POLYCHLOROPHENOLS AND THEIR SODIUM SALTS

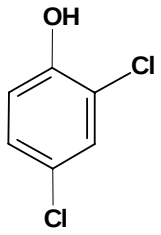
Data were last reviewed in IARC (1979, 1986, 1991) and the compounds were classified in *IARC Monographs* Supplement 7 (1987a).

1. Exposure Data

1.1 Chemical and physical data

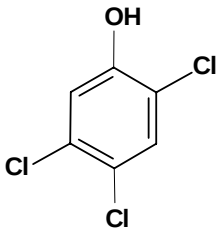
1.1.1 *Nomenclature, structural and molecular formulae and relative molecular masses*

Chem. Abstr. Serv. Reg. No.: 120-83-2
Chem. Abstr. Name: 2,4-Dichlorophenol
IUPAC Systematic Name: 2,4-Dichlorophenol
Synonym: 2,4-Dichlorophenic acid



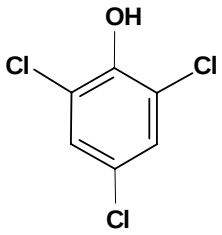
$C_6H_4Cl_2O$ Relative molecular mass: 163.00

Chem. Abstr. Serv. Reg. No.: 95-95-4
Chem. Abstr. Name: 2,4,5-Trichlorophenol
IUPAC Systematic Name: 2,4,5-Trichlorophenol
Synonym: TCP



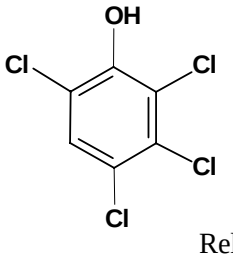
$C_6H_3Cl_3O$ Relative molecular mass: 197.46

Chem. Abstr. Serv. Reg. No.: 88-06-2
Chem. Abstr. Name: 2,4,6-Trichlorophenol
IUPAC Systematic Name: 2,4,6-Trichlorophenol



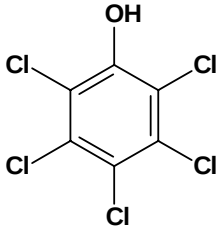
$C_6H_3Cl_3O$ Relative molecular mass: 197.46

Chem. Abstr. Serv. Reg. No.: 58-90-2
Chem. Abstr. Name: 2,3,4,6-Tetrachlorophenol
IUPAC Systematic Name: 2,3,4,6-Tetrachlorophenol



$C_6H_2Cl_4O$ Relative molecular mass: 231.89

Chem. Abstr. Serv. Reg. No.: 87-86-5
Chem. Abstr. Name: Pentachlorophenol
IUPAC Systematic Name: Pentachlorophenol
Synonyms: Chlorophenasic acid; PCP



C_6HCl_5O Relative molecular mass: 266.34

1.1.2 *Chemical and physical properties of the pure substances*

2,4-Dichlorophenol

(*a*) *Description*: Needle-like crystals (Budavari, 1996)
(*b*) *Boiling-point*: 210°C (Lide, 1997)
(*c*) *Melting-point*: 45°C (Lide, 1997)

(*d*) *Solubility*: Slightly soluble in water; soluble in benzene, carbon tetrachloride, diethyl ether and ethanol (Lewis, 1993; Lide, 1997)
(*e*) *Vapour pressure*: 10 Pa at 25°C; relative vapour density (air = 1), 5.62 (United States National Library of Medicine, 1997)
(*f*) *Flash-point*: 113°C (Lewis, 1993)
(*g*) *Conversion factor*: $mg/m^3 = 6.7 \times ppm$

2,4,5-Trichlorophenol

(*a*) *Description*: Colourless needles with a strong phenolic odour (Budavari, 1996)
(*b*) *Boiling-point*: 247°C (Lide, 1997)
(*c*) *Melting-point*: 69°C (Lide, 1997)
(*d*) *Solubility*: Slightly soluble in water; very soluble in acetone, benzene, diethyl ether and ethanol (Lewis, 1993; Lide, 1997)
(*e*) *Vapour pressure*: 2.9 Pa at 25°C (United States National Library of Medicine, 1997)
(*f*) *Conversion factor*: $mg/m^3 = 8.1 \times ppm$

2,4,6-Trichlorophenol

(*a*) *Description*: Colourless crystals with a strong phenolic odour (Budavari, 1996)
(*b*) *Boiling-point*: 246°C (Lide, 1997)
(*c*) *Melting-point*: 69°C (Lide, 1997)
(*d*) *Solubility*: Slightly soluble in water; soluble in acetone, acetic acid, diethyl ether and ethanol (Lewis, 1993; Lide, 1997)
(*e*) *Vapour pressure*: 133 Pa at 76.5°C (United States National Library of Medicine, 1997)
(*f*) *Conversion factor*: $mg/m^3 = 8.1 \times ppm$

2,3,4,6-Tetrachlorophenol

(*a*) *Description*: Brown flakes with a strong odour (Lewis, 1993)
(*b*) *Boiling-point*: 164°C (23 mm Hg) (Lewis, 1993)
(*c*) *Melting-point*: 70°C (Lide, 1997)
(*d*) *Solubility*: Insoluble in water; soluble in acetone, benzene, chloroform, diethyl ether and ethanol (Lewis, 1993; Lide, 1997)
(*e*) *Vapour pressure*: 8 kPa at 190°C (Verschueren, 1996)
(*f*) *Conversion factor*: $mg/m^3 = 9.5 \times ppm$

Pentachlorophenol

(*a*) *Description*: Needle-like crystals (Budavari, 1996)
(*b*) *Boiling-point*: 310°C (decomposes) (Lide, 1997)
(*c*) *Melting-point*: 174°C (Lide, 1997)
(*d*) *Solubility*: Slightly soluble in water; soluble in benzene; very soluble in diethyl ether and ethanol (Lide, 1997)

(*e*) *Vapour pressure*: 0.02 Pa at 20°C; relative vapour density (air = 1), 9.20 (Verschueren, 1996)

(*f*) *Conversion factor*: $mg/m^3 = 10.9 \times ppm$

1.2 Production and use

Production volumes for pentachlorophenol in the United States for the mid-1980s were reported as (thousand tonnes): 1983, 20.4; 1984, 19; 1985, 17.2; and 1986, 14.5 (Agency for Toxic Substances and Disease Registry, 1994). The volume for 1996, the last full year for which data are available, was 9.1 thousand tonnes. There is no known current European production of pentachlorophenol (Norman, 1998). Production data were not available for the other chlorophenols.

Information available in 1995 indicated that 2,4-dichlorophenol was produced in seven countries, 2,4,6-trichlorophenol in five, 2,4,5-trichlorophenol only in Japan and pentachlorophenol in six, while production of 2,3,4,6-tetrachlorophenol had been discontinued (Chemical Information Services, 1995).

2,4-Dichlorophenol and 2,4,5-trichlorophenol have been used in the synthesis of phenoxy acid herbicides, including 2,4-dichlorophenoxyacetic acid (2,4-D) and 2,4,5-trichlorophenoxyacetic acid (2,4,5-T). 2,4,5-Trichlorophenol has also been used as a fungicide and a bactericide. 2,4,6-Trichlorophenol has been used as a pesticide. 2,3,4,6-Tetrachlorophenol has been used as a fungicide (Lewis, 1993; Verschueren, 1996). Chlorophenols have also been formulated and used as salts in some applications.

Pentachlorophenol and its salt, sodium pentachlorophenate, are used primarily as wood preservatives on telephone poles, pilings and fence posts. In Europe, pentachlorophenol and its derivatives, sodium pentachlorophenate and pentachlorophenyl laurate are used to control sap stain in green lumber. It is also used in Europe on millwork to prevent the growth of mould and fungi, and as a preservative for waterproof materials (i.e., tarpaulins) that are used in outdoor applications. In the United States, it is used almost entirely for treatment of utility poles (Agency for Toxic Substances and Disease Registry, 1994).

1.3 Occurrence

1.3.1 *Occupational exposure*

According to the 1990–93 CAREX database for 15 countries of the European Union (Kauppinen *et al.*, 1998) and the 1981–83 National Occupational Exposure Survey (NOES) in the United States (NOES, 1997), approximately 45 000 workers in Europe and as many as 27 000 workers in the United States were potentially exposed to pentachlorophenol (see General Remarks). Recent figures give rough estimates of 500 pentachlorophenol-exposed workers in wood treatment facilities in the United States (Norman, 1998). No current data on numbers of workers exposed to other chlorophenols were available. Occupational exposures to chlorophenols have occurred in their production, in the production and use of some phenoxy acid herbicides, in sawmills and other wood-related industries, the textile industry and tanneries. Occupational exposures to penta-

chlorophenol may occur in its production and in its use as a wood preservative. These various occupational circumstances also involve exposure to polychlorinated dibenzo-dioxins (IARC, 1997).

1.3.2 *Environmental occurrence*

2,4-Dichlorophenol may be released to the environment in effluents from its manufacture and use as a chemical intermediate and from chlorination processes involving water treatment and wood-pulp bleaching. Releases can also occur from various incineration processes, from metabolism of various pesticides in soil or in the use of 2,4-D, in which it is an impurity. It has been detected at low levels in drinking-water, groundwater and ambient water samples (United States National Library of Medicine, 1997).

2,4,5-Trichlorophenol may be released to the environment through its production, use as a pesticide and pesticide intermediate, and use of pesticides in which it is an impurity (i.e. Silvex and 2,4,5-T). It has been detected at low levels in urban air, ambient water, drinking-water and wastewater samples (United States National Library of Medicine, 1997).

2,4,6-Trichlorophenol may enter the environment as emissions from combustion of fossil fuels and incineration of municipal wastes, as well as emissions from its manufacture and use as a pesticide, and in the use of 2,4-D, in which it is an impurity. Significant amounts may result from the chlorination of phenol-containing waters (United States National Library of Medicine, 1997).

In the past, 2,3,4,6-tetrachlorophenol entered the environment primarily in wastewater during its production and use as a wood preservative (United States National Library of Medicine, 1997).

Use of pentachlorophenol as a wood preservative may result in environmental release from treated wood and other materials. It has been detected at low levels in surface water, groundwater, drinking water, soil and urban air samples (United States National Library of Medicine, 1997).

1.4 Regulations and guidelines

The American Conference of Governmental Industrial Hygienists (ACGIH) (1997) has recommended 0.5 mg/m^3 as the 8-h time-weighted threshold limit value, with a skin notation, for occupational exposures to pentachlorophenol in workplace air. Values ranging from 0.05 to 0.5 mg/m^3 have been used as standards or guidelines in other countries (International Labour Office, 1991). The ACGIH has not proposed any occupational exposure limit for 2,4-dichlorophenol, 2,4,5-trichlorophenol, 2,4,6-trichlorophenol or 2,3,4,6-tetrachlorophenol. Finland and Sweden have an 8-h time-weighted average exposure limit of 0.5 mg/m^3, with a skin notation, for 2,3,4,6-tetrachlorophenol (United States National Library of Medicine, 1997).

The World Health Organization has established an international drinking-water guideline for 2,4,6-trichlorophenol of 200 µg/L and a provisional international drinking-water guideline for pentachlorophenol of 9 µg/L. No international guideline for 2,4-

dichlorophenol, 2,4,5-trichlorophenol or 2,3,4,6-tetrachlorophenol in drinking-water has been established (WHO, 1993).

2. Studies of Cancer in Humans

2.1 Case reports

Gilbert *et al*. (1990) identified 182 workers in Hawaii who had been continuously employed for at least three months during 1960–81 in the treatment of wood using various chemicals including pentachlorophenol. A search at the local tumour registry identified two registered cancers in the cohort, both of them colorectal. However, the expected numbers of cases were not calculated.

Cheng *et al*. (1993) analysed mortality in 109 workers who had been employed for one year or longer since 1974 in the pentachlorophenol section of a chemical manufacturing plant in China. During follow-up to 1990, three deaths were recorded, of which one was from lung cancer.

2.2 Studies of occupational populations (see Table 1 for the most relevant studies)

Mortality was reported for a small cohort of 204 workers involved in the manufacture of 2,4,5-T (IARC, 1987b) between 1950 and 1971 (Ott *et al*., 1980) and followed up to 1976, among whom reported exposures included 2,4,5-trichlorophenol. There were five deaths (7.0 expected) among those with one or more years of exposure, including one from cancer (1.3 expected).

Zack and Gaffey (1983) reported the mortality status of 884 white men employed for at least one year between 1955 and 1977 by a chemical plant in Nitro, WV, USA, involved in the production of 2,4,5-trichlorophenol and 2,4,5-T. 4-Aminobiphenyl, a human bladder carcinogen (see IARC, 1982), was produced from 1941 to 1952 in this plant. There were nine cases of bladder cancer, with 0.91 expected; deaths from cancer other than of the bladder were not in excess. One case of liposarcoma was reported among workers assigned to 2,4,5-T operations. Zack and Suskind (1980) reported cancer outcomes of a cohort of 121 males involved in a 1949 accident at the same plant. Follow-up revealed nine cancer deaths between 1949 and 1978, with 9.0 expected. Three of these were lymphatic or haematopoietic in origin (0.9 expected [$p = 0.047$]), and one was a primary dermal fibrous histiocytoma (0.15 expected).

In a cohort study of workers in two Danish chemical plants (Lynge, 1985), potential exposure to 2,4,5-trichlorophenol occurred between 1951 and 1959, when small amounts were produced or purchased to make 2,4,5-T. No overall increase in cancer incidence rate was observed, but there were significantly increased risks of soft-tissue sarcoma and lung cancer in certain subcohorts. [The Working Group noted that 2,4-dichlorophenol is an intermediate in the production of 2,4-D, which was produced by the larger of the two plants.]

Table 1. Industry-based studies and population-based studies of cancer in chlorophenol-exposed groups

Reference	Exposure	Measure of relative risk	Soft-tissue sarcoma		Non-Hodgkin lymphoma	
			Exposed cases	RR (95% CI)	Exposed cases	RR (95% CI)
Kogevinas *et al*. (1997)	Phenoxy acids or chlorophenols	SMR	9	2.0 (0.9–3.8)	34	1.3 (0.9–1.8)
Ramlow *et al.* (1996)	Pentachlorophenol	SMR			3 versus < 2.5 expected	
Mikoczy *et al*. (1994)	Tannery workers	SIR	5	3.2 (1.0–7.4)	4	0.7 (0.2–1.8)
Hertzman *et al*. (1997)	Workers at sawmills using chlorophenols	SMR	6	1.4 (0.6–2.8)	36	1.1 (0.8–1.4)
		SIR	11	1.2 (0.7–1.9)	65	1.2 (0.96–1.5)
Smith *et al*. (1984)	Potential exposure to chlorophenols	OR		1.6 (0.5–5.2)		
Hardell *et al*. (1995)	Chlorophenols (high-grade)	OR	34	3.3 (1.8–6.1)		
Pearce *et al*. (1986)	Potential exposure to chlorophenols	OR			9	1.3 (0.6–2.7)[a]
Hardell *et al*. (1994)	Chlorophenols (low-grade)	OR			19	3.3 (1.6–6.8)
	Chlorophenols (high-grade)				16	9.4 (3.6–25)
Woods *et al*. (1987)	High-exposure chlorophenols	OR		0.93 (0.5–1.8)		0.92 (0.91–1.4)[b]

RR, relative risk; CI, confidence interval; SMR, standardized mortality ratio; OR, odds ratio; SIR, standardized incidence ratio

[a] 90% CIs

[b] Figures as reported. The 95% CI appears incompatible with the point estimate of risk.

Cook *et al*. (1986) examined mortality between 1940 and 1979 among 2189 men involved in the manufacture of 2,4,5-trichlorophenol and 2,4,5-T. There were 298 deaths observed (standardized mortality ratio (SMR), 0.91), including 61 from cancer (SMR, 0.96) and five from non-Hodgkin lymphoma (SMR, 2.4; 95% confidence interval (CI), 0.8–5.6).

Cook *et al*. (1980) observed three cancer deaths (1.6 expected) among 61 male employees involved in an accident at a trichlorophenol-producing plant in Michigan and followed up to the end of 1978. One death was reported to be from a fibrosarcoma.

In the Federal Republic of Germany (Thiess *et al*., 1982), 74 workers were involved in an accident in 1953 in a plant producing 2,4,5-trichlorophenol. Follow-up through 1980 revealed three deaths from stomach cancer, with relative risks of the order of 4–5 depending on the comparison group; there was no excess of cancers at other sites combined.

With the exception of the accident cohort in Germany (Thiess *et al*., 1982), studies have since been incorporated in a multi-centre study coordinated by the International Agency for Research on Cancer, which collated data on 21 863 workers exposed to phenoxy acid herbicides, chlorophenols and polychlorinated dibenzodioxins from 36 cohorts of chemical manufacturers and herbicide sprayers in 12 countries (Kogevinas *et al*., 1997). The design and findings of the study have been reviewed in detail in an earlier monograph (IARC, 1997). Methods of follow-up varied between countries, and included use of national and municipal death registries, examination of plant records, and contact with workers and their families and physicians. The loss to follow-up was 4.4%. Mortality during 1939–92 was compared with that expected from the relevant national rates by the person–years method. In subjects with any exposure to phenoxy acids or chlorophenols there were 4159 deaths from all causes (SMR, 0.97; 95% CI, 0.94–1.00) including 1127 from cancer (SMR, 1.06; 95% CI, 1.00–1.13). Significant increases in mortality were seen for cancer of the larynx (21 deaths; SMR, 1.6; 95% CI, 1.0–2.5), other respiratory organs(12 deaths; SMR, 2.3; 95% CI, 1.2–3.9) and endocrine organs (ICD-9 code 194; 5 deaths; SMR, 3.6; 95% CI, 1.2–8.4). In addition, non-significant excesses were observed for cancer of the lung (380 deaths; SMR, 1.1; 95% CI, 1.0–1.2), cancers of connective and other soft tissues (9 deaths; SMR, 2.0; 95% CI, 0.9–3.8) and non-Hodgkin lymphoma (34 deaths; SMR, 1.3; 95% CI, 0.9–1.8). No analysis was presented for exposure specifically to chlorophenols.

Associations with chlorophenols were, however, analysed in two case–control studies nested within 24 of the 36 cohorts of the IARC study. These compared 11 cases of soft-tissue sarcoma and 32 cases of non-Hodgkin lymphoma with 55 and 158 controls, respectively (Kogevinas *et al.*, 1995). Exposure to chlorophenols, phenoxy acid herbicides, dibenzodioxins and -furans and other agents was assessed by a team of industrial hygienists (Kauppinen *et al.*, 1994). Odds ratios for non-Hodgkin lymphoma, not adjusted for exposure to other agents, were 1.3 (95% CI, 0.5–3.1) for any chlorophenol, 2.8 (0.5–17.0) for pentachlorophenol and 1.0 (0.3–3.1) for 2,4-dichlorophenol. No excess risk was found in relation to other chlorophenols, but the number of exposed cases was small. The odds

ratios for high cumulative exposure were 2.7 (0.9–8.0) for any chlorophenol and 4.2 (0.6–29.6) for pentachlorophenol. Only two cases of soft-tissue sarcoma were classified as exposed to chlorophenols (odds ratio, 1.3; 95% CI, 0.2–6.9) and neither was exposed to pentachlorophenol.

Ramlow *et al*. (1996) described a cohort of 770 male workers with potential exposure to pentachlorophenol who were employed by the Dow Chemical Company in the United States during 1937–80. The men were identified from employment records, and their cumulative exposure to pentachlorophenol and dibenzodioxins was classified on the basis of recorded job history and historical industrial hygiene measurements. The mortality of the cohort during 1940–89 was compared with that of the white male population of the United States by a modified life-table method. In addition, internal comparisons between different exposure categories were carried out by a Mantel–Haenszel method with baseline risks derived from 27 435 men employed by the same company during the same period but with no potential exposure to pentachlorophenol or dioxins. Mortality from all causes (229 deaths; SMR, 0.9; 95% CI, 0.8–1.1) and all cancers (50 deaths; SMR, 0.95; 95% CI, 0.7–1.3) was less than expected. Small excesses were observed for cancers of the stomach (4 deaths versus 2.4 expected; SMR, 1.7; 95% CI, 0.5–4.3), larynx (2 versus 0.7; SMR, 2.9; 95% CI, 0.4–10.3) and kidney (3 versus 1.3; SMR, 2.3; 95% CI, 0.5–6.7) and for non-Hodgkin lymphoma and myeloma combined (5 versus 2.5; SMR, 2.5; 95% CI, 0.7–4.7). Of the five observed deaths in the last category, three were from non-Hodgkin lymphoma and two from myeloma. With a lag period of 15 years, mortality from kidney cancer and from non-Hodgkin lymphoma and myeloma tended to increase with cumulative exposure to pentachlorophenol.

Mikoczy *et al*. (1994) studied 2026 workers at three Swedish leather tanneries, who had been employed for at least one year between 1900 and 1989. Chlorophenols had been used at these plants since about 1950 and were in use until 1980. Other potentially hazardous exposures included chromium compounds (IARC, 1990), vegetable tannins, arsenic sulfides (IARC, 1987c), mercury compounds (IARC, 1993), azo and benzidine dyes (IARC, 1987d), formaldehyde (IARC, 1995), solvents and aluminium compounds. Levels of exposure to chlorophenols were not reported, but blood samples from two tanners at one of the plants showed elevated concentrations of polychlorinated dibenzodioxins and dibenzofurans, which sometimes contaminate chlorophenols. Subjects were identified from company records, which were complete from as early as 1930 at one plant and from 1946 and 1966 at the other two, and were followed up through national death and tumour registries until death, emigration or their eightieth birthday. Five cohort members (0.2%) were lost to follow-up. Mortality during 1952–89 was compared with that in the two counties in which the plants were situated, and cancer incidence during 1958–89 with national rates, in each case by the person–years method. Mortality from all causes and from all cancers was close to expectation (SMR, 1.04 and 1.09, respectively). The overall incidence of cancer was somewhat elevated (233 cases observed versus 200 expected; standardized incidence ratio (SIR), 1.16; 95% CI, 1.02–1.32) with excesses of multiple myeloma (6 versus 2.8; SIR, 2.2; 95% CI, 0.8–4.7) and cancers of the lip

(5 versus 2.5; SIR, 2.0; 95% CI, 0.6–4.6), pancreas (9 versus 6.0; SIR, 1.5; 95% CI, 0.7–2.9), nose (2 versus 0.55; SIR, 3.8; 95% CI, 0.5–13.6), lung (20 versus 16.6; SIR, 1.2; 95% CI, 0.8–1.9), breast (20 versus 15.4; SIR, 1.2; 95% CI, 0.8–2.1), cervix (5 versus 3.0; SIR, 1.7; 95% CI, 0.5–3.9), prostate (32 versus 25.0; SIR, 1.3; 95% CI, 0.9–1.8) and soft tissues (5 versus 1.6; SIR, 3.2; 95% CI, 1.0–7.4). However, there were fewer cases of non-Hodgkin lymphoma than expected (4 versus 5.7; SIR, 0.7; 95% CI, 0.2–1.8). No analysis of cancer incidence was reported specifically for exposure to chlorophenols.

Hertzman and colleagues (1997) analysed mortality and cancer incidence among 26 487 men who had been employed at any of 14 sawmills in British Columbia, Canada, for one or more years between 1950 and 1985. Eleven of the mills had used tetra- and pentachlorophenol fungicides from the 1940s until 1989. Urine analyses in 172 employees from a pilot sawmill showed total levels of penta- and tetrachlorophenols ranging from 5 to 1252 μg/L, with a median of 108 μg/L in the summer and 52 μg/L in the fall (Hertzman *et al*., 1988). Personal cumulative exposures to chlorophenol in the full cohort were classified on the basis of job history. Individual records were linked with the provincial death file and the cancer incidence file, the Canadian mortality database and several other record systems, and mortality during 1950–90 and cancer incidence during 1969–89 were compared with those of the province by the person–years method. Among 23 829 workers at mills using chlorophenols, there were 4539 deaths (SMR, 0.96; 95% CI, 0.94–0.99) including 1155 from cancer (SMR, 1.07; 95% CI, 1.02–1.12), 369 from lung cancer (SMR, 1.10; 95% CI, 1.01–1.20), six from soft-tissue sarcoma (SMR, 1.4; 95% CI, 0.6–2.8), 116 from male genital cancer (SMR, 1.2; 95% CI, 1.0–1.4), 38 from cancer of the kidney (SMR, 1.4; 95% CI, 1.0–1.8), 23 from lymphosarcoma (SMR, 1.5; 95% CI, 1.0–2.1) and 36 from all non-Hodgkin lymphoma (SMR, 1.1; 95% CI, 0.8–1.4). Incidence rates were elevated for all cancers except skin (1498 cases; SIR, 1.05; 95% CI, 1.01–1.10), cancer of the rectum (105 cases; SIR, 1.2; 95% CI, 1.0–1.4), cancer of the lung (344 cases; SIR, 1.11; 95% CI, 1.02–1.22), cancer of the mediastinum (5 cases; SIR, 3.1; 95% CI, 1.2–6.5) and chronic lymphocytic leukaemia (24 cases; SIR, 1.7; 95% CI, 1.2–2.4). There were 11 incident cases of soft-tissue sarcoma (SIR, 1.2; 95% CI, 0.7–1.9). The risk of incident non-Hodgkin lymphoma increased significantly with cumulative exposure to chlorophenols, but this was due in part to a lower than expected incidence in the low-exposure categories. The risks in the five exposure categories from lowest to highest were 0.68 (4 cases), 0.59 (9 cases), 1.04 (11 cases), 1.02 (15 cases) and 1.30 (26 cases).

2.3 Studies in the general population

2.3.1 *Soft-tissue sarcoma*

A New Zealand study of soft-tissue sarcoma (see IARC, 1986) found an odds ratio of 1.6 (90% CI, 0.5–5.2) for potential exposure to chlorophenols for five days or more, more than 10 years before diagnosis (Smith *et al*., 1984). Work in pelt-treatment departments (where 2,4,6-trichlorophenol had been used) or in tanneries (where pentachlorophenol and

2,4,6-trichlorophenol were used) yielded an odds ratio of 7.2 (6 exposed cases; $p = 0.04$). When meat works and tanneries were contacted, it was found that two of the cases could not have been exposed to chlorophenols and exposure of a third was unlikely, while two could have been exposed to 2,4,6-trichlorophenol and one to pentachlorophenol.

In a case–control study in the north of Sweden, Hardell and Eriksson (1988) identified 55 men aged 25–80 years with histologically confirmed soft-tissue sarcomas that had been diagnosed during 1978–83 and reported to the local cancer registry. By the time of the study, 18 of these men were alive and 37 were dead. They were compared with three control groups: 220 men selected from the National Population Registry and matched to the cases for age and county of residence, 110 men similarly matched who had died during 1978–83 and 190 patients with other cancers who were selected from the Regional Cancer Registry and were of a similar age range to the cases. Exposure to various chemicals including chlorophenols was ascertained by a postal questionnaire sent to subjects or their next of kin, sometimes supplemented by a telephone interview. The overall response rate was 94.6%. No association was found with exposure to chlorophenols [numerical risk estimates were not reported], but the power to detect such a relationship was said to be low.

Eriksson *et al*. (1990) carried out a case–control study of soft-tissue sarcoma in central Sweden. Two hundred and thirty-seven histologically confirmed male cases, aged 25–80 years and diagnosed during 1978–86, were identified from the local cancer registry. The controls (one per case) were selected from population registries and individually matched for age, sex, county of residence and vital status. Exposure to suspected risk factors was ascertained by a questionnaire mailed to the subjects or their next of kin. If answers were incomplete, additional information was obtained by telephone interview. The response rates for cases and controls were 92% and 88%, respectively. With allowance for a latency of five years, high-grade exposure to chlorophenols (i.e., for at least one week continuously or at least one month in total) was reported for 15 cases and three controls (odds ratio, 5.3; 95% CI, 1.7–16.3). For pentachlorophenol specifically, the corresponding odds ratio was 3.9 (95% CI, 1.2–12.9) based on 11 exposed cases. No elevation of risk was found with shorter duration of exposure to chlorophenols.

Data from these two studies and from two earlier investigations (Hardell & Sandström, 1979; Eriksson *et al*., 1981) that have been summarized previously (IARC, 1986) were subsequently incorporated in a meta-analysis (Hardell *et al*., 1995). Risk was significantly elevated in subjects with high-grade exposure to chlorophenols (34 exposed cases; odds ratio, 3.3; 95% CI, 1.8–6.1), but in those with the most prolonged exposure (> 77 days), it was a little higher (odds ratio, 3.4; 95% CI, 1.7–7.8). Twenty-seven cases had high-grade exposure to pentachlorophenol (odds ratio, 2.8; 95% CI, 1.5–5.4). The associations were not specific to any single histological or anatomical subtype of sarcoma.

2.3.2 *Non-Hodgkin lymphoma*

A New Zealand case–control study of non-Hodgkin lymphoma involving 83 cases, 168 controls with other cancer and 228 general population controls, found an odds ratio of 1.3 (90% CI, 0.6–2.7) for potential exposure to chlorophenols when using other cancer

patients as controls, and an odds ratio of 0.9 (90% CI, 0.4–2.4) when using general population controls (Pearce *et al.*, 1986). The odds ratio for fencing work, which involves exposure to chemicals such as chromated copper-arsenate as well as pentachlorophenol, was 2.0 (90% CI, 1.3–3.0). The odds ratio for slaughterhouse employment, which involved potential exposure to 2,4,6-trichlorophenol, was 1.8 (90% CI, 1.1–3.1); however, only four of the 19 cases who had worked in a slaughterhouse reported working in the pelt department, where 2,4,6-trichlorophenol was used.

In a re-analysis of data from an earlier case–control study (Hardell *et al.*, 1981; see IARC, 1986), Hardell *et al.* (1994) compared 105 men aged 25–84 years who had been admitted to an oncology department in Sweden during 1974–78 and 335 controls from the same community who had been selected from the National Population Register and from a death registry. Information about exposure to chlorophenols and various other chemicals had been obtained through a postal questionnaire completed either by the subjects themselves or, if they had died, by their next of kin, and had been supplemented if necessary by telephone interview. Analysis by the Mantel–Haenszel method, with stratification by age and vital status, indicated associations with both low-grade (odds ratio, 3.3; 95% CI, 1.6–6.8) and high-grade (odds ratio, 9.4; 95% CI, 3.6–25) exposure to chlorophenols. These risk estimates were only slightly reduced in a multivariate analysis that allowed also for exposure to phenoxy acid herbicides, organic solvents, DDT and asbestos. The elevation of risk appeared to apply to all histological subtypes of non-Hodgkin lymphoma.

2.3.3 *Other cancers and multiple sites*

As described in an earlier monograph (IARC, 1986), a case–control study in Sweden found a significant association between nasal and nasopharyngeal cancer and exposure to chlorophenols, independent of exposure to wood dust (Hardell *et al.*, 1982). The same group of researchers also reported positive associations with high-grade exposure to chlorophenols in case–control studies of colon cancer (odds ratio, 1.8; 95% CI, 0.6–5.3) and primary liver cancer (odds ratio, 2.2; 95% CI, 0.7–7.3) (Hardell, 1981; Hardell *et al.*, 1984).

In a case–control study in the north of Sweden, Hallquist *et al.* (1993) compared 188 men and women aged 20–70 years who had thyroid cancer with age- and sex-matched controls (two per case) selected from a register of the local population. The cases were identified retrospectively from a cancer registry and excluded a proportion of patients (19%) who had died by the time of the study. Exposure to potential risk factors, including chlorophenols, was ascertained by postal questionnaire with a supplementary telephone interview if answers were incomplete. The response rates for the cases and controls were 95% and 90%, respectively. Of the 171 cases analysed, 107 had papillary tumours. Four cases and three controls reported exposure to chlorophenols (odds ratio, 2.8; 95% CI, 0.5–18). [The Working Group noted that the method of statistical analysis was not the most appropriate for individually matched data, but this is unlikely to have produced serious bias.]

Lampi *et al.* (1992) compared cancer registration rates during 1953–86 in each of three adjacent municipalities in southern Finland with those for the region in which these communities were situated. High concentrations of total chlorophenols had been found in tap-water (70–140 μg/L) in one of the municipalities, Kärkölä, and also in groundwater (up to 190 mg/L). These were thought to have originated from a sawmill where a fungicide containing tetrachlorophenol had been used to treat wood. In addition, some of the local population were exposed to chlorophenols occupationally and through consumption of contaminated fish. Overall cancer incidence in Kärkölä was close to that expected, but there was an excess of soft-tissue cancer (incidence rate ratio, 1.6; 95% CI, 0.7–3.5) that was not apparent in the other two municipalities. Rates of nodal non-Hodgkin lymphoma were elevated both in Kärkölä (incidence rate ratio, 2.1; 95% CI, 1.3–3.4) and in the two neighbouring communities.

To explore further the possible role of chlorophenols, 173 residents of the three municipalities in southern Finland who developed lymphoma, leukaemia or cancers of the colon, urinary tract or soft tissues during 1967–86 were compared with 688 controls randomly selected from the same population and individually matched for age (to within two years) and sex (Lampi *et al.*, 1992). Information about occupational and residential histories, water supplies and fish consumption was obtained by postal questionnaire, from either the subjects themselves or their next of kin (overall response rate, 88%). Risk of both soft-tissue cancer and non-Hodgkin lymphoma was increased in subjects with reported or inferred probable exposure to polluted drinking-water, the association with non-Hodgkin lymphoma being significant (risk ratio, 3.4; 95% CI, 1.0–12). In addition, three patients with non-Hodgkin lymphoma had consumed contaminated fish (risk ratio, infinity, lower 95% confidence limit, 1.1). Leukaemia was associated with most potential sources of exposure to chlorophenols, although not significantly. Findings for the other tumours were unremarkable.

In a population-based case–control study among men aged 20–79 years in 13 counties of Washington State, United States (Woods *et al.*, 1987), the case group comprised 128 patients with soft-tissue sarcoma and 576 with non-Hodgkin lymphoma, who were diagnosed during 1981–84 (79% response rate). The controls were 694 men randomly selected and group-matched to the cases for age and vital status (76% response rate). Living controls were obtained by random-digit dialling and from social security records, while deceased controls were identified from the death certificates of members of the study population who died during the study period from causes other than suicide or homicide. Information about occupational history and exposure to specific chemicals was obtained by interview of the subjects themselves or a proxy. Where reports of exposure to chemicals could be checked by questioning a supervisor or co-worker, agreement was found to be good. Analysis was by the Mantel–Haenszel method and by logistic regression with adjustment for age in 5- or 10-year groups. Neither disease was associated with reported exposure to chlorophenols. For the highest-exposure category, the odds ratios were 0.9 (95% CI, 0.5–1.8) for soft-tissue sarcoma and 0.92 (95% CI, 0.9–1.4) [the Working Group noted that the latter confidence interval appeared incompatible with the

risk estimate given] for non-Hodgkin lymphoma. Risks were elevated for work in some jobs entailing likely exposure to chlorophenols, such as manufacturers of chlorophenols, but not for all potentially exposed jobs combined. Nor did risk increase with duration of exposure or with allowance for latency.

As part of a nested case–control study that is described more fully in the monograph on phenol (see this volume), Kauppinen *et al*. (1993) assessed exposure to chlorophenols in 136 men with respiratory cancer and 408 matched controls from a cohort of Finnish woodworkers. Nine cases were classified as exposed (odds ratio, 0.9; 90% CI, 0.4–1.8), and, after adjustment for smoking habits (when known), the risk estimate was little changed.

In another nested case–control study based on the same cohort, Partanen *et al*. (1993) compared exposure to chlorophenols and other suspected risk factors in four cases of Hodgkin's disease, eight cases of non-Hodgkin lymphoma, 12 cases of leukaemia and 152 matched referents. Exposures were reconstructed through plant- and period-specific job–exposure matrices. Two of the cases were classed as exposed to chlorophenols (odds ratio, 0.9; 95% CI, 0.2–4.5).

3. Studies of Cancer in Experimental Animals

2,4,6-Trichlorophenol was tested for carcinogenicity in one experiment in two strains of mice by oral administration, and 2,4,5- and 2,4,6-trichlorophenols were tested in one experiment by subcutaneous injection in two strains of mice. 2,4,5-Trichlorophenol was also tested in one experiment for promoting activity in female mice. All three experiments were considered to be inadequate (IARC, 1979).

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 (IARC, 1991).

3.1 Oral administration

3.1.1 *2,4-Dichlorophenol*

Mouse: Groups of 50 male and 50 female B6C3F_1 mice, eight weeks of age, were administered 2,4-dichlorophenol (purity, > 99%) in the diet at concentrations of 0, 5000 and 10 000 mg/kg of diet (ppm) for two years. Mean body weights of high-dose groups of both sexes were reduced. Treatment did not affect survival rates. No increase in the incidence of tumours was found (United States National Toxicology Program, 1989).

Rat: Groups of 23–28 male and 22–29 female Sprague-Dawley rats were administered 2,4-dichlorophenol (purity, 99%) at concentrations of 0, 3, 30 and 300 mg/L (ppm) in the drinking-water starting prenatally for up to 24 months. Three-week-old weanling females were exposed to the same concentrations of 2,4-dichlorophenol through breeding to untreated males at 90 days of age and during lactation. Litter size was reduced at the highest dose. No increase in the incidence of total tumours was found [individual tumour types unspecified] (Exon & Koller, 1985).

Groups of 50 male and 50 female Fischer 344 rats, seven weeks of age, were administered 2,4-dichlorophenol (purity, > 99%) at concentrations of 0, 5000 and 10 000 ppm in the diet (males) and 0, 2500 and 5000 ppm (females) for 104 weeks. Mean body weights of the high-dose groups of both sexes were reduced. No increase in the incidence of tumours was found (United States National Toxicology Program, 1989).

3.1.2 *2,4,6-Trichlorophenol*

Mouse: Groups of 50 male B6C3F_1 mice, six weeks of age, were administered 2,4,6-trichlorophenol (96–97% pure with 17 minor contaminants; chlorinated dibenzo-*para*-dioxins were not determined) in the diet at concentrations of 5000 or 10 000 ppm for 105 weeks. Groups of 50 female B6C3F_1 mice, six weeks of age, received diets containing 10 000 or 20 000 ppm 2,4,6-trichlorophenol for 38 weeks, at which time the concentrations were reduced to 2500 and 5000 ppm because of excessive growth retardation, and the study was continued for a further 67 weeks. Groups of 20 untreated mice of each sex served as controls. Survival of males was 16/20 controls, 44/50 low-dose and 45/50 high-dose mice. Survival of females was 17/20 controls, 44/50 low-dose and 40/50 high-dose mice. Body weights of treated groups were lower than controls during the study. The incidences of hepatocellular adenomas (3/20 controls, 22/49 low-dose and 32/47 high-dose males and 1/20 control, 12/50 low-dose and 17/48 high-dose females) were increased in both sexes. The incidences of hepatocellular carcinomas in males were 1/20 control, 10/49 low-dose and 7/47 high-dose and those in females were 0/20 control, 0/50 low-dose and 7/48 high-dose. In males, combined incidences of hepatocellular adenomas and carcinomas were significantly increased (4/20 controls, 32/49 low-dose, 39/47 high-dose; $p < 0.001$ for each dose group). The combined incidence of hepatocellular adenomas and carcinomas was significantly elevated in the high-dose group of females (1/20 control, 12/50 low-dose, 24/48 high-dose; $p < 0.001$) (United States National Cancer Institute, 1979). [The Working Group noted the impurity of the test substance.]

Groups of 16 male and 16 female A/J mice, six to eight weeks of age, were given 2,4,6-trichlorophenol (reagent grade) by gavage in tricaprylin three times per week for eight weeks at a total dose of 1200 mg/kg bw. No increase in the incidence of lung tumours was found compared with vehicle-treated controls (Stoner *et al*., 1986).

Rat: Groups of 50 male and 50 female Fischer 344 rats, six weeks of age, were administered 2,4,6-trichlorophenol (96–97% pure with 17 minor contaminants; chlorinated dibenzo-*para*-dioxins were not determined) in the diet at concentrations of 5000 or

10 000 ppm for 106 or 107 weeks. Groups of 20 rats of each sex served as controls. Survival of males was 18/20 controls, 35/50 low-dose and 34/50 high-dose and of females was 14/20, 39/50 and 39/50. Body weights of treated rats were lower than those of controls throughout the study. The incidence of monocytic leukaemia was increased in both groups of treated males (3/20 controls, 23/50 low-dose, $p = 0.013$; 29/50 high-dose; $p = 0.002$) (United States National Cancer Institute, 1979). [The Working Group noted the impurity of the test substance.]

3.1.3 *Pentachlorophenol*

Rat: In an experiment not designed as a carcinogenicity study, groups of male and female MRC-Wistar rats [age unspecified] were administered pentachlorophenol (86% pure, containing 2,3,7,8-tetrachlorodibenzo-*para*-dioxin and 2,3,7,8-tetrachlorodibenzofuran) in the diet at 0 (12 male, 13 female) or 500 mg/kg (5 male, 9 female) for 94 weeks. In the group given pentachlorophenol, which had the longest survival, 6/9 female rats ($p < 0.01$) had liver adenomas compared with 0/13 controls (Mirvish *et al*., 1991). [The Working Group noted the low purity of the material tested and the inadequate reporting.]

Groups of 50 male and 50 female Fischer 344/N rats, six weeks of age, were administered diets containing pentachlorophenol (approximately 99% pure) at concentrations of 200, 400 and 600 ppm for 105 weeks. Two further groups of 60 males and 60 females received diets containing 0 (control) or 1000 ppm pentachlorophenol for 12 months followed by control diet. Ten male and 10 female controls and 10 males and 10 females receiving 1000 ppm were killed and evaluated histopathologically at seven months. All groups were evaluated histologically at 106 weeks. Weight gains of groups receiving 400 and 600 ppm were less than those of controls and weight gains of 1000 ppm groups were less than those of controls during treatment but recovered to control levels while on control diet. Survival was 12/50 controls, 16/50 at 200 ppm, 21/50 at 400 ppm, 31/50 at 600 ppm and 27/50 at 1000 ppm in males and 28/50, 33/50, 34/50, 28/50 and 28/50 in females. No significant increase in tumour incidence was observed in rats receiving pentachlorophenol in the diet for two years. In the group receiving 1000 ppm for 12 months, mesotheliomas of the tunica vaginalis occurred in 9/50 females versus 1/50 in controls ($p = 0.014$) (United States National Toxicology Program, 1997).

3.2 Intraperitoneal injection

Mouse: Groups of 16 male and 16 female A/J mice, six to eight weeks of age, were given 2,4,6-trichlorophenol (reagent grade) by intraperitoneal injection three times per week for eight weeks for total doses of 240, 600 or 1200 mg/kg bw. No increase in the incidence of lung tumours was found (Stoner *et al*., 1986).

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

4.1 Absorption, distribution, metabolism and excretion

4.1.1 *Humans*

The absorption of 2,4-dichloro-, 2,4,5-trichloro-, 2,4,6-trichloro-, 2,3,4,5- and 2,3,4,6-tetrachlorophenol is relatively rapid when they are given orally, dermally or by inhalation. Chlorophenols are almost exclusively metabolized to conjugates which are mainly excreted in the urine. Half-lives are from hours to days, the compounds with higher chlorine content having longer half-lives (IARC, 1986).

Although there are some discrepancies between different studies, the kinetics of pentachlorophenol can be summarized as follows. The half-times for oral absorption, plasma elimination and urinary excretion are of the order of 1.3 h, 10–20 days and 18–20 days, respectively, regardless of exposure level (although also shorter half-lifes have been calculated). The highest concentrations are found in liver, kidney and brain, but wide variations between different organs are found. Pentachlorophenol is metabolized *in vitro* by human liver microsomes to tetrachlorohydroquinone, which has also been found in urine of exposed workers, and to a lesser extent, to pentachlorophenol glucuronide. Blood and urine levels in occupationally exposed people and in people with no known exposure have been extensively measured (IARC, 1991). Pentachlorophenol is a strong inducer of cytochrome P450 enzymes, especially CYP3A, in cultured human hepatoma cells (Dubois *et al.*, 1996).

4.1.2 *Experimental systems*

The highest concentrations of studied chlorophenols (2,4-, 2,4,6- and 2,3,4,6-) have been found in kidney, liver and spleen and the lowest concentrations in muscle and brain, either after parenteral administration of these chlorophenols themselves or as metabolites of other organochlorine compounds. Over 80% of the dose is excreted in urine and 5–20% in faeces. Metabolism varies somewhat depending on chlorine content; the low-chlorine substances tend to be excreted as glucuronide and sulfate conjugates; with higher chlorine substitution, excretion of the unchanged substance tends to increase. Formation of chlorinated 1,4-quinones is a minor pathway except for 2,3,5,6-tetrachlorophenol (WHO, 1989).

Absorption of pentachlorophenol is relatively rapid in all species studied, but elimination differs between species and also between sexes. Metabolism occurs through glucuronic acid conjugation and hydrolytic dechlorination to tetrachlorohydroquinone, which is further conjugated. In contrast to rodents, rhesus monkeys eliminate pentachlorophenol in urine unchanged (IARC, 1991).

Five cysteinyl adducts of haemoglobin and albumin have been identified in the blood of rats following administration of pentachlorophenol up to 40 mg/kg. Adducts were formed by reactions with the pentachlorophenol metabolites tetrachloro-1,4-benzoquinone and its semiquinones (Waidyanatha *et al.*, 1996).

Detailed toxicokinetic studies have been performed in both rats (Yuan *et al*., 1994) and mice (Reigner *et al*., 1992), comparing intravenous and gavage (and in rat feed) administration of pentachlorophenol. In mice, after either intravenous or oral administration, the elimination half-life was about 5–6 h. Only 8% of the dose (15 mg/kg bw) was excreted unchanged in urine, while 20% was excreted as tetrachlorohydroquinone and its conjugates. Sulfate conjugates represented 90% of the total conjugates of pentachlorophenol and tetrachlorohydroquinone.

4.2 Toxic effects

4.2.1 *Humans*

One case report describes the accidental death of a worker following acute dermal exposure to 'pure' dichlorophenol (Kintz *et al*., 1992). [The purity of the solution was not reported nor were the levels of dioxin impurities reported.] The victim (an adult male) had a seizure within 20 min of the accident and died soon thereafter. Dichlorophenol levels in the blood, urine, bile and stomach contents were 24.3, 5.3, 18.7 and 1.2 mg/L, respectively.

Several cases of acute accidental, suicidal and occupational poisoning due to pentachlorophenol have been reported and reviewed, and the minimal lethal dose of pentachlorophenol in man has been estimated to be 29 mg/kg bw (WHO, 1987). Symptoms of acute poisoning include central nervous system disorders, dyspnoea and hyperpyrexia; the cause of death is cardiac arrest, and poisoning victims usually show marked rigor mortis. Examination *post mortem* shows non-specific organ damage. One case of fatal poisoning was associated with high pentachlorophenol concentrations in bile and kidney (Wood *et al*., 1983).

Occupational exposures to technical-grade pentachlorophenol have resulted in various disorders of the skin and mucous membranes (WHO, 1987). The incidence of chloracne was highest in people who 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). In addition, no adverse health effects or increased mortality were observed in 88 men employed in wood treatment. These men had worked for 0.33 to 26.3 years and had urinary pentachlorophenol concentrations of 174 ± 342 ppb (μg/kg; standard deviation) versus 35 ± 53 ppb for controls. Although workers were exposed to other wood-treatment chemicals (chromated copper-arsenate and tributyl tin oxide), no difference from controls was observed in urinary concentrations of these chemicals (Gilbert *et al*., 1990).

A study by McConnachie and Zahalsky (1991) reported on 38 individuals from 10 families who were exposed to pentachlorophenol by living in manufacturer-treated log homes. The exposure period lasted from 1.0 to 13.0 years and the serum pentachlorophenol levels of the subjects ranged from 0.01 to 3.4 ppm (mg/L). Altered immune function was

observed, including activated T cells, autoimmunity, functional immunosuppression and B cell dysregulation 0.0–9.0 years after pentachlorophenol exposure. [Control levels of pentachlorophenol were not reported. The controls were not screened for hypertension, smoking or use of alcohol or non-prescription drugs.]

Anecdotal exposure to pentachlorophenol has been associated with aplastic anaemia and/or red-cell aplasia (Roberts, 1983). Thirteen cases of industrial, home and accidental pentachlorophenol exposure in 11 men and two women having aplastic anaemia, pure red cell aplasia and associated disorders were reported. Exposure levels were not known except for one patient, who had concentrations in the serum of 250 ng/mL and in bone marrow of 330 ng/mL (Roberts, 1990).

4.2.2 *Experimental systems*

Repeated-dosing (14-day), subchronic (13-week) and chronic (two-year) toxicity studies of 2,4-dichlorophenol (> 99% pure) were conducted by the United States National Toxicology Program (1989). Male and female Fischer 344/N rats and $B6C3F_1$ mice were exposed to dichlorophenol in the feed. The repeated dosing study was conducted using five animals per group and dietary levels of 0, 2500, 5000, 10 000, 20 000 or 40 000 mg/kg [ppm] in the feed. In the high-dose group, one male mouse died before the end of the study. In rats and mice, feed consumption was reduced in the 20 000 and 40 000 mg/kg groups. Body weights were reduced at 20 000 mg/kg and higher in rats and at 40 000 mg/kg in mice. Gross pathology at necropsy revealed no treatment-related lesions.

The subchronic study was conducted using the same dietary levels as the repeated-dosing study but groups comprised 10 animals of each sex. All mice in the high-dose group died during the first three weeks. Body weights were reduced in mice at 20 000 mg/kg and in rats at 20 000 and 40 000 mg/kg. Feed consumption was decreased at 20 000 and 40 000 mg/kg in rats and at 10 000 mg/kg and higher in mice. Bone-marrow atrophy in rats and syncytial alteration of hepatocytes in mice were observed at 10 000 mg/kg and higher.

A chronic study was conducted by feeding diets containing 0, 5000 or 10 000 mg/kg to male and female mice and male rats or diets containing 0, 2500 or 5000 mg/kg to female rats (50 animals per sex per group). Body weights relative to controls were lower in the 10 000-mg/kg groups and at both dose levels for female rats. Survival was comparable in all groups. An increased incidence of syncytial alteration of hepatocytes was observed in treated male mice at 5000 and 10 000 mg/kg. No other treatment-related histological change was found.

Female Sprague-Dawley rats (12–14 animals/group) received the following chlorophenols in drinking-water: 2-chlorophenol (98% pure; impurities not reported) at 0, 5, 50 or 500 mg/L, 2,4-dichlorophenol (99% pure) or 2,4,6-trichlorophenol (98% pure) at 0, 3, 30 or 300 mg/L (Exon & Koller, 1985). The chemical was given to rats from three weeks of age throughout breeding (at 90 days of age with untreated males), gestation and lactation. To determine the effect of pre- and postnatal exposure to these chemicals, the offspring were weaned at three weeks of age and continued on treatment for 12–15 weeks (n = 8 per group, selected randomly from each dose group). Red blood-

cell counts, packed-cell volume and haemoglobin were increased in all groups of parental rats treated at the highest doses of 2-chlorophenol and 2,4-dichlorophenol. Other haematological parameters (white blood-cell count, mean corpuscular volume and packed-cell volume) were not affected at any dose level of the three chemicals. Immune response was affected in rats treated with 2,4-dichlorophenol. Cell-mediated immunity (measured as delayed-type hypersensitivity) was decreased at 30 and 300 mg/L, while humoral immunity was enhanced (increased serum antibody production) at 300 mg/L. Macrophage function was not affected. Liver and spleen weights were also increased at 300 mg/L 2,4-dichlorophenol. For 2,4,6-trichlorophenol, liver weight was increased at 30 and 300 mg/L and spleen weight at 300 mg/L.

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

The oral LD_{50} was 36–177 mg/kg bw in mice (Borzelleca *et al*., 1985) and 27–175 mg/kg bw in rats (Gaines, 1969). Cutaneous minimal lethal doses ranged from 39 to 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 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 in 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). Other

in-vitro assays have shown that the hydrophobicity of pentachlorophenol (log octanol/water partition coefficient = 3.32) correlates with the ability of the compound to bind to plasma proteins in trout (99.39%) and rat (99.52%) (Schmieder & Henry, 1988). However, the toxicity of chlorophenols in V79 Chinese hamster cells was correlated not only with hydrophobicity but also with electron-withdrawing properties of ring substituents (Jansson & Jansson, 1993).

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). Polychlorinated dibenzodioxin 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*

Two studies on birth outcomes of wives of employees potentially exposed to 2,4,5-trichlorophenol and/or pentachlorophenol did not show any significant association with regard to reproductive events (IARC, 1986).

The effect of pentachlorophenol exposure on reproductive outcome of 398 day-care teachers was evaluated. Exposed teachers (n = 221) came from day-care centres containing chemical-treated wood. A facility was deemed to be contaminated if the concentration of pentachlorophenol in the wood was greater than 100 mg/kg. A positive correlation existed between pentachlorophenol and polychlorinated dibenzodioxin/furan concentrations but not between these chemicals and γ-hexachlorocyclohexane. The median air concentrations of pentachlorophenol, polychlorinated dibenzodioxins/furans and γ-hexachlorocyclohexane in the exposed facilities were 0.25 μg/m^3, 0.5 pg/m^3 and 0.2 μg/m^3, respectively. Women exposed at any time during pregnancy were identified and after correction for lifestyle, 49 exposed and 507 unexposed pregnancies were analysed. Significantly reduced birth weight and length was observed in the offspring from exposed pregnancies. The women were mainly exposed to pentachlorophenol; however, the possible impact of polychlorinated dibenzodioxins/furans and γ-hexachlorocyclohexane on the effects reported is not clear (Karmaus & Wolf, 1995).

4.3.2 *Experimental systems*

Pregnant Fischer 344 rats (34 rats per group) were administered 2,4-dichlorophenol (99.2% pure; no dioxins detected) by gavage at 0, 200, 375 and 750 mg/kg per day on gestation days 6 to 15. Decreased maternal body weight gain and urogenital staining of the fur were observed at all dose levels. Maternal death, alopecia, respiratory rales and porphyrin accumulation in the area of the eyes, nares and mouth were observed at 750 mg/kg per day. Early embryonic death and decreased fetal weight were found at

750 mg/kg per day but were not significant. Delayed ossification of sternebrae and vertebral arches was observed at 750 mg/kg per day. The toxicity of 2,4-dichlorophenol to the embryo and fetus at 750 mg/kg per day may have been secondary to maternal toxicity (Rodwell *et al*., 1989).

Administration of 2,4,6-trichlorophenol (purified by recrystallization; 99% pure; the level of dioxin impurities was not reported) in corn oil by gavage at 0, 100, 500 and 1000 mg/kg per day (five days per week for 11 weeks) to adult male Long-Evans rats did not affect weight gain, organ weights, plasma testosterone or caudal sperm counts. When these males were mated with untreated females, fertility and reproductive performance (including litter size and pup weight) of the males in the trichlorophenol-treated groups were comparable to those of the control group. Female rats were also treated with the same daily dose levels of 2,4,6-trichlorophenol on five days per week for two weeks before mating with control males, then daily throughout pregnancy. At 1000 mg/kg per day, maternal toxicity including alopecia, decreased weight gain before and during pregnancy, lethargy, irregular breathing and, in a few instances, death were observed. 2,4,6-Trichlorophenol did not affect litter size or survival of pups to postnatal day 4. Pup weight was decreased at birth with the doses of 500 and 1000 mg/kg per day. This effect was transient and was not significant when corrected for litter size. Male and female reproductive functions were not affected at any dose level (Blackburn *et al*., 1986).

The developmental toxicity of 2,3,4,6-tetrachlorophenol was evaluated using purified and commercial grades of the compound. The commercial grade contained 73% 2,3,4,6-tetrachlorophenol, 27% pentachlorophenol and ppm levels of various dibenzo-*para*-dioxins and dibenzofurans, whereas the purified tetrachlorophenol was 99.6% pure, with only pentachlorophenol detected as an impurity (0.1%). Pregnant Sprague-Dawley rats were dosed by gavage at 0, 10 and 30 mg/kg per day on days 6–15 of gestation. In a preliminary study, 30 mg/kg per day was established as the maximum tolerated dose for the pregnant dam. These doses had no effect on maternal body weight, number of resorptions, fetal body weight, sex ratio or fetal crown–rump length. Data on litter size was not reported in this study. No maternal toxicity or teratogenicity was observed at any dose level. Delayed ossification of the skull bones occurred at 30 mg/kg/day with both grades of chemical, an effect indicative of fetotoxicity (Schwetz *et al*., 1974a).

Female Sprague-Dawley rats (12–14 animals/group) received the following chemicals in drinking-water: 2-chlorophenol (98% pure; impurities not reported) at 0, 5, 50 or 500 mg/L, 2,4-dichlorophenol (99% pure) or 2,4,6-trichlorophenol (98% pure) at 0, 3, 30 or 300 mg/L. The chemicals were given to rats from three weeks of age throughout breeding (at 90 days of age with untreated males), gestation and parturition. Conception, litter size (live and stillborn pups), birth weight, survival to weaning and weaning weight were recorded. For all three chemicals, litter size was decreased at the highest dose level. For 2-chlorophenol, the number of stillborn pups was increased at 500 mg/L. Whether these effects were secondary to maternal toxicity rather than fetotoxicity is not clear, since maternal parameters (body weight during pregnancy, feed consumption, clinical signs of toxicity) were not reported (Exon & Koller, 1985).

In contrast to these two drinking-water studies, gavage studies, conducted using much higher dose levels, saw no effect of 2,4-dichlorophenol and 2,4,6-trichlorophenol on litter size (Blackburn *et al*., 1986; Rodwell *et al.*, 1989). [These conflicting results may be due to the different modes of administration (gavage versus drinking-water) and vehicles (corn oil versus water).]

Purified and commercial grades of pentachlorophenol were administered orally to Sprague-Dawley rats at doses ranging from 3 to 70 mg/kg bw per day (preliminary study) and 5 to 50 mg/kg bw per day (teratology study) at various intervals during days 6–15 of pregnancy. Pentachlorophenol was determined to be embryotoxic and fetotoxic but not teratogenic. The most sensitive period was during early organogenesis. The maximal tolerated dose was determined to be 50 mg/kg per day. The no-observed-effect-level (NOEL) for maternal toxicity was 15 mg/kg per day. The NOEL for fetal effects was 5 mg/kg bw per day for commercial pentachlorophenol. Doses higher than 5 mg/kg bw per day (i.e., ≥ 15 mg/kg per day) induced dose-related maternal and fetal toxicity (e.g., increases in resorptions, subcutaneous oedema, dilated ureters and anomalies of the skull, ribs, vertebrae and sternebrae). Purified pentachlorophenol had slightly greater maternal and fetal toxicity, with a significant increase in delayed ossification of the skull bones but no other effect on embryonal or fetal development (Schwetz *et al.*, 1974b). 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).

Charles River CD rats were given a single oral dose of radiolabelled pentachlorophenol (purity, > 99%) equal to 75% of the LD_{50} (60 mg/kg bw) on day 15 of gestation, after having been given the same dose of unlabelled compound (purity not reported) on days 8–13 of gestation. Maternal serum pentachlorophenol levels peaked at approximately 1% of administered dose 8 h after dosing. Placental pentachlorophenol levels peaked at approximately 0.3% of administered dose/g tissue 12 h after dosing (most of this was due to the blood content). Fetal tissue pentachlorophenol levels remained constant at approximately 0.05%, demonstrating negligible transfer of pentachlorophenol to the fetus. Pentachlorophenol administration did not alter the number of resorptions, nor did it significantly affect malformations. Malformations in 3/51 fetuses (one each of exencephaly, macrophthalmia, and taillessness) were noted in the treated group compared with 0/44 in controls (no skeletal malformations were observed). Given the lack of significant pentachlorophenol placental transfer and malformations, the authors concluded that any effect observed in the fetuses was likely to have been indirectly related to the toxicity induced in the maternal rats (Larsen *et al.*, 1975).

In two later studies (Exon & Koller, 1982; Welsh *et al.*, 1987), pentachlorophenol was administered to Sprague-Dawley rats throughout mating and pregnancy. The results confirmed the findings of embryo- and fetotoxicity and lethality, in the absence of maternal toxicity. Adverse effects on the development of the rat conceptus occurred only at maternally toxic dosages.

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). Sea urchin

eggs exposed to pentachlorophenol (0.2 mg/L medium or above) had delayed development and were malformed (Ozretic & Krajnovic-Ozretic, 1985).

4.4 Genetic and related effects

4.4.1 *Humans*

Four studies have been published in which cytogenetic effects on peripheral lymphocytes were investigated in workers exposed occupationally to chlorophenols.

No significant difference was found between a control group and workers who had been exposed 10 years previously to 2,4,5-trichlorophenol, either as regards chromosomal damage or sister chromatid exchanges (Blank *et al*., 1983).

With regard to workers exposed to pentachlorophenol, two studies did not show increased incidence of sister chromatid exchanges (Willye *et al*., 1975) or sister chromatid exchanges and chromosomal aberrations (Ziemsen *et al*., 1987). However, increases in the incidence of dicentric chromosomes and acentric fragments were detected by Bauchinger *et al*. (1982), although no increase in sister chromatid exchanges was observed.

4.4.2 *Experimental systems* (see Table 2 for references)

Nineteen chlorophenols have been tested for prophage induction in *Escherichia coli*. Most showed negative, marginally positive or inconclusive activity, with the exception of 2,3,4-, 2,3,6-, 2,4,5-, 2,4,6- and 3,4,5-trichlorophenols, 2,3,4,5-tetrachlorophenol and pentachlorophenol, which were negative or weakly positive in the absence of and positive in the presence of metabolic activation. Various chlorophenols have been tested for mutagenicity in several strains of *Salmonella typhimurium*, with or without exogenous metabolic activation. Only pentachlorophenol showed marginal activity in TA98 with metabolic activation. 3- and 4-Chlorophenols and 2,3,6-, 2,4,5- and 2,4,6-trichlorophenols of unspecified purity appeared to be mutagenic in TA97, TA98, TA100 and/or TA104 strains, usually only in the presence of exogenous metabolic activation.

2,4- and 2,6-Dichlorophenols, 2,4,5-trichlorophenol, 2,3,4,6-tetrachlorophenol and pentachlorophenol, without exogenous metabolic activation, did not cause *hprt* mutations in V79 Chinese hamster cells.

2,4,6-Trichlorophenol demonstrated weak mutagenic activity in the *tk* locus of L5178Y mouse cells without exogenous metabolic activation. On the other hand, it did not induce *hprt* mutations and structural chromosomal aberrations in V79 cells without exogenous metabolic activation, but did induce hyperdiploidy and micronuclei. It was concluded that the genotoxic action of this chemical may primarily result from chromosome malsegregation. However, after detailed examination of the role of incubation and recovery times, it was shown that 2,4,6-trichlorophenol induces chromosomal aberrations in CHO cells with or without activation and in V79 cells without metabolic activation provided sufficient time is allowed for the cells to reach mitosis. It was reported that 2,3,4-, 2,3,6- and 3,4,5-trichlorophenols and 2,3,4,5-, 2,3,4,6- and 2,3,5,6-tetrachlorophenols without metabolic activation were negative or inconclusive for induction of chromosomal aberrations in Chinese hamster lung or ovary cells (with the exception of 2,3,6-trichlorophenol, which was positive

Table 2. Genetic and related effects of chlorophenols

Test system	Result[a]		Dose (LED or HID)[b]	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
2-Chlorophenol				
PRB, *Escherichia coli*, prophage λ induction	–	–	500	DeMarini *et al.* (1990)
3-Chlorophenol				
PRB, *Escherichia coli*, prophage λ induction	?	–	10	DeMarini *et al.* (1990)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	500	Strobel & Grummt (1987)
SA4, *Salmonella typhimurium* TA104, reverse mutation	–	(+)	125	Strobel & Grummt (1987)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	500	Strobel & Grummt (1987)
SAS, *Salmonella typhimurium* TA97, reverse mutation	+	+	5	Strobel & Grummt (1987)
4-Chlorophenol				
PRB, *Escherichia coli*, prophage λ induction	–	–	78	DeMarini *et al.* (1990)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	+	5	Strobel & Grummt (1987)
SA4, *Salmonella typhimurium* TA104, reverse mutation	–	(+)	125	Strobel & Grummt (1987)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	+	125	Strobel & Grummt (1987)
SAS, *Salmonella typhimurium* TA97, reverse mutation	–	+	5	Strobel & Grummt (1987)
2,3-Dichlorophenol				
PRB, *Escherichia coli*, prophage λ induction	–	(+)	13	DeMarini *et al.* (1990)
2,4-Dichlorophenol				
PRB, *Escherichia coli*, prophage λ induction	–	–	39	DeMarini *et al.* (1990)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	167	Haworth *et al.* (1983)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	–	167	Haworth *et al.* (1983)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	167	Haworth *et al.* (1983)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	167	Haworth *et al.* (1983)

Table 2 (contd)

Test system	Result[a]		Dose (LED or HID)[b]	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
2,4-Dichlorophenol (contd)				
URP, Unscheduled DNA synthesis, rat primary hepatocytes *in vitro*	–	NT	8	Probst *et al.* (1981)
G9H, Gene mutation, Chinese hamster lung V79 cells, *hprt* locus *in vitro*	–	NT	25	Jansson & Jansson (1986)
G5T, Gene mutation, mouse lymphoma L5178Y cells, *tk* locus *in vitro*	+	NT	30	US National Toxicology Program (1989)
SIC, Sister chromatid exchange, Chinese hamster ovary CHO cells *in vitro*	+	+	6.3	US National Toxicology Program (1989)
CIC, Chromosomal aberrations, Chinese hamster ovary CHO cells *in vitro*	–	–	150	US National Toxicology Program (1989)
AIA, Aneuploidy, Chinese hamster lung V79 cells *in vitro*	+	NT	81	Önfelt (1987)
2,5-Dichlorophenol				
PRB, *Escherichia coli*, prophage λ induction	–	(+)	3	DeMarini *et al.* (1990)
2,6-Dichlorophenol				
PRB, *Escherichia coli*, prophage λ induction	–	(+)	13	DeMarini *et al.* (1990)
G9H, Gene mutation, Chinese hamster lung V79 cells, *hprt* locus *in vitro*	–	NT	500	Jansson & Jansson (1986)
3,4-Dichlorophenol				
PRB, *Escherichia coli*, prophage λ induction	–	–	13	DeMarini *et al.* (1990)
3,5-Dichlorophenol				
PRB, *Escherichia coli*, prophage λ induction	–	(+)	3	DeMarini *et al.* (1990)

Table 2 (contd)

Test system	Result[a]		Dose (LED or HID)[b]	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
2,3,4-Trichlorophenol				
PRB, *Escherichia coli*, prophage λ induction	(+)	+	0.8	DeMarini *et al*. (1990)
CIC, Chromosomal aberrations, Chinese hamster lung V79 cells *in vitro*	–	–	120	Sofuni *et al*. (1990)
CIC, Chromosomal aberrations, Chinese hamster ovary CHO cells *in vitro*	–	+	70.2	Sofuni *et al*. (1990)
2,3,5-Trichlorophenol				
PRB, *Escherichia coli*, prophage λ induction	–	?	13	DeMarini *et al*. (1990)
2,3,6-Trichlorophenol				
PRB, *Escherichia coli*, prophage λ induction	–	+	3	DeMarini *et al*. (1990)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	50	Strobel & Grummt (1987)
SA4, *Salmonella typhimurium* TA104, reverse mutation	–	–	125	Strobel & Grummt (1987)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	+	5	Strobel & Grummt (1987)
SAS, *Salmonella typhimurium* TA97, reverse mutation	–	–	50	Strobel & Grummt (1987)
CIC, Chromosomal aberrations, Chinese hamster lung V79 cells *in vitro*	?	+	200	Sofuni *et al*. (1990)
CIC, Chromosomal aberrations, Chinese hamster ovary CHO cells *in vitro*	+	+	175	Sofuni *et al.* (1990)
CIC, Chromosomal aberrations, Chinese hamster ovary CHO cells *in vitro*	+	NT	400 (commercial)[c]	Armstrong *et al*. (1993)
2,4,5-Trichlorophenol				
PRB, *Escherichia coli*, prophage λ induction	(+)	+	0.8	DeMarini *et al*. (1990)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	25	Rasanen *et al*. (1977)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	25	Nestmann *et al*. (1980)

Table 2 (contd)

Test system	Result[a]		Dose (LED or HID)[b]	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
2,4,5-Trichlorophenol (contd)				
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	33	Haworth *et al*. (1983)
SA0, *Salmonella typhimurium* TA100, reverse mutation	(+)	–	5	Strobel & Grummt (1987)
SA4, *Salmonella typhimurium* TA104, reverse mutation	–	–	125	Strobel & Grummt (1987)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	–	25	Rasanen *et al*. (1977)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	–	25	Nestmann *et al*. (1980)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	–	33	Haworth *et al*. (1983)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	25	Rasanen *et al*. (1977)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	25	Nestmann *et al*. (1980)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	33	Haworth *et al*. (1983)
SA8, *Salmonella typhimurium* TA1538, reverse mutation	–	–	25	Nestmann *et al*. (1980)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	25	Rasanen *et al*. (1977)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	25	Nestmann *et al*. (1980)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	33	Haworth *et al*. (1983)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	5	Strobel & Grummt (1987)
SAS, *Salmonella typhimurium* TA97, reverse mutation	+	+	25	Strobel & Grummt (1987)
G9H, Gene mutation, Chinese hamster lung V79 cells, *hprt* locus *in vitro*	–	NT	50	Jansson & Jansson (1986)
CIC, Chromosomal aberrations, Chinese hamster ovary CHO cells *in vitro*	+	NT	140 (commercial)[c]	Armstrong *et al*. (1993)
SLH, Sister chromatid exchange, human lymphocytes *in vivo*	–		NG	Blank *et al*. (1983)
CLH, Chromosomal aberrations, human lymphocytes *in vivo*	–		NG	Blank *et al*. (1983)

Table 2 (contd)

Test system	Result[a]		Dose (LED or HID)[b]	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
2,4,6-Trichlorophenol				
PRB, *Escherichia coli*, prophage λ induction	(+)	+	3	DeMarini *et al*. (1990)
BSD, *Bacillus subtilis rec* strains, differential toxicity	(+)	NT	500 µg/disk	Kinae *et al*. (1981)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	25	Rasanen *et al*. (1977)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	0.5	Kinae *et al*. (1981)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	166	Haworth *et al*. (1983)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	125	Strobel & Grummt (1987)
SA4, *Salmonella typhimurium* TA104, reverse mutation	–	(+)	25	Strobel & Grummt (1987)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	–	25	Rasanen *et al*. (1977)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	–	166	Haworth *et al*. (1983)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	25	Rasanen *et al*. (1977)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	0.5	Kinae *et al*. (1981)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	166	Haworth *et al*. (1983)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	25	Rasanen *et al*. (1977)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	0.5	Kinae *et al*. (1981)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	166	Haworth *et al*. (1983)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	+	5	Strobel & Grummt (1987)
SAS, *Salmonella typhimurium* TA97, reverse mutation	–	+	5	Strobel & Grummt (1987)
SCG, *Saccharomyces cerevisiae* MP1, gene conversion	–	NT	400	Fahrig *et al*. (1978)
SCH, *Saccharomyces cerevisiae* MP1, homozygosis by mitotic recombination or gene conversion	–	NT	400	Fahrig *et al*. (1978)
SCF, *Saccharomyces cerevisiae* MP1, forward mutation	+	NT	400	Fahrig *et al*. (1978)
DMX, *Drosophila melanogaster*, sex-linked recessive lethal mutations	–		10000 inj	Valencia *et al*. (1985)

Table 2 (contd)

Test system	Result[a]		Dose (LED or HID)[b]	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
2,4,6-Trichlorophenol (contd)				
DIA, DNA strand breaks, PM2 DNA *in vitro*	NT	+	NG	Juhl *et al*. (1989)
G9H, Gene mutation, Chinese hamster lung V79 cells, *hprt* locus *in vitro*	–	NT	100	Jansson & Jansson (1986)
G9H, Gene mutation, Chinese hamster lung V79 cells, *hprt* locus *in vitro*	–	NT	180	Jansson & Jansson (1992)
G5T, Gene mutation, mouse lymphoma L5178Y cells, *tk* locus *in vitro*	+	NT	80	McGregor *et al*. (1988)
SIC, Sister chromatid exchange, Chinese hamster ovary CHO cells *in vitro*	–	–	500	Galloway *et al*. (1987)
CIC, Chromosomal aberrations, Chinese hamster ovary CHO cells *in vitro*	–	–	500	Galloway *et al*. (1987)
CIC, Chromosomal aberrations, Chinese hamster lung V79 cells *in vitro*	–	NT	60	Jansson & Jansson (1992)
CIC, Chromosomal aberrations, Chinese hamster lung V79 cells *in vitro*	+	NT	400 (commercial)[c]	Armstrong *et al*. (1993)
CIC, Chromosomal aberrations, Chinese hamster ovary CHO cells *in vitro*	+	NT	500 (repurified)[c]	Armstrong *et al*. (1993)
CIC, Chromosomal aberrations, Chinese hamster ovary CHO cells *in vitro*	+	+	400 (commercial)[c]	Armstrong *et al*. (1993)
AIA, Aneuploidy, Chinese hamster lung V79 cells *in vitro*	+	NT	100 (commercial)	Armstrong *et al*. (1993)
AIA, Aneuploidy, Chinese hamster lung V79 cells *in vitro*	+	NT	30	Jansson & Jansson (1992)

Table 2 (contd)

Test system	Result[a]		Dose (LED or HID)[b]	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
2,4,6-Trichlorophenol (contd)				
MIA, Micronucleus test, Chinese hamster lung V79 cells *in vitro*	+	NT	30	Jansson & Jansson (1992)
MST, Mouse spot test	+	NT	50	Fahrig *et al*. (1978)
3,4,5-Trichlorophenol				
PRB, *Escherichia coli*, prophage λ induction	–	+	0.8	DeMarini *et al*. (1990)
CIC, Chromosomal aberrations, Chinese hamster lung V79 cells *in vitro*	–	?	30	Sofuni *et al*. (1990)
CIC, Chromosomal aberrations, Chinese hamster ovary CHO cells *in vitro*	–	–	30	Sofuni *et al*. (1990)
2,3,4,5–Tetrachlorophenol				
PRB, *Escherichia coli*, prophage λ induction	–	+	0.8	DeMarini *et al*. (1990)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	5	Zeiger *et al*. (1988)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	–	5	Zeiger *et al*. (1988)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	5	Zeiger *et al*. (1988)
SAS, *Salmonella typhimurium* TA97, reverse mutation	–	–	5	Zeiger *et al*. (1988)
CIC, Chromosomal aberrations, Chinese hamster lung V79 cells *in vitro*	–	(+)	60	Sofuni *et al*. (1990)
CIC, Chromosomal aberrations, Chinese hamster ovary CHO cells *in vitro*	–	+	29.8	Sofuni *et al*. (1990)
2,3,4,6-Tetrachlorophenol				
PRB, *Escherichia coli*, prophage λ induction	–	–	39	DeMarini et al. (1990)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	25	Rasanen *et al*. (1977)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	50	Zeiger *et al*. (1988)

Table 2 (contd)

Test system	Result[a]		Dose (LED or HID)[b]	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
2,3,4,6-Tetrachlorophenol				
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	–	25	Rasanen *et al*. (1977)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	–	50	Zeiger *et al*. (1988)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	25	Rasanen *et al*. (1977)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	25	Rasanen *et al*. (1977)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	50	Zeiger *et al*. (1988)
SAS, *Salmonella typhimurium* TA97, reverse mutation	–	–	50	Zeiger *et al*. (1988)
G9H, Gene mutation, Chinese hamster lung V79 cells, *hprt* locus *in vitro*	–	NT	100	Jansson & Jansson (1986)
CIC, Chromosomal aberrations, Chinese hamster lung V79 cells *in vitro*	?	(+)	250	Sofuni *et al*. (1990)
CIC, Chromosomal aberrations, Chinese hamster ovary CHO cells *in vitro*	(+)	+	100	Sofuni *et al*. (1990)
2,3,5,6-Tetrachlorophenol				
PRB, *Escherichia coli*, prophage λ induction	?	(+)	25	DeMarini *et al*. (1990)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	50	Zeiger *et al*. (1988)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	–	50	Zeiger *et al*. (1988)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	50	Zeiger *et al*. (1988)
SAS, *Salmonella typhimurium* TA97, reverse mutation	–	–	17	Zeiger *et al*. (1988)
CIC, Chromosomal aberrations, Chinese hamster lung V79 cells *in vitro*	–	+	60	Sofuni *et al*. (1990)
CIC, Chromosomal aberrations, Chinese hamster ovary CHO cells *in vitro*	–	+	175	Sofuni *et al*. (1990)

Table 2 (contd)

Test system	Result[a]		Dose (LED or HID)[b]	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
Pentachlorophenol				
PRB, Prophage PM2 induction, SOS repair test, DNA strand breaks, cross-links or related damage	–	NT	26650	Witte *et al*. (1985)
PRB, *Escherichia coli*, prophage λ induction	(+)	+	13	DeMarini *et al*. (1990)
BSD, *Bacillus subtilis rec* strains, differential toxicity	+	NT	5	Shirasu *et al*. (1976)
BSD, *Bacillus subtilis rec* strains, differential toxicity	–	–	2.2	Matsui *et al*. (1989)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	5	Nishimura *et al*. (1982)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	10	Haworth *et al*. (1983)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	5	Nishimura & Oshima (1983)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	–	10	Haworth *et al*. (1983)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	10	Haworth *et al*. (1983)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	+	5	Nishimura *et al*. (1982)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	10	Haworth *et al*. (1983)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	+	5	Nishimura & Oshima (1983)
SCG, *Saccharomyces cerevisiae* D4, gene conversion	+	NT	50	Fahrig (1974)
SCG, *Saccharomyces cerevisiae* MP1, gene conversion	+	NT	400	Fahrig *et al*. (1978)
SCH, *Saccharomyces cerevisiae* MP1, homozygosis by mitotic recombination or gene conversion	–	NT	400	Fahrig *et al*. (1978)
SCF, *Saccharomyces cerevisiae* MP1, forward mutation	+	NT	400	Fahrig *et al*. (1978)
ACC, *Allium cepa*, chromosomal aberrations	–		1.5	Venegas *et al*. (1993)
DMX, *Drosophila melanogaster*, sex-linked recessive lethal mutations	–		1865 feed	Vogel & Chandler (1974)
DMN, *Drosophila melanogaster*, aneuploidy	–		400 ppm feed	Ramel & Magnusson (1979)

Table 2 (contd)

Test system	Result[a]		Dose (LED or HID)[b]	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
Pentachlorophenol (contd)				
DIA, DNA strand breaks, cross-links or related damage, Chinese hamster ovary CHO cells *in vitro*	–	NT	10	Erlich (1990)
G9H, Gene mutation, Chinese hamster lung V79 cells, *hprt* locus *in vitro*	–	NT	15	Hattula & Knuutinen (1985)
G9H, Gene mutation, Chinese hamster lung V79 cells, *hprt* locus *in vitro*	–	NT	50	Jansson & Jannson (1986)
SIC, Sister chromatid exchange, Chinese hamster ovary CHO cells *in vitro*	(+)	–	3	Galloway *et al*. (1987)
CIC, Chromosomal aberrations, Chinese hamster ovary CHO cells *in vitro*	–	(+)	100	Galloway *et al*. (1987)
CIC, Chromosomal aberrations, Chinese hamster lung V79 cells *in vitro*	+	+	240	Ishidate (1988)
SHL, Sister chromatid exchange, human lymphocytes *in vitro*	–	NT	90	Ziemsen *et al*. (1987)
CHL, Chromosomal aberrations, human lymphocytes *in vitro*	–	NT	90	Ziemsen *et al*. (1987)
HMM, Host-mediated assay in NMRI mice	–		75 sc × 1	Buselmaier *et al*. (1972)
MST, Spot test, C57BL/6JHan × T mice	(+)		50 ip × 1	Fahrig *et al*. (1978)
MVA, Micronucleus test, amphibian *Caudiverbera caudiverbera* larvae *in vivo*	–		1.5 µg/mL	Venegas *et al*. (1993)
BID, Binding (covalent) to DNA, quail and fetal rat hepatocytes *in vitro*	+	NT	13	Dubois *et al*. (1997)

Table 2 (contd)

Test system	Result[a]		Dose (LED or HID)[b]	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
Pentachlorophenol (contd)				
BID, Binding (covalent) to DNA, human hepatoma HepG2 cells *in vitro*	+	NT	13	Dubois *et al*. (1997)
SPM, Sperm morphology, (C57BL/6×C3H)F_1 mice *in vivo*	–		50 ip × 5	Osterloh *et al*. (1983)

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

[b] LED, lowest effective dose; HID, highest ineffective dose; in-vitro tests, μg/mL; in-vivo tests, mg/kg bw/day; NG, not given; inj, injection; ip, intraperitoneal; sc, subcutaneous

[c] With 3 h incubation + 17 h recovery

in the ovary cells). In the presence of metabolic activation, all of the above were clearly or weakly positive in both cell lines, with the exception of 2,3,4-trichlorophenol (negative in the lung cell line) and 3,4,5-trichlorophenol (negative in the ovary cell line).

Pentachlorophenol caused gene conversion and forward mutation in yeast. It did not cause micronucleated erythrocytes in the amphibian *Caudiverbera caudiverbera* or chromosomal aberrations in the root tips of the plant *Allium cepa*. *In vitro*, positive results were reported for the induction of chromosomal aberrations in Chinese hamster lung V79 cells but no effect was observed in human lymphocytes without exogenous metabolic activation. In single studies, sister chromatid exchanges were not induced in human lymphocytes but a weak effect was reported in Chinese hamster ovary CHO cells. Pentachlorophenol gave weakly positive results in a mouse spot test. It did not modify the recombinogenic or mutagenic effects of *N*-ethyl-*N*-nitrosourea in the mouse spot test or sperm morphology *in vivo* in mice. It generated low levels of unidentified DNA adducts, as detected by ^{32}P-postlabelling, upon incubation *in vitro* with primary liver cells of quail (*Coturnix coturnix*) or fetal rat or the human liver cell line HepG2.

In addition to genotoxicity studies with chlorophenols themselves, the corresponding activity of some of their metabolites has also been examined. The major metabolite of pentachlorophenol in mice and rats, tetrachloro-*para*-hydroquinone, induced mutations in the *hprt* locus (but not the ouabain-resistance locus) of V79 Chinese hamster cells (Jansson & Jansson, 1991), covalent damage (including 8-hydroxyguanine) in naked DNA in the presence of Cu(II) (Naito *et al*., 1994), DNA strand breaks and accumulation of p53 in NIH 3T3 cells *in vitro* and transformation of mouse embryo fibroblasts in a two-stage model (Wang *et al*., 1997). The same metabolite, as well as tetrachloro-1,4-benzoquinone and tetrachloro-1,2-benzoquinone, caused DNA strand breaks in V79 Chinese hamster cells (Dahlhaus *et al*., 1996).

A mixture of metabolites obtained after incubation of 2,4,6-trichlorophenol with rat liver S9 mix induced strand breaks in plasmid DNA. The strand breakage was prevented by dimethylsulfoxide or catalase, suggesting that oxygen radicals were responsible (Juhl *et al*., 1989).

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Exposures to chlorophenols and their salts have occurred in their production, in the production of some phenoxy acid herbicides, in the wood industry, the textile industry and tanneries. They have been detected at low levels in ambient air and water.

5.2 Human carcinogenicity data

Mortality and/or cancer incidence has been analysed in several cohort studies of chemical manufacturers, almost all of which have been incorporated within a multicentre international collaborative study, and also in a case–control study nested within this

cohort. Two other cohort studies have focused on leather tanneries in Sweden and sawmills in Canada where chlorophenols were used. In addition, case–control studies have examined the association of chlorophenols with soft-tissue sarcoma (one study in New Zealand, four in Sweden and one in the United States), non-Hodgkin lymphoma (one study in New Zealand, one in Sweden and one in the United States), thyroid cancer (one study in Sweden), nasal and nasopharyngeal cancer (one study in Sweden), colon cancer (one study in Sweden) and liver cancer (one study in Sweden).

These investigations have shown significant associations with several types of cancer, but the most consistent findings have been for soft-tissue sarcoma and non-Hodgkin lymphoma. Although the odds ratios in some case–control studies may have been inflated by recall bias, this cannot explain all of the findings. Nor are they likely to have arisen by chance. It is not possible, however, to exclude a confounding effect of polychlorinated dibenzo-*para*-dioxins which occur as contaminants in chlorophenols.

5.3 Animal carcinogenicity data

2,4-Dichlorophenol was tested in one study in mice and in two studies in rats by oral administration. No increase in the incidence of tumours was found.

2,4,5-Trichlorophenol has not been adequately tested for carcinogenicity.

2,4,6-Trichlorophenol was tested in one study in mice and in one study in rats by oral administration and in one study in mice in a screening test for lung tumours. In mice, it increased the incidences of benign and malignant tumours of the liver and in rats mononuclear cell leukaemia. It did not induce lung adenomas in mice.

No data on the carcinogenicity of tetrachlorophenols in experimental animals were available to the Working Group.

Three different pentachlorophenol formulations were tested for carcinogenicity by oral administration in two experiments in mice and in one study in rats. 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. In rats, no increase in tumours was seen following oral administration of pentachlorophenol for 24 months. However, in rats in the same study receiving a higher concentration for 12 months and held for an additional year, an increased incidence of mesotheliomas of the tunica vaginalis was observed.

5.4 Other relevant data

Chlorophenols are absorbed fairly rapidly, distributed mainly to the kidney and liver and excreted principally via urine; low chlorine-substituted compounds are conjugated with sulfate and glucuronide to a greater extent than the more highly chlorine-substituted compounds. Chlorinated *para*-hydroquinone formation is a minor metabolic pathway

but not for 2,3,5,6-tetrachlorophenol and pentachlorophenol. In rats, the liver is the main target organ. Otherwise, few remarkable effects have been observed.

2,4,6-Trichlorophenol may exhibit weak aneugenic and clastogenic activity. Information on other chlorophenols is inadequate to allow assessment of their genotoxicity.

Pentachlorophenol, after metabolic activation, may exhibit weak clastogenic activity by enhancing oxidative DNA damage.

5.5 Evaluation

There is *limited evidence* in humans for the carcinogenicity of combined exposures to polychlorophenols or to their sodium salts.

There is *evidence suggesting lack of carcinogenicity* of 2,4-dichlorophenol in experimental animals.

There is *inadequate evidence* in experimental animals for the carcinogenicity of 2,4,5-trichlorophenol.

There is *limited evidence* in experimental animals for the carcinogenicity of 2,4,6-trichlorophenol.

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

Overall evaluation

Combined exposures to polychlorophenols or to their sodium salts are *possibly carcinogenic to humans (Group 2B).*

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