1987) in Sprague-Dawley rats administered pentachlorophenol in the feed throughout mating and pregnancy confirmed findings of embryo- and fetotoxicity and lethality, as judged by decreased litter size, and, at 13 mg/kg bw per day for 181 days (Welsh *et al.*, 1987), decreased body weight and crown–rump length and an increase in skeletal variations.

Pentachlorophenol was reported not to be embryolethal or teratogenic in CD rats given 75 mg/kg bw per day on days 7-18 of gestation (Courtney *et al.*, 1976).

As reported in an abstract, fetal deaths and/or resorptions were observed in three of six test groups of Syrian golden hamsters after oral administration of doses varying from 1.25 to 20.0 mg/kg bw per day on days 5-10 of gestation (Hinkle, 1973). Sea urchin eggs exposed to pentachlorophenol (0.2 mg/l medium or above) had delayed development and were malformed (Ozretić & Krajnović-Ozretić, 1985).

4.4 Genetic and related effects (see also Table 9 and Appendices 1 and 2)

The genotoxicity of pentachlorophenol has been reviewed (Seiler, 1991).

4.4.1 *Humans*

Sister chromatid exchange and chromosomal aberrations were analysed in peripheral lymphocytes from 22 exposed male workers with 1-30 years of exposure at a pentachlorophenol plant. Exposure to pentachlorophenol and sodium pentachlorophenate was estimated by measurements of concentrations in blood and urine. A matched control group of 22 unexposed workers was used, although matching was not quite complete since all exposed workers but only nine of the 22 controls were smokers. [The Working Group noted that pentachlorophenol was not measured in controls.] A total of 300 first-division metaphases were evaluated from each exposed and 500 from each unexposed person. Significant increases in the frequencies of dicentric chromosomes and of acentric fragments were observed in exposed *versus* control men, and the increases were not influenced by smoking habits. When smoking was controlled for, there was no effect of exposure to pentachlorophenol or its sodium salt upon the frequency of sister chromatid exchange (Bauchinger *et al.*, 1982).

In a study of 20 workers, with exposures to pentachlorophenol ranging from three to 34 years, divided into two groups according to their main occupation, exposure was estimated by measurement of the serum concentration of pentachlorophenol. No difference in the frequency of chromosomal aberration or of sister chromatid exchange was detected in peripheral lymphocytes from the two groups (Ziemsen *et al.*, 1987). [The Working Group noted that no unexposed control was used and that the time of culturing for metaphase analysis was not given]. Biological monitoring data showed exposure to be much lower than in the study of Bauchinger *et al.* (1982).

4.4.2 *Experimental systems*

In bacteria, pentachlorophenol gave equivocal results in tests for DNA damage and mostly negative results for induction of gene mutation. It was inactive in a host-mediated assay in mice with bacteria as the indicator organism. In yeast, pentachlorophenol induced gene mutation and mitotic gene conversion, but not mitotic recombination. It did not induce aneuploidy or, in the form of the sodium salt, recessive lethal mutation in *Drosophila melanogaster*. Pentachlorophenol did not induce gene mutation at the *hprt* locus in Chinese hamster V79 cells. It marginally increased the frequency of sister chromatid exchange in Chinese hamster CHO cells *in vitro* but not in human peripheral lymphocytes *in vitro*. Pentachlorophenol induced chromosomal aberrations in cultured Chinese hamster CHO cells but not in cultured human peripheral lymphocytes.

Pentachlorophenol exhibited a weak, but apparently dose-dependent effect in the mouse coat colour spot test for somatic gene mutation. It was reported in one study that high doses of pentachlorophenol did not induce sperm abnormality in mice. [The Working Group noted that no positive control was used.]

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Since its introduction in the 1930s, pentachlorophenol has been used in large quantities, mainly as a wood preservative. It has also found minor use as a herbicide, defoliant, bactericide and molluscicide. In recent years, its use in agriculture has been restricted in many countries.

Pentachlorophenol is usually formulated and applied to wood with a hydrocarbon diluant. Technical-grade pentachlorophenol has been shown to contain a large number of impurities, including tetrachlorophenols and, to a much lesser extent, polychlorodibenzodioxins, polychlorodibenzofurans, polychlorodiphenyl ethers, polychlorophenoxy phenols and chlorinated hydrocarbons.

Pentachlorophenol has been detected in fruits, vegetables, meats, water and soils. It has been detected in the urine of the general population in several countries and at higher levels in the urine of workers in wood treatment plants.

Exposure to pentachlorophenol can occur during its production and use; from contact with pentachlorophenol-treated wood; at lower levels, from consumption of foods and water containing residues; and as a result of its ubiquitous presence as an environmental contaminant.

Table 9. Genetic and related effects of pentachlorophenol

Test system	Result[a]		Dose[b]	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
PRB, prophage induction	(+)	(+)	12.0000	DeMarini *et al.* (1990)
PRB, PM2 phage, DNA strand breaks	-	0	26600.0000	Witte *et al.* (1985)
BSD, *Bacillus subtilis rec* strain, differential toxicity (spot test)	+	0	5.0000	Shirasu *et al.* (1976)
BSD, *Bacillus subtilis rec* strain, differential toxicity	-	-	2.2000	Matsui *et al.* (1989)
SA0, *Salmonella typhimurium* TA100, reverse mutation	-	-	5.0000	Nishimura *et al.* (1982)
SA0, *Salmonella typhimurium* TA100, reverse mutation	-	-	5.0000	Nishimura & Oshima (1983)
SA0, *Salmonella typhimurium* TA100, reverse mutation	-	-	15.0000	US National Toxicology Program (1989)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	-	-	15.0000	US National Toxicology Program (1989)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	-	-	15.0000	US National Toxicology Program (1989)
SA9, *Salmonella typhimurium* TA98, reverse mutation	-	+	5.0000	Nishimura *et al.* (1982)
SA9, *Salmonella typhimurium* TA98, reverse mutation	-	+	5.0000	Nishimura & Oshima (1983)
SA9, *Salmonella typhimurium* TA98, reverse mutation	-	-	15.0000	US National Toxicology Program (1989)
SCG, *Saccharomyces cerevisiae*, mitotic gene conversion	+	0	50.0000	Fahrig (1974)
SCG, *Saccharomyces cerevisiae* MP1, mitotic gene conversion	+	0	400.0000	Fahrig *et al.* (1978)
SCH, *Saccharomyces cerevisiae* MP1, mitotic crossing-over	-	0	400.0000	Fahrig *et al.* (1978)
SCF, *Saccharomyces cerevisiae* MP1, gene mutation	+	0	400.0000	Fahrig *et al.* (1978)
DMX, *Drosophila melanogaster*, sex-linked recessive lethal mutation	-	0	1860.0000	Vogel & Chandler (1974)
DMN, *Drosophila melanogaster*, chromosomal loss	-	0	400.0000	Ramel & Magnusson (1979)
DIA, DNA damage, Chinese hamster ovary cells *in vitro*	-	0	10.0000	Ehrlich (1990)
G9H, Gene mutation, Chinese hamster lung V79 cells *in vitro, hprt* locus	-	0	15.0000	Hattula & Knuutinen (1985)
G9H, Gene mutation, Chinese hamster lung V79 cells *in vitro, hprt* locus	-	0	50.0000	Jansson & Jansson (1986)
SIC, Sister chromatid exchange, Chinese hamster CHO cells *in vitro*	(+)	-	3.0000	Galloway *et al.* (1987)
CIC, Chromosomal aberrations, Chinese hamster CHO cells *in vitro*	-	(+)	100.0000	Galloway *et al.* (1987)
CIC, Chromosomal aberrations, Chinese hamster CHO cells *in vitro*	+	+	240.0000	Ishidate (1988)
SHL, Sister chromatid exchange, human lymphocytes *in vitro*	-	0	90.0000	Ziemsen *et al.* (1987)

Table 9 (contd)

Test system	Result[a]		Dose[b]	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
CHL, Chromosomal aberrations, human lymphocytes *in vitro*	-	0	90.0000	Ziemsen *et al.* (1987)
HMM, Host-mediated assay, *Salmonella typhimurium* G46, NMRI mouse	-	0	75.0000	Buselmaier *et al.* (1972)
HMM, Host-mediated assay, *Serratia marcescens* 21a, NMRI mouse	-	0	75.0000	Buselmaier *et al.* (1972)
MST, Spot test, C57Bl/6JHan×T mouse	(+)	0	50.0000	Fahrig *et al.* (1978)
SPM, Sperm morphology, (C57Bl/6×C3H)F_1 mouse	-	0	50.0000 × 5 i.p.	Osterloh *et al.* (1983)
SLH, Sister chromatid exchange, human lymphocytes *in vivo*	-	0	4.7300	Bauchinger *et al.* (1982)
CLH, Chromosomal aberrations, human lymphocytes *in vivo*	+	0	4.7300	Bauchinger *et al.* (1982)

[a] +, positive; (+), weakly positive; -, negative; 0, not tested; ?, inconclusive (variable response in several experiments within an adequate study)
[b] In-vitro tests, μg/ml; *in-vivo* tests, mg/kg bw

5.2 Carcinogenicity in humans

Two population-based case-control studies of soft-tissue sarcoma and non-Hodgkin's lymphoma in New Zealand found no increased risk associated with potential exposure to sodium pentachlorophenate through work in a sawmill or timber company. A similar study of multiple myeloma showed a slightly increased risk. A Swedish population-based case-control study found an increased risk for soft-tissue sarcoma associated with self-reported exposure to pentachlorophenol.

Excess incidences of cancers of the skin and of the lip, mouth and pharynx and of leukaemia were found in a cohort study of sawmill workers in Finland. Pentachlorophenol constituted only a minor proportion of the chlorophenols to which the workers were exposed.

5.3 Carcinogenicity in experimental animals

Two different pentachlorophenol formulations were tested for carcinogenicity by oral administration in two separate experiments in mice. A dose-related increase in the incidence of hepatocellular adenomas and carcinomas was observed in males exposed to either formulation and of hepatocellular adenomas in females exposed to one of the formulations. A dose-related increase in the incidence of adrenal phaeochromocytomas was observed in male mice exposed to either formulation, and an increase was also seen in females exposed to one of the formulations at the highest dose. A dose-related increase in the incidence of malignant vascular tumours of the liver and spleen was seen in female mice exposed to either formulation.

5.4 Other relevant data

Pentachlorophenol was embryotoxic and embryolethal and caused a slight increase in the number of malformations in rats.

Significant increases in the incidence of dicentric chromosomes and acentric fragments were detected in the peripheral lymphocytes of workers exposed occupationally to pentachlorophenol in one study, but no increase in the frequency of sister chromatid exchange was observed.

Pentachlorophenol gave negative results in most tests for genetic and related effects. It gave weakly positive results for somatic gene mutation in a mouse spot test. It induced chromosomal aberrations in cultured rodent cells but not in human cells and caused gene conversion in yeast.

5.5 Evaluation[1]

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

There is *sufficient evidence* in experimental animals for the carcinogenicity of pentachlorophenol.

Overall evaluation

Pentachlorophenol *is possibly carcinogenic to humans (Group 2B).*

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[1]For definition of the italicized terms, see Preamble, pp. 26-28.

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