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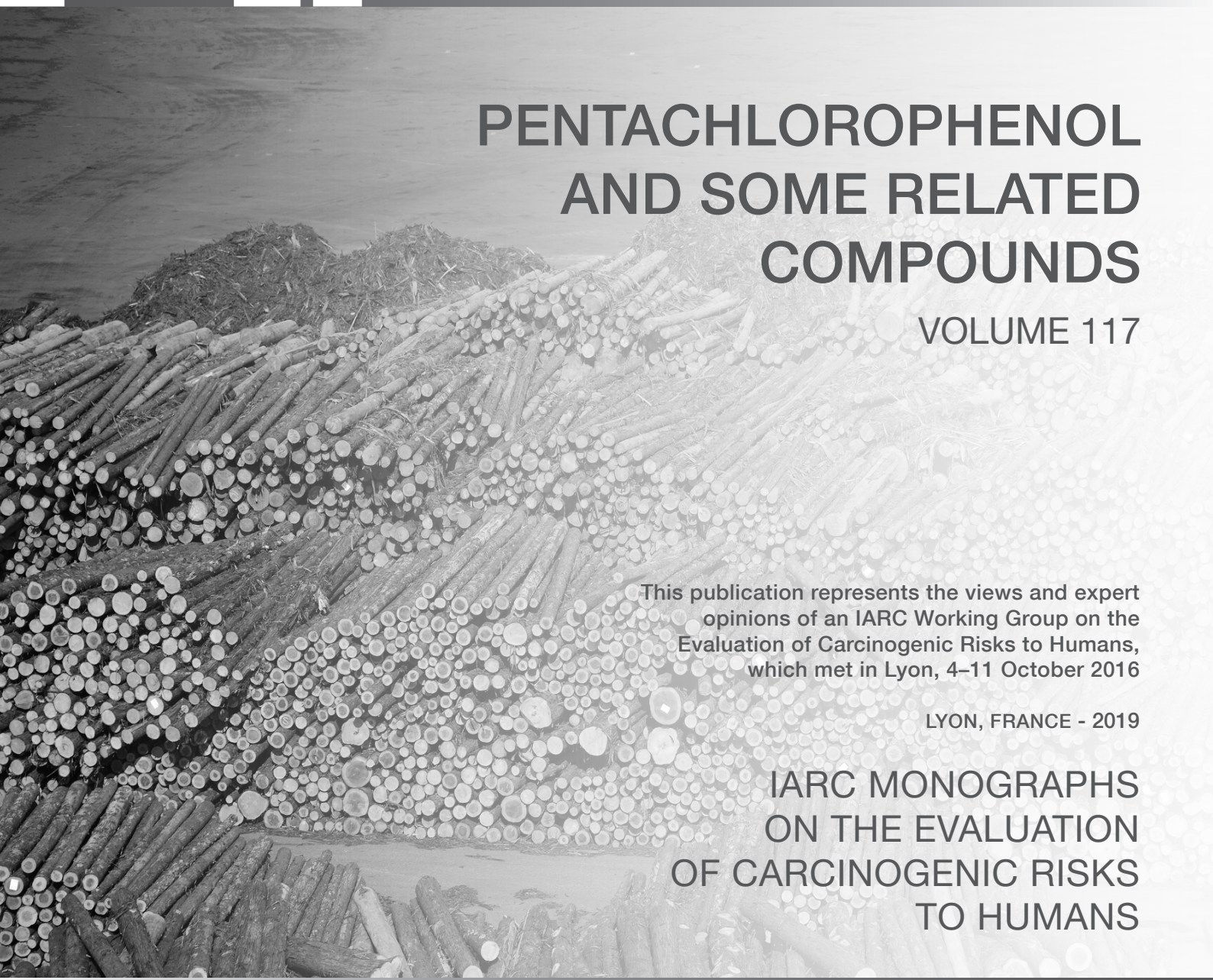

PENTACHLOROPHENOL AND SOME RELATED COMPOUNDS

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International Agency for Research on Cancer

World Health Organization

PENTACHLOROPHENOL

1. Exposure Data

1.1 Identification of the agent

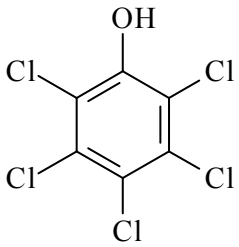
1.1.1 Nomenclature

Chem. Abstr. Serv. Reg. No.: 87-86-5

Chem. Abstr. Serv. Name: Pentachlorophenol

IUPAC Systematic Name: Pentachlorophenol

Synonyms: Chlorophenasic acid; Chlorophen; PCP; penchlorol; penta; pentachlorophenate; 2,3,4,5,6-pentachlorophenol; 1-hydroxy-2,3,4,5,6-pentachlorobenzene



Molecular formula: C_6HCl_5O

Relative molecular mass: 266.34

1.1.2 Chemical and physical properties of the pure substance

Description: Colourless to light brown needle-like crystals with characteristic phenolic odour (Budavari, 1996; IARC, 1999; NTP, 1999)

Boiling point: 310 °C (decomposes) (Lide, 1997; IARC, 1999)

Melting point: 191 °C (anhydrous) (EPA, 2010a)

Density: 1.978 g/mL (at 22 °C/4 °C) (EPA, 2010a)

Solubility: Slightly soluble in water (80 mg/L at 20 °C); soluble in acetone and benzene; very soluble in diethyl ether, ethanol, and methanol (EPA, 2010a)

Vapour pressure: 1.1×10^{-4} mm Hg (0.02 Pa) at 20 °C; relative vapour density (air = 1), 9.20 (EPA, 2010a; PubChem, 2018)

Log K_{ow}: 5.01 (EPA, 2010a)

Conversion factor: 1 ppm = 10.9 mg/m^3 (air), at normal temperature (25 °C) and pressure (1 atm) (EPA, 2010a)

Dissociation constant (pK_a): 4.7 at 25 °C (WHO, 2003)

1.1.3 Technical products and impurities

(a) Some trade names

Acutox; Chem-Penta; Chem-Tol; Cryptogil ol; Dowicide 7; Dowicide EC-7; Dow Pentachlorophenol DP-2 Antimicrobial; Durotox; Fungifen; Fungol; Glazd Penta; Grundier Arbezol Lauxtol; Lauxtol A; Liroprem; Moosuran; Penta; Pentacon; Penta-Kil; Pentasol; Penwar; Peratox; Permacide; Permagard; Permasan; Permatox; Priltox; Permite; Santophen; Santophen 20; Sinituho; Term-i-Trol; Thompson's Wood Fix; Weedone; Witophen P (NTP, 1999).

(b) Impurities

Pentachlorophenol is manufactured in a multistage chlorination process that results in contamination with dioxins, furans, and other chlorophenols. Consequently, the formulation that is used and that people are exposed to is a chemical grade, commonly referred to as the technical or commercial grade, which is composed of approximately 90% pentachlorophenol and 10% impurities. Depending on the specific synthesis process, the level of these impurities may vary with differing grades of manufactured pentachlorophenol (EPA, 2010a). In general, technical-grade pentachlorophenol contains 85–90% pentachlorophenol, 4–10% tetrachlorophenol, ~5% chlorinated diphenyl ethers, and < 1% trichlorophenol. Trace amounts to thousands of parts per million of polychlorinated dibenzo-*para*-dioxins (PCDDs) and chlorinated dibenzofurans can be detected. Grades described as analytical or pure are generally ≥ 98% pentachlorophenol, and the concentrations of dioxins and furans are low to non-detectable (IARC, 1991; NTP, 1999; EPA, 2010a).

The impurities consist of several chlorophenol congeners, PCDDs, and polychlorinated dibenzofurans (PCDFs). Of the PCDD and PCDF contaminants, the higher chlorinated congeners are predominantly found as impurities within technical-grade pentachlorophenol: isomers of hexachlorodibenzo-*para*-dioxin (HxCDD), heptachlorodibenzo-*para*-dioxin (HpCDD), and octachlorodibenzo-*para*-dioxin (OCDD), and isomers of tetrachlorodibenzofuran (TCDF), pentachlorodibenzofuran (PeCDF), hexachlorodibenzofuran (HxCDF), heptachlorodibenzofuran (HpCDF), and octachlorodibenzofuran (OCDF) (McLean et al., 2009). An analytical study in 1973 on 19 samples of commercial pentachlorophenol or pentachlorophenol sodium salt products from Switzerland reported concentration ranges of PCDD contaminants as 2,3,7,8-tetrachlorodibenzo-*para*-dioxin (TCDD) (< 0.01–0.25 ppm), pentachlorodibenzo-*para*-dioxin (PeCDD) (< 0.03–0.08 ppm), HxCDD (< 0.03–10 ppm), HpCDD (0.3–240 ppm), and OCDD (1.2–370 ppm); for PCDF contaminants, the ranges were TCDF (< 0.02–0.45 ppm), PeCDF (< 0.03–0.65 ppm), HxCDF (< 0.03–39 ppm), HpCDF (< 0.1–320 ppm), and OCDF (< 0.1–300 ppm) (Buser & Bosshardt, 1976). Dioxin and dioxin-like polychlorinated biphenyl (PCB) impurities have also been measured in agrochemical formulations of pentachlorophenol produced in Japan during the 1960s and early 1970s. Four pentachlorophenol samples exhibited dioxin impurity concentrations in a wide range from 14 to 24 000 µg/g active ingredient (Masunaga et al., 2001). The presence of dioxin and dioxin-like congeners and several other impurities have also been measured in most samples of the pesticides studied that were derived from chlorophenols in the USA in the early 1970s (Woolson et al., 1972; Plimmer, 1973). In addition to PCDD and PCDF contaminants, hexachlorobenzene and chlorophenoxy constituents may also be present in technical-grade pentachlorophenol (United Nations, 2010). 2,4,6-Tetrachlorophenol was also reported to be a by-product in the manufacture of pentachlorophenol (Kauppinen et al., 1994).

Table 1.1 gives a detailed list of contaminants of concern measured in Canadian products containing pentachlorophenol (United Nations, 2010), and their conversion to TCDD toxicity equivalence factors (TEFs), also called TCDD-equivalents (EPA, 2010b).

1.2 Production and use

1.2.1 Production process

Pentachlorophenol is produced via two pathways, either by stepwise chlorination of phenols in the presence of catalysts (anhydrous aluminium chloride or ferric chloride) or alkaline hydrolysis of hexachlorobenzene. Use of the analytical grade of pentachlorophenol requires a

Table 1.1 Contaminants of concern in Canadian products containing pentachlorophenol

Compound	CAS No.	TEF[a]	Concentration (ng/g)		Concentration (ng TCDD-eq/g)	
			Minimum	Maximum	Minimum	Maximum
Polychlorinated dibenzo-para-dioxins (PCDDs)						
2,3,7,8-TCDD	1746-01-6	1	0.028	0.175	0.028	0.175
1,2,3,7,8-PeCDD	40321-76-4	1	0.247	1.08	0.247	1.08
1,2,3,4,7,8-HxCDD	39227-28-6	0.1	1.1	86.8	0.11	8.68
1,2,3,6,7,8-HxCDD	57653-85-7	0.1	232	344	23.2	34.4
1,2,3,7,8,9-HxCDD	19408-74-3	0.1	14.8	203	1.48	20.3
1,2,3,4,6,7,8-HpCDD	35822-46-9	0.01	4570	13 500	45.7	135
OCDD	3268-87-9	0.0003	34 000	130 000	10.2	39
Polychlorinated dibenzofurans (PCDFs)						
2,3,7,8-TCDF	51207-31-9	0.1	0.022	0.068	0.0022	0.0068
1,2,3,7,8-PeCDF	57117-41-6	0.03	0.099	0.309	0.00297	0.00927
2,3,4,7,8-PeCDF	57117-31-4	0.3	0.431	2.74	0.1293	0.822
1,2,3,4,7,8-HxCDF	70648-26-9	0.1	176	577	17.6	57.7
1,2,3,6,7,8-HxCDF	57117-44-9	0.1	12	38.2	1.2	3.82
2,3,4,6,7,8-HxCDF	60851-34-5	0.1	34.9	245	3.49	24.5
1,2,3,7,8,9-HxCDF	72918-21-9	0.1	31.1	178	3.11	17.8
1,2,3,4,6,7,8-HpCDF	67562-39-4	0.01	3140	17 700	31.4	177
1,2,3,4,7,8,9-HpCDF	55673-89-7	0.01	681	3150	6.81	31.5
OCDF	39001-02-0	0.0003	54 400	283 000	16.32	84.9
Sum					*161*	*637*

[a] TCDD-equivalents are derived from EPA (2010b)
PCDDs are: tetra- (TCDD), penta- (PeCDD), hexa- (HxCDD), hepta- (HpCDD), and octachlorodibenzo-*para*-dioxin (OCDD)
PCDFs are: tetra- (TCDF), penta- (PeCDF), hexa- (HxCDF), hepta- (HpCDF), and octachlorodibenzofuran (OCDF)
TEF, toxic equivalency factor
Courtesy of Annemiek van der Zande. Adapted from: https://www.unece.org/fileadmin/DAM/env/documents/2013/air/PCP.pdf

purification process to remove the contaminants that were created during the manufacture of pentachlorophenol (EPA, 2010a).

1.2.2 Production volume

The worldwide production of pentachlorophenol in 1981 was estimated to be 90 000 tonnes per year (United Nations, 2010). No more recent global information was available to the Working Group.

Production volume in the USA was 45 million pounds [~20 400 tonnes] in 1983 and decreased to 24 million pounds [~10 900 tonnes] in 1987 (ATSDR, 2001). The production volume in the USA was 9100 tonnes in 1996 and 7257 tonnes in 2009 (United Nations, 2010). In 2010, one company was still manufacturing pentachlorophenol at three facilities, located in Alabama and Kansas, USA, and in Mexico (United Nations, 2010).

Production volume for pentachlorophenol in Canada for 1981 (last year of production) was reported as 2200 tonnes. Canada imported 472 tonnes from the USA and Mexico in 2007 (CAREX Canada, 2009).

There is no known current European production of pentachlorophenol since it ceased in 1992 in most countries (OSPAR, 2004). Before then, production occurred in Poland, Germany, the Netherlands, Switzerland, the United

Kingdom, Spain, and France. Spain stopped production in 2003 (United Nations, 2010).

China still produces pentachlorophenol with an annual production volume of 5000 tons [~4536 tonnes] reported in 2010 (United Nations, 2010).

1.2.3 Use

Pentachlorophenol was first introduced for use as wood preservative in the 1930s, and this use remains by far the major application (United Nations, 2010). The salt, sodium pentachlorophenate (Na-PCP) (Chemical Abstracts Service (CAS) No. 131-52-2), was used for similar purposes as pentachlorophenol and readily degrades to pentachlorophenol. The ester, pentachlorophenyl laurate (CAS No. 3772-94-9), was used in textiles. The environmental behaviour of all three substances is quite similar (United Nations, 2010).

In the USA, pentachlorophenol was widely used as an herbicide, algicide, defoliant, wood preservative, germicide, fungicide, and molluscicide, and could be found in ropes, paints, adhesives, canvas, leather, insulation, and brick walls (NTP, 1999; EPA, 2010a). The common use of chlorophenols including pentachlorophenol in tanneries was reported in Tuscany, Italy, and in Sweden, from the early 1950s to the late 1980s (Seniori-Costantini et al., 1989; Mikoczy et al., 1994; Mikoczy & Hagmar, 2005). Pentachlorophenol was used as a molluscicide for fish-pond cleaning for schistosomiasis vector control in China (Zheng et al., 2012). Pentachlorophenol was also used for the production of pentachlorophenol laurate, used in textiles and other fabrics (United Nations, 2010).

In 1984 in the USA, indoor applications of pentachlorophenol were prohibited (NTP, 1999; EPA, 2010a). In 1986 in the USA, approximately 97% of pentachlorophenol usage was as a wood preservative, 1% as a general herbicide, and the remainder for miscellaneous smaller applications (IARC, 1991). Pentachlorophenol is also no longer contained in wood-preserving solutions or insecticides and herbicides available for home and garden use, because it is a restricted-use pesticide (ATSDR, 2001). Currently, application of pentachlorophenol (and its sodium salt) is limited to industrial areas (e.g. utility poles, cross arms, railroad cross ties, wooden pilings, fence posts, and lumber/timbers for construction) in Canada and the USA; products containing pentachlorophenol remain registered for heavy-duty wood preservation, predominantly to treat utility poles and cross arms (CAREX Canada, 2009; EPA, 2010a).

The marketing and use of pentachlorophenol and its compounds was prohibited in the European Union in 1994, except for the treatment of wood, impregnation of fibres and heavy-duty textiles not intended for clothing, as an ingredient in chemical synthesis and, under individual authorizations, treatment in situ of buildings of cultural or historic interest (OSPAR, 2004; INERIS, 2011). In 2001 in Europe (mainly France, Portugal, and Spain), pentachlorophenol and its derivatives, Na-PCP and pentachlorophenyl laurate, were used to control sap stain in green lumber. It was also used 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 (IARC, 1999; OSPAR, 2004). In the European Union, pentachlorophenol was no longer used for wood preservation by 2009 (United Nations, 2010).

Current use of pentachlorophenol for wood preservation is mainly in North America (United Nations, 2010). Several companies were registered as manufacturing pentachlorophenol in 2016: USA (10 companies), Mexico (2), Germany (2), Canada (1), Hong Kong Special Administrative Region (1), South Africa (1), Switzerland (2), India (1), the United Kingdom (3), Israel (1), the Netherlands (1), China (1), and Japan (1) (Chem Sources, 2016).

1.3 Analytical methods

Analytical methods for most biological and environmental media mostly rely on gas chromatography–mass spectrometry or high-performance liquid chromatography–ultraviolet methods, which are described in detailed elsewhere (IARC, 1991; ATSDR, 2001; WHO, 2003; INERIS, 2011).

1.4 Occurrence and exposure

1.4.1 Occupational exposure

Occupational exposure to pentachlorophenol may occur during the manufacture of pentachlorophenol and formulations containing pentachlorophenol (as main ingredient and as contaminant), during mixing or spraying of pentachlorophenol-containing formulations for agricultural use, during treatment of wood products with pentachlorophenol-containing formulations, or during handling of or contact with the treated wood products. Pentachlorophenol exposure may also occur in workers employed in waste incineration, during treatment of materials such as textiles, leathers, or pelts, or in handling the treated materials (Karci, 2014). Dermal contact with pentachlorophenol formulations and treated products is expected to be a main exposure route.

(a) Air

In a wood-treatment plant in the USA that used pentachlorophenol, average air concentrations ranged from 263 to 1888 ng/m^3 (Wyllie et al., 1975). Area air concentrations for two workers in United States wood-treatment plants involved in brush application of pentachlorophenol in enclosed spaces had mean air concentrations of 230–430 µg/m^3 (Casarett et al., 1969). For lumber mill workers exposed to pentachlorophenol-containing wood preservatives, mean tetrachlorophenol air concentrations ranged from 31 to 498 ppb [317–5000 µg/m^3]; pentachlorophenol concentrations were below the detection limit of 0.5 µg/m^3. Canadian sawmill workers exposed to chlorophenol wood preservatives had personal air pentachlorophenol concentrations of 5–6 ppb [54.5–65.4 µg/m^3] (Embree et al., 1984). In a Finnish sawmill that used 2,3,4,6-tetrachlorophenol containing 10–20% 2,4,6-trichlorophenol and 5% pentachlorophenol, mean chlorophenol air concentrations (measured as the sum of tetrachlorophenol and pentachlorophenol) were highest in the vicinity of machine stacking (75 µg/m^3), preparation of treatment solution (66 µg/m^3), indoor vat-dipping (64 µg/m^3), and trough dipping (55 µg/m^3) (Kauppinen & Lindroos, 1985).

Workers involved in the production of pentachlorophenol at one plant in the USA in the 1980s had an overall mean pentachlorophenol concentration in personal air samples of 1.26 mg/m^3 (Marlow, 1986). These workers also experienced air exposure to hexachlorobenzene (range, < 0.0003 to 0.015 mg/m^3), HpCDD (mean, 0.038 µg/m^3), and OCDD (mean, 0.336 µg/m^3) (Marlow, 1986). At a pentachlorophenol-production plant in Germany, 10 of 67 area air samples in the production area exceeded 0.5 mg/m^3 and 18 were less than 0.1 mg/m^3 (Bauchinger et al., 1982). In the area of the same facility where Na-PCP was produced, 8 of 55 area air measurements exceeded 0.5 mg/m^3, and 7 were less than 0.1 mg/m^3. In another pentachlorophenol-production facility in Germany, air measurements of pentachlorophenol ranged from 1.2 to 180 µg/m^3 (Ziemsen et al., 1987).

(b) Biological markers and intake

Pentachlorophenol has been measured in the urine, and occasionally blood, of agricultural workers, wood-processing workers, electrical utility workers, hazardous and municipal waste incinerator workers, harbour workers involved in river dredging, sawmill workers, and workers involved in treating wood products (Table 1.2). Urinary and blood pentachlorophenol

concentrations were generally highest in workers directly involved in treating wood or lumber with pentachlorophenol-containing formulations or who had direct contact with the treated product, with mean urinary and blood concentrations often reported to be > 100 µg/L. Urinary pentachlorophenol concentrations in hazardous and municipal waste incinerator workers were similar to those in unexposed workers. No information on pentachlorophenol concentrations in textile or leather workers was available to the Working Group.

Pentachlorophenol-exposed workers were often monitored for serum concentrations of PCDDs and PCDFs, which are impurities in the pentachlorophenol. In these studies, concentrations of some, but not all congeners, were higher in pentachlorophenol-exposed workers than in unexposed workers. Workers in a Michigan plant that manufactured 2,4,5-trichlorophenol and pentachlorophenol, and formulated chlorophenol-based products had serum concentrations of several dioxin, furan, and PCB congeners that increased with increasing years of employment in a 2,4,5-trichlorophenol- or pentachlorophenol-exposed job (Collins et al., 2007, 2008; Burns et al., 2008). Mean concentrations of TCDD in the pentachlorophenol-only, 2,4,5-trichlorophenol-only, and the community reference group were 8.0, 15.9, and 3.3 pg/g lipid, respectively, and mean WHO 2005-TEQs (Van den Berg et al., 2006) were 56.7, 51.3, and 33.0 toxic equivalency (TEQ), respectively (Collins et al., 2008). 2,4,5-Trichlorophenol workers have a relatively simple congener profile, consisting primarily of elevated TCDD. In contrast, pentachlorophenol workers have a more complex profile, with significantly higher percentages of the contribution to the TEQ for the following congeners compared with the community reference: 1,2,3,4,7,8-HxCDD (2.6% vs 2.2%), 1,2,3,6,7,8-HxCDD (26.3% vs 20.5%), 1,2,3,7,8,9-HxCDD (3.6% vs 2.3%), 1,2,3,4,6,7,8-HpCDD (3.3% vs 2.0%), and OCDD (0.4% vs 0.1%) percentages (Collins et al., 2008). No significant difference was observed between pentachlorophenol workers and the community referents for TCDD (12.2% vs 15.0%).

A consistent congener profile was seen in former sawmill workers in New Zealand after exposure to pentachlorophenol-based anti-sapstain fungicides or to commercial-grade pentachlorophenol (McLean et al., 2009). The highest mean serum concentrations were observed for OCDD (309.25 pg/g lipid). The mean concentration of TCDD in exposed workers was similar to never-exposed workers (1.88 vs 1.48 pg/g lipid, respectively). The serum dioxin levels of these workers remained elevated 20 years after they had been exposed compared with never-exposed workers, with mean WHO2005-TEQs of 13.67 and 9.56, respectively. Their serum dioxin concentrations increased with both employment duration and estimated exposure intensity, with a mean TEQ of 14.1 in those with more than 10 years of exposure to pentachlorophenol.

Former, retired workers at a plant manufacturing pentachlorophenol, and nearby residents in Taiwan, China, had levels of 2,3,4,7,8-PeCDF, 1,2,3,7,8-PeCDD, 1,2,3,6,7,8-HxCDD, and total TEQ levels that were significantly higher than those of the reference groups. Their 2,3,7,8-TCDF, 1,2,3,7,8,9-HxCDF, 1,2,3,4,7,8,9-HxCDF, and OCDF levels were significantly lower than those of the reference groups. Mean WHO98-TEQs (Van den Berg et al., 1998) were 95.8–109.6 TEQ/g lipid in the retired workers who had been exposed to Na-PCP, and 22.9 TEQ/g lipid in the general population (Chang et al., 2012).

Serum PCDD/F concentrations of hazardous waste incinerator workers did not show significant differences between workplace groups after 1, 3, 8, and 12 years of operation compared with baseline concentrations or non-occupationally exposed subjects (Schuhmacher et al., 2002; Agramunt et al., 2003; Mari et al., 2009, 2013).

Table 1.2 Concentrations of pentachlorophenol in biological samples from occupationally exposed workers

Sample matrix	Country, year	Occupation	Work tasks, type of worker, or specific exposure	No. of workers	Exposure		Reference
					Level	Range	
Blood	USA, NR	Wood treatment	Treatment of lumber, furniture, and other wood products	18	Mean, 2190–5140 µg/L	190–14 000 µg/L	Begley et al. (1977)
Blood	Portugal, NR	Wood transformation unit	Mean, 6 years of exposure	11	Mean, 2273 µg/L	133–6884 µg/L	Ferreira et al. (1997)
Plasma	Italy, NR	Wooden strip board factory	Applied PCP by brush to wooden boards	14	Mean, 288.7 µg/L; median, 67 µg/L	2–1442 µg/L	Colosio et al. (1993)
Plasma	Italy, NR	Wooden strip board factory	Handled treated wood and other indirect exposure	18	Mean, 144.7 µg/L; median, 130 µg/L	14–350 µg/L	Colosio et al. (1993)
Plasma	Italy, NR	Wooden strip board factory	Unexposed	37	Mean, 8.9 µg/L; Median, 5.6 µg/L	0–76 µg/L	Colosio et al. (1993)
Plasma	United Kingdom, 1982–1983	PCP manufacturing	Formulation of PCP-containing fluids	29	Mean, 1.3 mmol/L [3.46×10^5 µg/L]	0.4–4.8 mmol/L [1.06×10^5–12.8×10^5 µg/L]	Jones et al. (1986)
Plasma	United Kingdom, 1982–1983	Wood treatment	Remedial sprayers working on house timber treatment	108	Mean, 6.0 mmol/L [16×10^5 µg/L]	0.2–29 mmol/L [0.5×10^5–77.2×10^5 µg/L]	Jones et al. (1986)
Plasma	United Kingdom, 1982–1983	Wood treatment	Handled treated wood in fabrication of pallets, roof trusses	68	Mean, 4.8 mmol/L [12.8×10^5 µg/L]	0.3–45 mmol/L [0.8×10^5 to 120×10^5 µg/L]	Jones et al. (1986)
Plasma	United Kingdom, 1982–1983	Wood treatment	Timber-treatment operators (unexposed)	9	Mean, 0.7 mmol/L [1.8×10^5 µg/L]	0.3–1.8 mmol/L [0.8×10^5 to 4.8×10^5 µg/L]	Jones et al. (1986)
Plasma	United Kingdom, 1982–1983	Wood treatment	Furniture joiners	61	Mean, 0.2 mmol/L [0.5×10^5 µg/L]	0.1–0.6 mmol/L [0.3×10^5 to 1.6×10^5 µg/L]	Jones et al. (1986)
Serum	Canada, NR	Sawmill workers	Tasks involving dermal contact with treated lumber	5	Mean, 714 ± 383 µg/L	NR	Embree et al. (1984)
Serum	Canada, NR	Sawmill workers	Close proximity to treated lumber, but no dermal contact	5	Mean, 241 ± 232 µg/L	NR	Embree et al. (1984)
Serum	USA, 1967–1973	Agricultural workers and wood processing workers	Farmers or pest control operators	280	Mean, 250 µg/L	< 10–8400 µg/L	Klemmer et al. (1980)

Table 1.2 (continued)

Sample matrix	Country, year	Occupation	Work tasks, type of worker, or specific exposure	No. of workers	Exposure		Reference
					Level	Range	
Serum	USA, 1967–1973	Agricultural workers and wood processing workers	Workers involved in dipping wood products in a 5% PCP mixture	22	Mean, 3780 µg/L	150–17 400 µg/L	Klemmer et al. (1980)
Serum	USA, 1967–1973	Agricultural workers and wood processing workers	Workers involved in pressure treatment of wood products	24	Mean, 1720 µg/L	20–7700 µg/L	Klemmer et al. (1980)
Serum	USA, 1967–1973	Agricultural workers and wood processing workers	Unexposed	32	Mean, 320 µg/L	20–7200 µg/L	Klemmer et al. (1980)
Serum	Finland, NR	Sawmill workers	Moving lumber that was dipped in chlorophenol solution containing 23% TCP, 74% tetrachlorophenol, 3% PCP	7	Mean, (p.m.) 0.85 µmol/L [226 µg/L]	NR	Pekari et al. (1991)
Serum	USA, 1972	Wood treatment plant	Plant workers, including managers, loaders, labourers, pressure treaters	6	Monthly mean, 769.1–2215.8 µg/L	NR	Wyllie et al. (1975)
Serum	USA, 1972	Wood treatment plant	Chemists	1	NA	38–68 µg/L	Wyllie et al. (1975)
Urine	Germany, NR	Municipal waste incinerator	Municipal waste workers	53	Mean, 2.60 µg/g creatinine	0.43–8.88 µg/g creatinine	Angerer et al. (1992)
Urine	Germany, NR	Municipal waste incinerator	Unexposed	248	Mean, 3.21 µg/g creatinine	< 0.8–67.79 µg/g creatinine	Angerer et al. (1992)
Urine	Germany, 1990–1993	PCP-exposed construction painters; bricklayers	Painters, 40% reported exposure to wood preservatives (assumedly PCP free) at least once per week	189	Median, 2.4 µg/g creatinine	< 0.2–52 µg/g creatinine	Bader et al. (2007)
Urine	Germany, 1990–1993	PCP-exposed construction painters; bricklayers	Bricklayers, < 10% reported contact with wood preservatives once per month	148	Median, 1.8 µg/g creatinine	< 0.2–25 µg/g creatinine	Bader et al. (2007)

Table 1.2 (continued)

Sample matrix	Country, year	Occupation	Work tasks, type of worker, or specific exposure	No. of workers	Exposure		Reference
					Level	Range	
Urine	USA, NR	Wood treatment	Treatment of lumber, furniture, and other wood products	18	Mean, 590–1360 µg/L	30–3600 µg/L	Begley et al. (1977)
Urine	Spain, 1999–2011	Hazardous waste incinerator	Plant workers, including incinerator operators; boiler maintenance, furnace maintenance, and control panel workers; and waste-gas-washing operators	16	Annual means, 0.1–1.9 µg/g creatinine	NR	Agramunt et al. (2003); Mari et al. (2009); Mari et al. (2013)
Urine	Spain, 1999–2011	Hazardous waste incinerator	Laboratory workers	6	Annual means, 0.1–2.7 µg/g creatinine	NR	Agramunt et al. (2003); Mari et al. (2009); Mari et al. (2013)
Urine	Spain, 1999–2011	Hazardous waste incinerator	Administrative/ management workers	5	Annual means, 0.4–2.0 µg/g creatinine	NR	Agramunt et al. (2003); Mari et al. (2009); Mari et al. (2013)
Urine	USA, NR	Wood treating plant	PCP application to the lumber – vat dipping	11	Mean, 2600 µg/L	NR	Casarett et al. (1969)
Urine	USA, NR	Wood treating plant	PCP application to the lumber – tank	11	Mean, 1600 µg/L	NR	Casarett et al. (1969)
Urine	Italy, NR	Wooden strip board factory	Applied PCP by brush to wooden boards	14	Mean, 127.3 µg/L; median, 69.5 µg/L	2–324 µg/L	Colosio et al. (1993)
Urine	Italy, NR	Wooden strip board factory	Handled treated wood and other indirect exposure	18	Mean, 154 µg/L; median, 125 µg/L	31–363 µg/L	Colosio et al. (1993)
Urine	Italy, NR	Wooden strip board factory	Unexposed	37	Mean, 4.7 µg/L; median, 3.7 µg/L	0–27 µg/L	Colosio et al. (1993)
Urine	Spain, 1999–2000	Hazardous waste incinerator	Plant workers	19	Annual means 0.5–1.9 µg/g creatinine	NR	Domingo et al. (2001); Schuhmacher et al. (2002)
Urine	Spain, 1999–2000	Hazardous waste incinerator	Laboratory workers	3	Annual means, 0.14–1.9 µg/g creatinine	NR	Domingo et al. (2001); Schuhmacher et al. (2002)

Table 1.2 (continued)

Sample matrix	Country, year	Occupation	Work tasks, type of worker, or specific exposure	No. of workers	Exposure		Reference
					Level	Range	
Urine	Spain, 1999–2000	Hazardous waste incinerator	Administrative workers	1	Annual means, 0.51–1.7 µg/g creatinine	NR	Domingo et al. (2001); Schuhmacher et al. (2002)
Urine	Spain, 1999–2000	Hazardous waste incinerator	Pre-employment baseline	28	0.45 µg/g creatinine	0.03–1.40 µg/g creatinine	Domingo et al. (2001); Schuhmacher et al. (2002)
Urine	Canada, NR	Sawmill workers	Close proximity to treated lumber, but no dermal contact	3	Mean, 45 ± 15 µg/L	NR	Embree et al. (1984)
Urine	Canada, NR	Sawmill workers	Dermal contact with treated lumber	3	Mean, 105 ± 18 µg/L	NR	Embree et al. (1984)
Urine	Portugal, NR	Wood transformation unit	Mean, 6 years of exposure	11	Mean, 1200 µg/L	70–5566 µg/L	Ferreira et al. (1997)
Urine	USA, NR	Wood treatment	Wood treaters	88	Mean, 174 ± 342 µg/L	NR	Gilbert et al. (1990)
Urine	USA, NR	Wood treatment	Unexposed	61	Mean, 35 ± 53 µg/L	NR	Gilbert et al. (1990)
Urine	United Kingdom, NR	PCP manufacturing	Formulation of PCP-containing fluids	26	Mean 39.6 nmol/mmol creatinine	7.4–300 nmol/mmol creatinine	Jones et al. (1986)
Urine	United Kingdom, NR	Wood treatment	Remedial sprayers working on house timber treatment	112	Mean, 274 nmol/mmol creatinine	11–1260 nmol/mmol creatinine	Jones et al. (1986)
Urine	United Kingdom, NR	Wood treatment	Handled treated wood in fabrication of pallets, roof trusses	54	Mean, 74 nmol/mmol creatinine	5–655 nmol/mmol creatinine	Jones et al. (1986)
Urine	United Kingdom, NR	Wood treatment	Timber-treatment operators (unexposed)	9	Mean, 35.5 nmol/mmol creatinine	10.3–151.4 nmol/mmol creatinine	Jones et al. (1986)
Urine	USA, NR	Lumber mill	Unexposed workers from a lumber mill engaged in wood treatment with PCP	114	Monthly geometric mean, 32.2 µg/L	3–137 µg/L	Kalman (1984)
Urine	USA, 1981–1982	Lumber mill	Sapstain preparation and treatment	88	Monthly means, 69–103 µg/L	4–636 µg/L	Kleinman et al. (1986)
Urine	USA, 1981–1982	Lumber mill	Unexposed	38	Monthly means, 29–39 µg/L	NR	Kleinman et al. (1986)

Table 1.2 (continued)

Sample matrix	Country, year	Occupation	Work tasks, type of worker, or specific exposure	No. of workers	Exposure		Reference
					Level	Range	
Urine	USA, 1967–1973	Agriculture and wood processing	Farmers or pest control operators	210	Mean, 10 µg/L	< 10- 400 µg/L	Klemmer et al. (1980)
Urine	USA, 1967–1973	Agriculture and wood processing	Workers involved in dipping wood products in a 5% PCP mixture	18	Mean, 950 µg/L	< 10–7800 µg/L	Klemmer et al. (1980)
Urine	USA, 1967–1973	Agriculture and wood processing	Workers involved in pressure treatment of wood products	23	Mean, 270 µg/L	< 10–2400 µg/L	Klemmer et al. (1980)
Urine	USA, 1967–1973	Agriculture and wood processing	Unexposed	32	Mean, 30 µg/L	< 10–1000 µg/L	Klemmer et al. (1980)
Urine	Finland, NR	Sawmill workers	Contact with chlorophenols	35	NR	< LOD–15.9 µg/g creatinine	Kontsas et al. (1995)
Urine	Finland, NR	Sawmill workers	Unexposed	17	NR	< LOD–13.7 µg/g	Kontsas et al. (1995)
Urine	Finland, 1980–1981	Sawmill workers	Primarily dermal contact with chlorophenols	112	Median, 7.8 µmol/L [2 × 10^3 µg/L]	0.1–211 µmol/L [26–56 × 10^3 µg/L]	Lindroos et al. (1987)
Urine	Finland, 1980–1981	Sawmill workers	Skin and respiratory exposure to chlorophenols	84	Median, 1.4 µmol/L [373 µg/L]	0.1–48 µmol/L [26–13 × 10^3 µg/L]	Lindroos et al. (1987)
Urine	Finland, 1980–1981	Sawmill workers	Primarily respiratory exposure to chlorophenols	34	Median, 0.9 µmol/L [240 µg/L]	0.1–13 µmol/L [26–3.5 × 10^3 µg/L]	Lindroos et al. (1987)
Urine	Finland, NR	Sawmill workers	Moving lumber that was dipped in chlorophenol solution containing 23% trichlorophenol, 74% tetrachlorophenol, 3% PCP	7	Mean, 0.34 µmol/L [90 µg/L]	0.2–0.9 µmol/L [53–240 µg/L]	Pekari et al. (1991)
Urine	Germany, 1997	Harbor workers	River dredging	83	Median, 1.4 µg/g creatinine	0.1–18.1 µg/g creatinine	Radon et al. (2004)
Urine	Germany, 1997	Harbor workers	Office workers	80	Median, 1.0 µg/g creatinine	0.1–8.1 µg/g creatinine	Radon et al. (2004)
Urine	Canada, 1989	Electrical utility	Linemen	23	Geometric mean, 29.6 µg/g creatinine	NR	Thind et al. (1991)
Urine	Canada, 1989	Electrical utility	Administrative workers	5	Geometric mean, 10.2 µg/g creatinine	NR	Thind et al. (1991)
Urine	USA, 1972	Wood treatment plant	Plant workers, including managers, loaders, labourers, pressure treater	6	Monthly mean, 84–312 µg/L	NR	Wyllie et al. (1975)

Table 1.2 (continued)

Sample matrix	Country, year	Occupation	Work tasks, type of worker, or specific exposure	No. of workers	Exposure		Reference
					Level	Range	
Urine	USA,1972	Wood treatment plant	Chemists	1	NA	2.6–4.3 µg/L	Wyllie et al. (1975)
Urine	Canada, 1987	Sawmills	67 sawmill jobs	225	Mean, 99 µg/L; geometric mean, 43 µg/L	2–989 µg/L GSD, 3.6	Teschke et al. (1989)
Urine	Germany, NR	PCP production facility	PCP production area	8	2380 ± 1910 µg/L	NR	Bauchinger et al. (1982)
Urine	Germany, NR	PCP production facility	Na-PCP sacking area	14	840 ± 650 µg/L	NR	Bauchinger et al. (1982)
Blood	Germany, NR	PCP production facility	PCP production area	8	4730 ± 3410 µg/L	NR	Bauchinger et al. (1982)
Blood	Germany, NR	PCP production facility	Na-PCP sacking area	14	2230 ± 1510 µg/L	NR	Bauchinger et al. (1982)
Blood	Germany, NR	PCP production facility	Transported, weighed raw materials for PCP production	9	Mean, 58 µg/L	23–116 µg/L	Ziemsen et al. (1987)
Blood	Germany, NR	PCP production facility	Handled finished PCP solutions	11	Mean, 330 µg/L	59–775 µg/L	Ziemsen et al. (1987)

GSD, geometric standard deviation; LOD, limit of detection; Na-PCP, sodium pentachlorophenate; NA, not applicable; NR, not reported; PCP, pentachlorophenol

1.4.2 Community exposure

Pentachlorophenol is a persistent organic pollutant (EPA, 2008; United Nations, 2010). Community exposure may continue long after the cessation of pentachlorophenol use. The general population may be exposed from proximity to pentachlorophenol-treated wood products, and from food, land, air, and water contaminated with pentachlorophenol. Exposure may also occur from dermal contact with leathers and textiles treated with pentachlorophenol, such as leather car seats in hot weather (Favaro et al., 2008). The largest sources of pentachlorophenol emissions are wood preservation and hazardous waste handling of pentachlorophenol-treated wood products. In the USA in 2008, an estimated 172 kg of pentachlorophenol was released to the air, 513 kg to the water, and 1865 kg was placed in landfills (United Nations, 2010).

Dietary exposure to pentachlorophenol has been estimated to account for nearly all non-occupational human exposure because pentachlorophenol partitions mainly into the soil (96.5%) and accumulates in the food chain, especially in fruits, vegetables, and grains (Hattemer-Frey & Travis 1989; Coad & Newhook, 1992); however, a more recent study suggested that inhalation exposure may account for 43–54% of pentachlorophenol exposure in children aged 3 years (Wilson et al., 2010).

(a) Water

Pentachlorophenol has low water solubility (14 mg/L at 25 °C) (Choudhary et al., 2013). Tap and well water concentrations of pentachlorophenol in China were on average 0.01–0.12 µg/L, with a maximum of 0.77 µg/L (Zheng et al., 2012). Drinking-water samples in Poland had mean pentachlorophenol concentrations ranging from 0.70 to 3.27 µg/L, and river-water samples had pentachlorophenol concentrations ranging from 0.03 to 640 µg/L (Michałowicz et al., 2011), and examples of private drinking-water sources being contaminated from new installations of pentachlorophenol-treated utility poles have been reported (Karlsson et al., 2013). In surface water samples in China, average pentachlorophenol concentrations ranged from not detected to 7.4 µg/L, varying by water type, location, year, and use of pentachlorophenol (Zheng et al., 2012). Freshwater and marine water samples from Belgium, France, Germany, the Netherlands, and the United Kingdom contained pentachlorophenol at concentrations that typically ranged from 0.01 to 0.17 µg/L, with maximum average concentrations up to 1.5 µg/L (Muir & Eduljee, 1999).

(b) Sediment and soil

In China, mean soil and sediment concentrations of pentachlorophenol were < 10 µg/kg dry weight (dw) for 29 of the 37 locations tested, between 10–63 µg/kg dw for 7 locations, and the remaining location had a mean concentration of 15 850 µg/kg dw (Zheng et al., 2012). Pentachlorophenol concentrations in the soil of rice fields in Japan decreased by half from the 1980s (0.72–41 ng/g dw; mean, 10 ng/g) to the 2000s (not detected to 21 ng/g dw; mean, 4.9 ng/g dw); however, concentrations of PCDD/Fs remained steady (Kobayashi et al., 2008). The observed PCDD/F congeners were consistent with impurities in pentachlorophenol and in 2,4,5-trichlorophenyl-4′-nitrophenylether (chlornitrofen). In Belgium, France, Germany, the Netherlands, and the United Kingdom, pentachlorophenol concentrations in freshwater sediments fell from levels of 200 µg/kg in 1991 to 15 µg/kg in 1997 (Muir & Eduljee, 1999).

(c) Air

Detectable concentrations of pentachlorophenol were present in 29 of 30 air samples collected in Canada, with mean air concentrations of 0.23 ng/m^3 in Waskesiu, 0.30 ng/m^3 in Regina, and 1.53 ng/m^3 in Yellowknife (Cessna et al., 1997). Pentachlorophenol was present in

7 of 11 air samples from two Canadian cities, with concentrations ranging from 0.2 to 6.8 ng/m^3 (Waite et al., 1998). In the same study, pentachlorophenol concentrations in the air of rural sites ranged from 0.1 to 1.5 ng/m^3 and were detected less frequently. Pentachlorophenol was also found in all air samples collected adjacent to a utility-pole storage site with concentrations ranging from 0.7 to 1233 ng/m^3 (Waite et al., 1998). Pentachlorophenol was detected in the air in all seven precipitation samples collected during rain events in Portland, Oregon, USA, in 1984, with a mean concentration of 54 ng/L; pentachlorophenol was not detected in the concurrently collected air samples (Leuenberger et al., 1985).

(d) Residential exposure

Pentachlorophenol was detected in 94% of household dust samples taken from rooms in which children spent the most time, in California, USA, in 2001–2006, with arithmetic and geometric mean concentrations of pentachlorophenol of 199 ng/g and 77 ng/g, respectively (Ward et al., 2009).

Pentachlorophenol was detected in more than 50% of the indoor air (median, 1.2–2.1 ng/m^3), outdoor air (median, 0.22–0.91 ng/m^3), and dust samples (median, 35–81 ng/g) from the homes and day-care facilities in North Carolina and Ohio, USA, in 2000–2001 (Wilson et al., 2007). Household dust concentrations in homes in Germany had low concentrations of pentachlorophenol, with a 95th percentile of 2.8 mg/kg in 1990/91 and 1.2 mg/kg in 1997/98 (Heudorf et al., 2000). The median pentachlorophenol concentration in household dust samples in homes in Germany with wooden panelling to which wood preservatives had been applied earlier was 5.0 ppm, with 72% of samples less than 25 ppm and 5% greater than 100 ppm (Meissner & Schweinsberg, 1996). Pentachlorophenol was detected in 96% of 861 vacuum-dust samples from German homes, with a median concentration of 0.3 µg/g (range, < 0.03–30.9 µg/g) (Seifert et al., 2000).

(e) Food

Pentachlorophenol was used for fish-pond cleaning in China for control of the schistosomiasis vector via molluscicide activity (Zheng et al., 2012). A review found low concentrations of pentachlorophenol in aquatic organisms, ranging from < 0.02 to 172 µg/kg wet weight (ww) (Zheng et al., 2012). Seafood samples contained pentachlorophenol at concentrations ranging from 37.7 ng/g ww in fish to 146 ng/g ww in crab (Basheer et al., 2004). Common carp contained pentachlorophenol at concentrations of < 0.5–61 µg/kg ww (Ge et al., 2007).

Pentachlorophenol was detected in fewer than 21% of the solid food samples of 257 children in the USA (Wilson et al., 2007). The proportion of pork samples containing pentachlorophenol at > 0.1 ppm dropped from 32% in 1981–82 to 6.6% in 1987–88 (MacNeil et al., 1990). For animals exposed to pentachlorophenol in wood shavings, serum pentachlorophenol concentrations ranged from 0.08 to 5.26 ppm in bovines, and liver pentachlorophenol concentrations ranged from 0.02 to 2.16 ppm in chickens (MacNeil et al., 1990). Pentachlorophenol concentrations in eggs of hens reared on pentachlorophenol-contaminated wood shavings was 500 ng/g whole weight (Brambilla et al., 2009). Egg concentrations dropped after pentachlorophenol-contaminated shavings were removed. Pentachlorophenol concentrations in the threshing floor material of henhouses in Poland were 11 ± 2.8 µg/kg (Piskorska-Pliszczynska et al., 2016).

Pentachlorophenol concentrations ranging from 0.054 to 0.11 µg/g were detected in 5 of 12 recycled paper/paperboard food packaging samples, but none was detected in 16 virgin paper products (Ozaki et al., 2004).

Chlorophenols have been used during the production of bark cork, and may inadvertently

form from the use of hypochlorite solutions to clean cork stoppers and wooden barrels (Ozhan et al., 2009). Pentachlorophenol has been measured in oak barrels that are used to age wine and other spirits, with concentrations ranging from 5 to 120 µg/g (Pizarro et al., 2006). Pentachlorophenol concentrations in red wine varied from 12 to 123 ng/L and were correlated with trichlorophenol concentrations in the cork (Ozhan et al., 2009).

In northern Bavaria, Germany, the mean concentration of pentachlorophenol in the diet was 13.9 ± 8.0 µg/kg, with a range of 2.7 to 27.6 µg/kg, excluding one high value of 516 µg/kg (Geyer et al., 1987).

(f) Biological markers

Pentachlorophenol has been measured in the urine and blood of populations of varying ages and geographical locations over the past several decades (Table 1.3). The proportion of samples with detectable concentrations of pentachlorophenol ranged from ≈50 to 100%. Reported mean and median urinary concentrations ranged from 1 to 14 µg/g creatinine, and from < 1 to 25 µg/L, respectively. In a literature review of studies from China, Zheng et al. (2012) found urinary pentachlorophenol concentrations ranging from < 0.1 to 2523 µg/L, with significantly higher concentrations in areas where schistosomiasis is epidemic and where Na-PCP was used as a biocide than in control areas (mean, 111 vs 0.35 µg/L, respectively). In the epidemic areas, the mean concentration of pentachlorophenol in body fluids was 253 µg/L (Zheng et al., 2012).

In the USA, mean serum pentachlorophenol concentrations were higher in people living in pentachlorophenol-treated homes than in conventional homes (not treated with pentachlorophenol) (420 vs 40 ppb [µg/L]) (Cline et al., 1989).

In Sweden, breast milk was found to have median concentrations of pentachlorophenol of 20 pg/g (range, 10–570 pg/g) (Guvenius et al., 2003). Concentrations of pentachlorophenol in breast milk in China ranged from 0.32 to 13 ng/g (mean, 2.2 ng/g) (Hong et al., 2005) and from 2 to 3 µg/L (Zheng et al., 2012).

In 17 males aged 16–87 years in northern Bavaria, Germany, mean concentrations of pentachlorophenol were 80 µg/kg, 50 µg/kg, 50 µg/kg, 20 µg/kg, 14 µg/kg, 25 µg/L, and 6.9 µg/L, respectively, in liver, kidney, brain, spleen, adipose, blood, and urine (Geyer et al., 1987). Similar concentrations were observed in four females.

In a meta-analysis of data from various geographical regions, pentachlorophenol levels in human blood decreased exponentially between 1978 and 2008 (Zheng et al., 2011). Worldwide blood concentrations were predicted to be 2.5–7 µg/L between 1995 and 2003, and 39–90 µg/L between 1967 and 1979. Highest body burdens of pentachlorophenol in the 1980s were observed in North America (geometric mean, 123.26 µg/L), but after 1995 pentachlorophenol body burdens in North America and Europe were similar (mean, 1.15–3.14 µg/L). The geometric mean for Sweden during 1976–2001 was only 5.34 µg/kg, reduced by 80% compared with 21.7 µg/kg in the 1970s and 1980s. Mean pentachlorophenol concentrations in breast milk and adipose samples were 14 µg/kg and 11 µg/kg, respectively. The rate of decline in pentachlorophenol concentrations was slower in blood than in urine, with a weak decreasing trend in lipid samples (Zheng et al., 2011).

The long-term average daily intake of pentachlorophenol in the 1980s was estimated to be 16 µg/day (Hattemer-Frey & Travis, 1989). Estimated total daily pentachlorophenol exposure in the Canadian general population was estimated to be 99, 105, 50, and 28 ng/kg body weight (bw) per day in infants, toddlers, children, and adults, respectively (Coad & Newhook, 1992). In the same study, aboriginal subsistence fishermen were estimated to have a daily pentachlorophenol intake of 58 ng /kg bw per day. The median measured aggregate potential dose was

7–9 ng/kg bw per day in children aged 3 years and younger, and was estimated to be 37–51% from the diet, 43–54% from inhalation, and 6–9% from other sources (Wilson et al., 2010). Estimated pentachlorophenol intake of infants from breast milk ranged from 0.09 to 3.73 mg/infant-year in China (Hong et al., 2005).

1.5. Regulations and guidelines

A list of regulations and guidelines for occupational exposure to pentachlorophenol in air is provided in Table 1.4.

Before 2014, recommended American Conference of Governmental Industrial Hygienists (ACGIH) limits for biological measures of exposure were 2 mg/g creatinine in urine (before last shift of work week) and 5 mg/L in plasma (end of shift) (ATSDR, 2001). In 2014, those recommended limits were removed; ACGIH currently recommends monitoring in urine for occupationally exposed individuals without recommending any particular limit (ACGIH, 2014).

There are additional restrictions and requirements regarding pentachlorophenol in food packaging and additives, transportation, hazardous waste, and releases to the environment in the USA, and some states within the USA impose additional restrictions (ATSDR, 2001).

Pentachlorophenol is also regulated as a potential water contaminant in some regions. For example, in the USA the maximum allowable concentration for pentachlorophenol in drinking-water (bottled or tap water) is 1 µg/L (EPA, 2016). The World Health Organization (WHO) has a provisional guideline value of 9 µg/L in drinking-water (WHO, 2003).

Pentachlorophenol and its salts and esters are listed in Annex A of the Stockholm Convention on Persistent Organic Pollutants, under which parties must take steps to eliminate production and use unless they have registered for an exemption (Stockholm Convention, 2008).

As of 2009, pentachlorophenol may not be placed on the market or used as a substance, or used in a concentration equal to or greater than 0.1% by weight in substances or preparations placed on the market in the European Community (European Commission, 2014). According to the European Union harmonized classification and labelling system, pentachlorophenol is "suspected of causing cancer (Carc. 2)" [H351], "fatal if inhaled (Acute Tox. 2)" [H330], "toxic if swallowed (Acute Tox. 3)" [H301], "toxic in contact with skin (Acute Tox. 3)" [H311], "very toxic to aquatic life (Aquatic Acute 1)" [H400], and "very toxic to aquatic life with long lasting effects (Aquatic Chronic 1)" [H410], and "causes serious eye irritation (Eye Irrit. 2)" [H319], "causes skin irritation (Skin Irrit. 2)" [H315], and "may cause respiratory irritation (STOT SE 3)" [H335] (ECHA, 2016). Before this European Community directive, Austria, Denmark, Finland, Germany, the Netherlands, Norway, Sweden, and Switzerland had more restrictive policies or bans on the use of pentachlorophenol (OSPAR, 2004). France, Ireland, Portugal, Spain, and the United Kingdom were directed to phase out the use of pentachlorophenol in treatment of wood and certain heavy-duty textiles between 2006 and 2009 (European Commission, 2007).

Pentachlorophenol-containing products including treated wood and glue cannot be produced, used or imported into Japan, where pentachlorophenol is listed as a class I specified chemical due to its persistence, potential for bioaccumulation, and toxicity (Ministry of Health, Labour and Welfare, 2016).

The sale and use of pesticides containing pentachlorophenol are restricted to limited commercial uses in the USA (ATSDR, 2001).

Table 1.3 Concentrations of pentachlorophenol in biological samples from the general population

Country, year	Age (years)	Sample matrix	No. of samples	Exposure		Comments	Reference
				Level	Range, % detects		
Japan, 1974	28–79	Adipose tissue	25	Mean, 0.14 ppm	< 0.005–0.57 ppm, 76% detects		Ohe (1979)
Belgium, NR	21–74	Spinal fluid	16	Mean, 0.75 ± 0.49 µg/L	0.24–2.03 µg/L, 100% detects	No correlation with serum PCP levels; 3 subjects had previously used PCP-containing wood preservatives	Jorens et al. (1991)
Sweden, 2000–2001	Mean, 32	Breast milk	15	20 pg/g fresh weight	10–570 pg/g fresh weight, 100% detects		Guvenius et al. (2003)
		Maternal plasma	15	2830 pg/g fresh weight	1360–13 200 pg/g fresh weight, 100% detects		
		Cord blood plasma	15	1960 pg/g fresh weight	820–7580 pg/g fresh weight, 100% detects		
Canada, 1993–96	21–74	Umbilical cord plasma	30	Median, 1670 pg/g wet weight	628–7680 pg/g wet weight, 100% detects		Sandau et al. (2002)
Germany, 1998	0–62	Plasma	623	Mean, 2.4 µg/L; Median, 1.7 µg/L	< LOD–59.3 µg/L		Heudorf et al. (2000)
Norway	48–62	Plasma	281	Mean, 958 ng/L; Median, 711 ng/L	< LOD–7686 ng/L, 94% detects	Women	Rylander et al. (2012)
Nigeria	Adults	Blood	29	NR	< trace–21.3 ppb, [trace–0.23 µg/L] 100% detects		Atuma & Okor (1985)
Spain, 2001–2003	4	Serum	66	Mean, 6.4 µg/L	1.5–35 µg/L, NR	Children in the area of a large factory producing organochlorine solvents	Carrizo et al. (2008)
Spain, 2001–2003	4	Serum	131	Mean, 0.61 µg/L	< 0–4.7 µg/L, NR	Children in a rural environment not exposed to high HCB or PeCB inputs	Carrizo et al. (2008)
USA, 1980–86	NR	Serum	34	Mean, 40 µg/L; median, 40 µg/L	15–75 µg/L, 100% detects	Higher in those living in PCP-treated homes than in conventional homes (means 420 vs 40 ppb [µg/L], respectively)	Cline et al. (1989)
Portugal, NR	Adults	Serum	10	Mean, 15 µg/L	3–17 µg/L, 100% detects		Ferreira et al. (1997)
Spain, 1985	Adults	Serum	50	Mean, 21.9 µg/L	2.5–116.5 µg/L, 100% detects		Gómez-Catalán et al. (1987)

Table 1.3 (continued)

Country, year	Age (years)	Sample matrix	No. of samples	Exposure		Comments	Reference
				Level	Range, % detects		
Belgium, NR	21–74	Serum	16	Mean, 22 ± 16 µg/L	4 to 60 µg/L, 100% detects	Three patients had previously used PCP-containing wood preservatives	Jorens et al. (1991)
Nigeria, NR	Adults	Urine	35	NR	< 0.025–0.23 ppm, [25–230 µg/L] 100% detects		Atuma & Okor (1985)
USA, 1980–86	NR	Urine	143	Mean, 3.4 µg/L; median, 3.0 µg/L	1–17 µg/L, 100% detects		Cline et al. (1989)
Portugal, NR	Adults	Urine	10	Mean, 6 µg/L	1–31 µg/L, 100% detects		Ferreira et al. (1997)
Spain, 1985	Adults	Urine	50	Mean, 25 µg/L	4–136 µg/L, 100% detects	Correlation with tetrachlorophenol, r = 0.883	Gómez-Catalán et al. (1987)
USA, 1976–80	12–74	Urine	6990	Median detected, 6 µg/L	< 2–2670 µg/L, 72% detects		Kutz et al. (1992)
Germany, 1990–1998	25–69	Urine	1895	GM, 2.7 µg/L (1990/92), 1 µg/L (1998)	< 1–13 (95th percentile) µg/L, 82% detects (1990/92), 50% detects (1998)	No difference by presence of wood preservatives at home	Schulz et al. (2007)
Canada, NR	6–87	Urine	69	Mean, 0.75 µg/L; median, 0.5 µg/L	0.05–3.6 µg/L, 94% detects	24-h urine collection, 0.5–20.2 nmol/day	Treble & Thompson (1996)
USA, 1998–2001	Pregnant women	Urine	361	Median, 7.3 µg/g creatinine	10–90th percentile: 1.1–67 µg/g creatinine		Berkowitz et al. (2003)
USA, 1999–2002	Pregnant women	Urine	747	NR	< 0.9–29.5 µg/L, 2–4% detects; NHANES: < 0.5–15.2 µg/L, 10% detects	Agricultural area, California	Castorina et al. (2010)
USA, NR	2–6	Urine	197	Median, 14 µg/g creatinine	> 1 (minimum NR) –330 µg/g creatine, 100% detects		Hill et al. (1989)
USA, 1988–94	20–59	Urine	886	Median, 1.2 µg/g creatinine	< 1–29 µg/g creatinine, 59% detects		Hill et al. (1995)
USA, 2001	Adults	Urine	106	Mean, 0.7 µg/g creatinine; median, 0.4 µg/g creatinine	< 0.2–6.4 µg/g creatinine, 96% detects		Morgan (2015)
Canada, 1993	36–76	Urine	31	Mean, 1.3 µg/L	< 2–3.2 µg/L	Sport fish consumers from three Great Lakes	Anderson et al. (1998)

Table 1.3 (continued)

Country, year	Age (years)	Sample matrix	No. of samples	Exposure		Comments	Reference
				Level	Range, % detects		
Germany, 1990–1992	18–79	Urine	1295	GM, 2.67 µg/L (adults)	95th percentile, 12.8 µg/L		Seifert et al. (2000)
Germany 1990–1992	6–14	Urine	695	GM, 4.15 µg/L	95th percentile, 14.9 µg/L		Seifert et al. (2000)
USA, NR	1.5–5	Urine	254	Mean, 0.61–1.27 µg/L; GM, 0.63, 2.20 µg/L	< 0.1–23.8 µg/L, 94% detect		Wilson et al. (2007)

GM, geometric mean; HCB, hexachlorobenzene; NHANES, National Health and Nutrition Examination Survey; NR, not reported; PCP, pentachlorophenol; PeCB, pentachlorobenzene; TCP, trichlorophenol

Table 1.4 Regulations and guidelines for occupational limits for pentachlorophenol in air

Country or region	Concentration (mg/m³)	Value
Australia	0.5	TWA
Belgium	0.5	TWA
Canada, Ontario	0.5	TWA
Canada, Quebec	0.05	TWA
Denmark	0.05	TWA
Denmark	0.1	STEL
Finland	0.5	TWA
Finland	1.5	15-min STEL
Hungary	0.001	TWA
Ireland	0.5	TWA
Ireland	1.5	15-min STEL
Japan, JSOH	0.5	TWA
New Zealand	0.5	TWA
China	0.3	TWA
Poland	0.5	TWA
Poland	1.5	STEL
Singapore	0.5	TWA
Republic of Korea	0.5	TWA
Spain	0.5	TWA
Sweden	0.5	TWA
Sweden	1.5	15-min STEL
Switzerland	0.05	TWA inhalable aerosol
United Kingdom	0.5	TWA
United Kingdom	1.5	STEL
USA		
ACGIH (TLV)	0.5	TWA
ACGIH[a]	1	STEL
NIOSH (REL)	0.5	10-h TWA
NIOSH (IDLH)	2.5	TWA
OSHA (PEL)	0.5	TWA

[a] Confirmed animal carcinogen with unknown relevance to humans (A3)

ACGIH, American Conference of Governmental Industrial Hygienists; IDLH, immediately dangerous to life or health; IRIS, Integrated Risk Information System; JSOH, Japan Society for Occupational Health; NIOSH, National Institute for Occupational Safety and Health; OSHA, Occupational Safety and Health Administration; PEL, permissible exposure limit; REL, recommended exposure limit; STEL, short-term exposure limit; TLV, threshold limit value; TWA, 8-hour time-weighted average (unless otherwise specified)

From ATSDR (2001); IFA (2016)

2. Cancer in Humans

Several epidemiological studies have examined risk of cancer associated with exposure to pentachlorophenol. A series of population-based case–control studies conducted in Sweden, New Zealand, and the USA have investigated associations between a range of chlorophenols and phenoxy herbicides and lymphatic and haematopoietic cancers and soft tissue sarcoma. In addition, a case–control study nested within a cohort identified from an international register of occupationally exposed workers also examined risk of non-Hodgkin lymphoma (NHL) and soft tissue sarcoma. There have been four informative studies in occupational cohorts that have included exposure assessment techniques designed to separate the effects attributable to pentachlorophenol from those associated with the other chlorophenols or phenoxy herbicides and their dioxin contaminants. Studies that reported results only for chlorophenols in general (see Section 1.3.2 for a list of studies) were judged to be uninformative and were not considered further by the Working Group.

2.1 Cohort studies

See Table 2.1.

Kogevinas et al. (1995) conducted two case–control studies of soft tissue sarcoma and NHL nested within an international register of workers exposed to phenoxy herbicides, chlorophenols, and dioxins, which had previously been used for a cohort study of mortality, coordinated by IARC. The IARC cohort consisted of more than 21 000 workers from 24 cohorts in 11 countries: 11 cases of soft tissue sarcoma and 32 cases of NHL were identified. Five controls per case, matched for age, sex, and country of residence were selected from the cohort. Quantitative estimates of exposure of all participants to 21 chemicals or mixtures were developed by a panel of industrial hygienists on the basis of information obtained from company exposure questionnaires and company records combined with individual job history. Study participants were categorized as non- or ever-exposed, and the ever-exposed assigned to low, medium, or high exposure categories. Conditional logistic regression analyses were used to calculate odds ratios (OR) and 95% confidence intervals (CI) for each chemical. No cases of soft tissue sarcoma were observed in those exposed to pentachlorophenol, while there were three pentachlorophenol-exposed cases of NHL, giving an elevated but not statistically significant risk estimate (OR , 2.75; 95% CI, 0.45–17.00; 3 cases). In the analyses by level of exposure (lagged by 5 years), all three cases of NHL with exposure to pentachlorophenol were in the high exposure category (OR, 4.19; 95% CI, 0.59–29.59); however, the cases were all from one British cohort originally assembled to investigate a cluster of lymphoma cases at the plant. Several other exposures were also associated with a non-statistically significant excess risk of NHL including "any dioxin or furan" and TCDD. Exposure–response relationships of increasing risk with increasing exposure to "any dioxin or furan" and TCDD were observed. [The Working Group noted that this was a large cohort, with objective exposure assessment methods. The limitations included that only mortality was assessed, that exposures to several compounds were highly correlated, and that only three cases of NHL were exposed to pentachlorophenol and all were from the same plant.]

Demers et al. (2006) conducted an extended follow-up of mortality and cancer incidence in a cohort of about 27 000 male workers employed for at least 1 year between 1950 and 1995 in 14 sawmills in British Columbia, Canada. This cohort had previously been studied by Hertzman et al. (1997). Eleven of these sawmills had used chlorophenates as antifungal wood treatments (either tetrachlorophenol or pentachlorophenol, or a mixture of both), while the remaining three

Table 2.1 Cohort studies on cancer and exposure to pentachlorophenol

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Kogevinas et al. (1995) Australia, Denmark, Finland, Germany, Netherlands, New Zealand, Sweden, and United Kingdom 1939–1992 Nested case–control	Cases: 32 NHL; 11 STS; International Register of Workers Exposed to Phenoxy Herbicides Controls: 158 NHL; 55 STS; Incidence density sampling (5 controls per case matched for age, sex, country) Exposure assessment method: company records; review by industrial hygienists to estimate exposure to 21 chemicals	NHL (incidence)	All PCP-exposed workers	3	2.75 (0.45–17.00)	Age, sex, country of residence when employed	Strengths: large study; objective exposure assessment methods; estimates of exposure to PCP, phenoxy herbicides, dioxins and furans Limitations: no quantitative exposure information; exposures to several compounds highly correlated; low power
			High cumulative PCP exposure relative to non-exposed	3	4.19 (0.59–29.59)		
		STS (incidence)	Ever exposed	0	–	Age, sex, country	
Demers et al. (2006) British Columbia, Canada 1950–1995 Cohort	25 685; 27 464 men employed ≥ 1 year in 14 sawmills, 1950–1995; 25 685 men included for incidence analysis Exposure assessment method: company records; job history combined with historical records on type of chlorophenol used by time period and estimates from senior workers on intensity of dermal exposure	All cancers combined	Sawmill workers			Age, calendar period	This cohort was previously studied by Hertzman et al. (1997) Strengths: large cohort; completeness and duration of follow-up; exposure assessment discriminated between PCP and TCP Limitations: limited power for rare cancers
			Mortality	1495	1 (0.95–1.05)		
			Incidence	2571	0.99 (0.95–1.04)		
		NHL (incidence)	PCP exposure-years			Age, time period, race	
			Years of exposure in quartiles: sawmill workers	92	0.99 (0.81–1.21)		
			< 1	38	1		
			1–2	13	1.33 (0.7–2.52)		
			2–5	24	1.88 (1.08–3.28)		
			5+	17	1.71 (0.91–3.24)		
			Trend-test *P*-value: 0.03				
		MM (incidence)	PCP exposure-years			Age, time period, race	
			Years of exposure in quartiles: sawmill workers	25	0.8 (0.52–1.18)		
			< 1	6	1		
			1–2	4	2.09 (0.57–7.61)		
			2–5	4	1.3 (0.34–4.98)		

Table 2.1 (continued)

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Demers et al. (2006) (cont.)			5+	11	4.18 (1.36–12.9)		
			Trend-test *P*-value: 0.02				
		Kidney (incidence)	PCP exposure-years			Age and time period	
			Sawmill workers	79	1.1 (0.88–1.38)		
			< 1	32	1		
			1–2	9	1.03 (0.49–2.18)		
			2–5	22	1.79 (0.99–3.24)		
			5+	16	1.66 (0.85–3.23)		
			Trend-test *P*-value: 0.07				
		Lung (incidence)	PCP exposure-years			Age and time period	
			Sawmill workers	519	1.02 (0.93–1.11)		
			< 1	216	1		
			1–2	78	1.11 (0.86–1.45)		
			2–5	119	1.07 (0.84–1.36)		
			5+	106	1.12 (0.87–1.44)		
			Trend-test *P*-value: 0.45				
		Liver/HCC (incidence)	PCP exposure-years			Age and time period	
			Sawmill workers	21	0.79 (0.49–1.21)		
			< 1	3	1		
			1–2	4	4.09 (0.89–18.76)		
			2–5	12	8.47 (2.21–32.45)		
			5+	2	1.41 (0.21–9.22)		
			Trend-test *P*-value: 0.18				
		STS (incidence)	PCP exposure-years			Age and time period	
			Sawmill workers	13	0.84 (0.49–1.44)		
			< 1	18	1		
			1–2	3	0.64 (0.18–2.2)		
			2–5	2	0.18 (0.04–0.85)		
			5+	0	–		
			Trend-test *P*-value: 0.11				

Table 2.1 (continued)

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Collins et al. (2009) Dow Chemical Co., Michigan, USA 1950–1985 Cohort	773 men; subcohort of a larger dioxin-exposed cohort, selected on the basis of employment in departments with known exposure to PCP Exposure assessment method: company records	All cancers combined	All PCP workers	94	1 (0.8–1.2)	Age, calendar period	Strengths: complete ascertainment of vital status Limitations: small cohort size; men only
			PCP (no TCP)	71	1 (0.8–1.3)		
		NHL	All exposed workers	8	2.4 (1–4.7)		
			PCP (no TCP)	7	2.8 (1.1–5.7)		
			High cumulative exposure to TCDD, > 0.825 ppb-years	3	3.1 (0.6–9.1)		
			High cumulative exposure to HxCDD, > 8 ppb-years	5	5.3 (1.7–12.4)		
			High cumulative exposure to HpCDD, > 142 ppb-years	4	4.6 (1.3–11.8)		
			High cumulative exposure to OCDD, > 470 ppb-years	4	4.7 (1.3–12)		
		Kidney	All PCP workers	4	1.7 (0.5–4.4)		
			PCP (no TCP)	4	2.3 (0.6–5.8)		
		Lung	All exposed workers	30	1 (0.6–1.4)		
			PCP (no TCP)	25	1.1 (0.7–1.6)		

Table 2.1 (continued)

Reference, location enrolment/follow-up period, study design	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Ruder &Yiin (2011) USA 1936–2005 Cohort	2122 members of NIOSH Dioxin Registry, Exposure assessment method: work in exposed jobs	All cancers combined	All exposed workers	326	1.17 (1.05–1.31)	Age (5 year categories), sex, race	Strengths: length of follow-up from first exposure Limitations: most had exposure to multiple chemicals
			PCP + TCP	88	1.01 (0.81–1.24)		
			PCP (no TCP)	238	1.25 (1.09–1.42)		
		NHL	All exposed workers	17	1.77 (1.03–2.84)		
			PCP + TCP	8	2.5 (1.08–4.93)		
			PCP (no TCP)	9	1.41 (0.64–2.67)		
		MM	All exposed workers	7	1.5 (0.6–3.1)		
			PCP + TCP	1	0.72 (0.02–3.99)		
			PCP (no TCP)	6	1.84 (0.68–4)		
		Kidney	All exposed workers	8	1.2 (0.52–2.37)		
			PCP + TCP	4	1.8 (0.49–4.61)		
			PCP (no TCP)	4	0.9 (0.25–2.31)		
		Lung	All exposed workers	126	1.36 (1.13–1.62)		
			PCP + TCP	27	0.91 (0.6–1.33)		
			PCP (no TCP)	99	1.56 (1.27–1.9)		

CI, confidence interval; HCC, hepatocellular carcinoma; HpCDD, 1,2,3,4,6,7,8-heptachlorodibenzo-*para*-dioxin; HxCDD, 1,2,3,4,7,8-hexachlorodibenzo-*para*-dioxin; MM, multiple myeloma; NHL, non-Hodgkin lymphoma; NIOSH, National Institute for Occupational Safety and Health; OCDD, octachlorodibenzo-*para*-dioxin; PCP, pentachlorophenol; STS, soft tissue sarcoma; TCDD, 2,3,7,8-tetrachlorodibenzo-*para*-dioxin; TCP, 2,4,6-trichlorophenol

mills had not. Cumulative dermal exposure to chlorophenate was calculated by combining historical use records and job title-based exposure patterns with duration of employment, and historical records on the chlorophenate formulations used in each mill at different time periods, which were used to assign separate indices of exposure to tetrachlorophenol and pentachlorophenol. In a validation study, the results of urinary chlorophenate measurements in 226 workers in one sawmill currently exposed to pentachlorophenol were strongly correlated with the estimates made by groups of raters including hygienists and senior workers. Urinary chlorophenate levels ranged from 2 to 989 μg/L, with a geometric mean of 43 μg/L, and a geometric standard deviation of 3.6. In comparisons between the overall sawmill cohort and the general population of British Columbia, there was no excess in all cancer mortality (SMR, 1.0; 95% CI, 0.95–1.05) or incidence (standardized incidence ratio, SIR, 0.99; 95% CI, 0.95–1.04). There was a moderate elevation in kidney cancer mortality (standardized mortality ratio, SMR, 1.31; 95% CI, 0.98–1.73), but not incidence (SIR, 1.10; 95% CI, 0.88–1.38). Internal analyses based on quartiles of cumulative exposure to pentachlorophenol, after adjustment for age, calendar period, and race, showed significant positive trends in mortality from kidney cancer ($P = 0.02$) and multiple myeloma ($P = 0.03$). There were significant positive trends in incidence of NHL ($P = 0.03$) and multiple myeloma ($P = 0.02$). When the pentachlorophenol exposures were lagged by 10 or 20 years, the statistically significant positive trends for incidence of both NHL and multiple myeloma remained, as did the trend for kidney cancer with a 20 year lag. By contrast, internal analyses by exposure to tetrachlorophenol showed no significant dose–response relationship for either mortality or incidence of NHL or multiple myeloma, although there was a significant positive trend ($P = 0.04$) for mortality from kidney cancer, and latency analyses also showed no significant trends apart from cancer of the rectum. [The Working Group noted that the strengths of this study included the large sample size, the completeness of follow up, the high-quality exposure assessment that discriminated between pentachlorophenol and tetrachlorophenol, the conduct of internal analyses, and the examination of both mortality and incidence. A limitation was that the effect estimates for kidney cancer were not adjusted for tetrachlorophenol, but exposure to pentachlorophenol and tetrachlorophenol were not strongly correlated.]

Collins et al. (2009) extended for an additional 9 years the mortality follow-up of a small cohort ($n = 773$) of pentachlorophenol production workers employed between 1937 and 1980 by a chemical company in Michigan, USA. This cohort consisted of employees who had worked at any time in any department in which exposure to pentachlorophenol could have occurred, and was a subset of a cohort of 2192 workers with exposure to PCDDs that had been assembled previously. Exposure estimates in the form of ordinal rankings of intensity of exposure to pentachlorophenol, to TCDD, and to the higher chlorinated dioxins that are characteristic of the pattern of congeners found as contaminants in pentachlorophenol. Exposure estimates were based on job history and a combination of historical occupational hygiene and process data (Ramlow et al., 1996). Results of a survey of serum dioxin levels in a small group of workers ($n = 128$) were also used to define separate exposure categories for TCDD and for the specific pentachlorophenol-related HxCDDs, HpCDDs, and OCDD. A subset of 577 workers who were determined to have been exposed to pentachlorophenol but not to 2,4,6-trichlorophenol were also identified from historical records. In comparisons of the overall cohort with the general population of the USA, no excess risk of mortality from all cancers (SMR, 1.0; 95% CI, 0.8–1.2) was observed, although mortality from NHL was significantly elevated in both the overall cohort

(SMR, 2.4; 95% CI, 1.0–4.7; 8 deaths) and in the pentachlorophenol-only cohort (SMR, 2.8; 95% CI, 1.1–5.7; 7 deaths). There was also a non-statistically significant increase in the SMR for kidney cancer among all workers exposed to pentachlorophenol (SMR, 1.7; 95% CI, 0.5–4.4; 4 deaths), and in the pentachlorophenol-only cohort (SMR, 2.3; 95% CI, 0.6–5.8; 4 deaths). Internal analyses stratified on the basis of cumulative exposure to the dioxin congeners tested showed a statistically significant increase in mortality from NHL at the highest tertile of exposure to the pentachlorophenol-related congeners, but not to TCDD [which suggests a stronger association with pentachlorophenol (and the characteristic dioxin congeners) than with dioxins per se]. Mortality from NHL was elevated but not significantly in the high-exposure category for TCDD (SMR, 3.1; 95% CI, 0.6–9.1; 3 deaths), but the elevation was higher and significant for HxCDD (SMR, 5.3; 95% CI, 1.7–12.4; 5 deaths), HpCDD (SMR, 4.6; 95% CI, 1.3–11.8; 4 deaths), and OCDD (SMR, 4.7; 95% CI, 1.3–12.0; 4 deaths). [The Working Group noted that the strengths of this study included complete ascertainment of vital status, and the exposure assessment discriminated between pentachlorophenol, trichlorophenol, and dioxin congeners allowing the effects to be attributed with more confidence to pentachlorophenol. Limitations were the size of cohort and the examination of mortality only.]

Ruder & Yiin (2011) identified a cohort of 2122 individuals who had ever worked in a pentachlorophenol-production department at one of four chemical manufacturing plants in the USA from the NIOSH Dioxin Registry, and compared mortality with that of the general population. Most (90%) of the cohort members had recognized exposure to other chemicals produced at these plants, and more than 40% were also exposed to 2,4,5-trichlorophenol (and therefore to TCDD as a contaminant). Standardized mortality ratios were calculated for the entire cohort, and separately for those exposed to both 2,4,5-trichlorophenol and pentachlorophenol (n = 720) and to pentachlorophenol only (n = 1402). All cancer mortality was significantly elevated in both the full cohort (SMR, 1.17; 95% CI, 1.05–1.31) and in the pentachlorophenol-only cohort (SMR, 1.25; 95% CI, 1.09–1.42), but not elevated in the 2,4,5-trichlorophenol/pentachlorophenol cohort (SMR, 1.01; 95% CI, 0.81–1.24). Mortality from lung cancer was also significantly elevated in the full cohort (SMR, 1.36; 95% CI, 1.13–1.62) and the pentachlorophenol-only cohort (SMR, 1.56; 95% CI, 1.27–1.90), but not in the 2,4,5-trichlorophenol/pentachlorophenol cohort (SMR, 0.91; 95% CI, 0.60–1.33). The significant elevation in mortality from lung cancer occurred in one plant only, and it was noted that more than 70% of those dying from lung cancer had worked for less than a year in departments with exposure to pentachlorophenol. Non-Hodgkin lymphoma was significantly elevated in the full cohort (SMR, 1.77; 95% CI, 1.03–2.84; 17 deaths) and in the 2,4,5-trichlorophenol/pentachlorophenol cohort (SMR, 2.50; 95% CI, 1.08–4.93; 8 deaths), and elevated but not significantly in the pentachlorophenol-only cohort (SMR, 1.41; 95% CI, 0.64–2.67; 9 deaths). There was no clear association between duration of exposure to pentachlorophenol and mortality overall or from either lung cancer or NHL. [The Working Group noted that the strengths of the study included the length of follow up, and the good-quality exposure assessment, while the limitations were that most study participants had exposures to multiple chemicals and that the study examined mortality only.]

2.2 Case–control studies

See Table 2.2.

Seven case–control studies from Sweden, New Zealand, and California, USA have reported data relevant to exposure to pentachlorophenol and cancer risk, and are summarized below.

Table 2.2 Case–control studies on cancer and exposure to pentachlorophenol

Reference, location enrolment/follow-up	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Pearce et al. (1986a) New Zealand 1977–1981	Cases: 83; cancer registry Controls: 396; 168 cancer patients from cancer registry; 228 general population controls Exposure assessment method: questionnaire; job-title based	NHL	Ever exposed to fencing as a farmer			Age, respondent type (proxy/ direct), sex	Strengths: population-based study; good response rates Limitations: limited exposure assessment
			Cancer controls	33	1.9 [1.1–3.4]		
			General population controls	33	1.9 [1.0–3.7]		
			Ever exposed to fencing as a contractor				
			Cancer controls	4	1.4 [0.6–3.3]		
			General population controls	4	6.1 [0.9–40.2]		
			Pooled estimate - farmer and/ or fencing contractor	37	2.0 [1.2–3.4]		
Hardell et al. (1994) Umea, Sweden 1974–1978	Cases: 105; oncology department records Controls: 335; national population registry and death registry Exposure assessment method: self-administered questionnaire; next-of-kin proxy respondents for deceased cases and controls; lifetime work history recorded	NHL	Exposure duration > 1 week continuously or 1 month in total			Sex, age, place of residence and vital status	Strengths: use of population registries for ascertainment of both cases and controls Limitations: potential for recall bias in self-reported exposure; little information was provided on the exposure assessment methods
			"High grade" PCP exposure	15	8.8 (3.4–24.0)		

Table 2.2 (continued)

Reference, location enrolment/follow-up	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Hardell et al. (2002) Sweden; four northern counties and three counties in mid-Sweden 1987–1992	Cases: 515; Swedish cancer registry Controls: 1141; national population registry Exposure assessment method: questionnaire; self-report; 43% of NHL cases had proxy and only living HCL cases were recruited; minimum exposure, 1 day; exposures lagged 1 year	NHL and HCL combined	All exposed workers	64	1.40 (0.99–1.98)	Study, study area and vital status	Pooled analysis of earlier studies of NHL and HCL Overlaps with Nordström et al. (1998), Hardell & Eriksson (1999), Hardell et al. (2002), Eriksson et al. (2008). Strengths: large population-based study; high response rates Limitations: potential for recall bias with high proportion of proxy respondents.; limited power for chlorophenol exposure
Pearce et al. (1986b) New Zealand 1977–1981	Cases: 76; cancer registry Controls: 315; other cancer patients from cancer registry Exposure assessment method: questionnaire; Telephone interview with clarification of circumstances for certain occupations	MM	Ever worked as a fencer	29	1.6 (0.9–2.7)	Age, sex, respondent type (proxy/direct)	Strengths: population-based study, good response rates Limitations: limited exposure assessment
Smith et al. (1984) New Zealand 1976–1980	Cases: 82; cancer registry Controls: 92; cancer registry Exposure assessment method: questionnaire	STS	Fencing as a farmer Fencing contractor Sawmill worker or Timber merchant Potential chlorophenol exposure at sawmill	20 5 12 3	0.8 (0.4–1.5) 1.9 (0.5–8.6) 1.3 (0.6–2.9) 0.7 (0.1–2.7)	Age	Strengths: population-based study Limitations: limited exposure assessment; use of cancer subjects as controls

Table 2.2 (continued)

Reference, location enrolment/follow-up	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Hardell et al. (1995) Sweden 1970–1980	Cases: 434; from four previous studies identified through cancer registries Controls: 948; population controls from same four studies Exposure assessment method: questionnaire; self or proxy report of exposure; minimum exposure time, 1 day; exposures lagged by 5 years	STS (Soft tissue sarcoma)	All exposed workers	27	2.8 (1.5–5.4)	Age, vital status, and study	Strengths: cases from cancer registries and controls from population registers; study size and power Limitations: potential for recall bias in self-report
Ward et al. (2009) California, USA 2001–2006	Cases: 184; children aged < 7 years from 9 paediatric clinics Controls: 212; birth certificates matched on age, sex, race, ethnicity and maternal residence Exposure assessment method: environmental monitoring; analysis of carpet dust	ALL	PCP concentration (ng/g) in carpet dust			Age, sex, race/ ethnicity, income, year and season of the interview/dust collection	Strengths: quantitative assessment of residential exposure Limitations: lower response rate in controls
			Low (< 32.2)	38	1		
			32.2 to < 75.8	46	1.28 (0.68–2.4)		
			75.8 to < 164.7	47	1.46 (0.78–2.74)		
			164.7–22 676	31	0.84 (0.43–1.65)		
			Trend-test *P*-value: 0.476				
		ALL	PCP loading (ng/m^2) in carpet dust				
			< 32.7	51	1		
			32.7 to < 82.2	34	0.56 (0.29–1.08)		
			82.2 to < 272.5	43	0.78 (0.42–1.47)		
			≥ 272.5	32	0.47 (0.24–0.92)		
			Trend-test *P*-value: 0.045				

ALL, acute lymphoblastic/lymphocytic leukaemia; CI, confidence intervals; HCL, hairy cell leukaemia; NHL, non-Hodgkin lymphoma; PCP, pentachlorophenol

A series of case–control studies were conducted in Sweden using similar methods to examine associations between phenoxyacetic acids, chlorophenols and organic solvents and NHL, hairy cell leukaemia, and soft tissue sarcoma (Hardell et al., 1994, 1995, 2002). In all of these studies, cases were identified from either oncology departments or cancer registries, with living controls identified from the national population registry and deceased controls identified from a national death registry for matching to deceased cases. A self-administered questionnaire was used to obtain data on demographics, lifestyle factors, and a lifetime work history, as well as occupational and recreational exposure to specific substances. Proxy interviews with next of kin were conducted for deceased cases or controls, and where answers from either living or proxy study participants were incomplete or unclear, a telephone interview was used to clarify the information. For pentachlorophenol (assessed separately), exposure was classified as low grade where it was used for less than 1 week continuously or less than 1 month in total; if exposure was greater than this, it was classified as high grade. Data were analysed by the specific self-reported exposures, with odds ratios and 95% confidence intervals calculated after stratification by age, vital status, and study. The relevant studies are summarized below. [The Working Group noted that a strength of these studies was that they were population-based and used national registers for identification of study participants. The limitations included the use of self-reported exposure, and the large proportion of proxy respondents, increasing concerns about recall bias.]

Two cancer registry-based case–control studies of multiple myeloma and NHL examined associations with exposure to phenoxy herbicides and chlorophenols in New Zealand (Pearce et al., 1986a, b). Both studies identified cases from the national cancer registry, and recruited controls with other cancers from the register, and in the case of the NHL study supplemented these with controls from the general population, recruited from the electoral roll. Interviews were conducted by telephone, with stem questions leading to more specific questions on certain occupations determined a priori to entail exposure to pentachlorophenol. [The Working Group noted that the strengths of these studies were that they were population-based studies, identifying cases from tumour registries, while the limitations included the crude exposure assessment and potential for co-exposure to other chlorophenols, phenoxy herbicides, and wood preservatives.]

Smith and colleagues conducted a case–control study of cases of soft tissue sarcoma (International Classification of Diseases, ninth revision, ICD-9, 171) in men diagnosed in New Zealand between 1976 and 1980 and identified from the national cancer registry (Smith et al., 1984). [The Working Group noted that this study had several limitations, namely that other cancer patients, with cancer sites not stated, were used as controls; that the majority of interviews were conducted with proxies; and the low power to detect an excess risk. The conduct of follow-up interviews was a strength.]

A population-based case–control study in California, USA, examined risk of childhood leukaemia and examined associations with a range of persistent organochlorine pesticides measured in carpet dust (Ward et al., 2009). [The Working Group noted that the strengths included the quantitative assessment of residential exposure, while the limitations were the relevance of exposure measurements in dust to exposure in individuals, and the low response rate in controls.]

2.2.1 Non-Hodgkin lymphoma

In a study in New Zealand, Pearce et al. (1986a) compared 83 cases of NHL (ICD, 202) recruited from the national cancer registry with 168 controls with other types of cancer recruited

from the same register and 228 general population controls recruited from the electoral roll. In telephone interviews, participants reported occupational history, with more specific information on work circumstances sought from those who had held certain occupations. As there was potential for exposure to chemicals used to treat wood products used for fencing, fencing as a farmer or work as a fencing contractor was examined. A significantly elevated risk was observed in both jobs in comparison with the general population controls, and in a pooled estimate combining both occupations. It was acknowledged that these associations may be with either pentachlorophenol used as an antifungal treatment on all wood products used for fencing or with the chromated copper arsenate treatment applied to timber for outside use or ground contact. [The Working Group noted that there is no known association between exposure to arsenic or hexavalent chromium and NHL.] No excess risk was observed among sawmill workers, many of whom are known to be exposed to pentachlorophenol (OR, 0.9; [95% CI, 0.0–2.7]).

Hardell et al. (1994) re-analysed data from a case–control study of malignant lymphoma conducted previously in which a 6-fold risk of NHL had been observed in people exposed to phenoxyacetic acids or chlorophenols in Sweden (Hardell et al., 1981). The study compared 105 men aged 25–85 years with histopathologically verified NHL who had been admitted to an oncology department between 1974 and 1978 with 335 controls matched for sex, age, place of residence, and vital status. When the data was analysed by occupation no significant elevation of risk was observed. Significantly elevated risks were observed for estimated high grade (OR, 8.8; 95% CI, 3.4–24.0) pentachlorophenol exposure.

Hardell et al. (2002) also reported the results of a pooled analysis of two case–control studies on 404 cases of NHL and 111 cases of hairy cell leukaemia recruited between 1987 and 1992 in Sweden. Response rates were 91% for cases and 84% for controls in the study on NHL, and 91% for cases and 83% for controls in the study on hairy cell leukaemia. Conditional logistic regression was used to calculate odds ratios and 95% confidence intervals for each exposure. In the combined analysis of NHL and hairy cell leukaemia, an odds ratio of 1.40 (95% CI, 0.99–1.98; 64 cases) was reported for exposure to pentachlorophenol. When applying different latency periods, the highest risk associated with exposure to pentachlorophenol was observed with an induction period of 20–30 years (OR, 2.13; 95% CI, 1.07–4.25). [The Working Group noted discrepancies in the number of participants reported in different analyses in this paper.]

Pearce et al. (1986b) conducted a case–control study of multiple myeloma and farming in which they recruited 102 male public hospital patients aged less than 70 years and compared these with 4 cancer patient controls for each case matched on year of registration and within 2 years of birth date. In telephone interviews that were similar to those in the study on NHL, information was sought on work history, with extra questions for specific occupations. A non-significant association with fencing work, which has the potential for exposure to both pentachlorophenol and chromated copper arsenate was observed (OR, 1.6; 90% CI: 0.9–2.7). [The Working Group noted that exposures to chromium, copper, and arsenic are not known to be risk factors for multiple myeloma.]

2.2.2 Soft tissue sarcoma

In light of early reports of an association between exposure to phenoxy herbicides or chlorophenols and soft tissue sarcoma in Sweden, Smith et al. (1984) conducted a case–control study in New Zealand.

Smith and colleagues conducted a case–control study of cases of soft tissue sarcoma (ICD-9, 171) in men diagnosed in New Zealand

between 1976 and 1980 and identified from the national cancer registry. In the study by Smith et al. (1984), cases were histologically reviewed by a pathologist. One control per case, with the same year of registration and within 2 years of age, was randomly selected from among other cancer patients in the registry. After excluding ineligible participants, 82 cases (84%) and 111 controls (83%) were included. Data on activities with a potential for exposure to chlorophenoxy herbicides and chlorophenols were collected in telephone interviews with patients or next of kin. This study found no evidence of any association with several occupations known to have potential exposure to wood treatment compounds containing pentachlorophenol.

Hardell et al. (1995) conducted a pooled analysis of data from four earlier studies in Sweden to examine associations between exposure to pesticides and soft tissue sarcoma in men, including 434 cases and 948 controls. In total, 63% of cases in the three studies where this was reported were deceased. A significant excess risk (OR, 2.8; 95% CI, 1.5–5.4; 27 cases) was observed in those ever exposed to pentachlorophenol.

2.2.3 Childhood acute lymphocytic leukaemia

In the study by Ward et al. (2009), noted above, analyses focused on a subset of cases aged 7 years or younger that were ascertained from nine major paediatric clinics in the study area. Controls were individually matched to cases on age, sex, race, Hispanic ethnicity, and maternal residence, and were selected from birth certificate files. The distribution of pentachlorophenol was categorized into quartiles based on the measured values in household carpet dust among controls. The concentration of pentachlorophenol in carpet dust was not associated with increased risk, and a significant inverse trend in risk of acute lymphocytic leukaemia with increased chemical loading of pentachlorophenol in carpet dust was observed.

2.3 Exposure assessment and biological markers in epidemiological studies

Individual exposure to pentachlorophenol has been assessed in epidemiological studies using several different methods. The simplest method, commonly used in case–control studies, uses retrospective interviews or questionnaires to ascertain whether each individual worked in particular jobs for which investigators had determined that exposure to chlorophenols was likely, e.g. wood treatment or chlorophenol manufacturing. Some studies on chlorophenols did not obtain sufficient information to distinguish jobs using pentachlorophenol from jobs using other chlorophenols (e.g. Woods et al., 1987; Ali et al., 2004). Job classifications may be adequate to detect some differences in cancer risk ('t Mannetje & Kromhout, 2003), but may also be surrogates for a variety of co-exposures in addition to pentachlorophenol.

Several population-level studies collected more detailed information that could be used to distinguish jobs exposed to pentachlorophenol. A series of case–control studies in New Zealand used retrospective telephone interviews with patients or next of kin to determine whether each individual had worked in particular jobs for which investigators had determined that exposure to phenoxy herbicides or chlorophenols was likely (Smith et al., 1984; Pearce et al., 1986a, b). Initial questions used a pre-specified list of occupations, and for those who reported having worked in those occupations subsidiary questions were asked regarding the specific nature of work and potential for exposure to specific chemicals. A series of Swedish case–control studies obtained complete occupational histories, and included questions regarding duration of use of specific

chemicals, including pentachlorophenol and classes of chemicals including chlorophenols, phenoxy acids, and organic solvents (Hardell et al., 1994, 1995, 2002). This allowed for additional epidemiological analyses comparing "low grade" (exposure duration greater than 1 week continuously or 1 month in total) to "high grade" exposures (Hardell et al., 2002). There was some evidence that workers in stable careers can reliably report on past production methods and use of frequently handled chemicals (Friesen et al., 2015; IARC, 2017). For example, orchardists in one study showed good consistency in recalling commonly used pesticides and pesticide categories for repeated exposure questionnaires after 21–25 years (Engel et al., 2001). However, recall for infrequently used chemicals can be poor (Engel et al., 2001), and the use of next-of-kin proxies for deceased participants may exacerbate exposure misclassification and the potential for recall bias (Nam et al., 2005).

A mortality study with the National Institute for Occupational Safety and Health (NIOSH) dioxin registry used work records from four pentachlorophenol production facilities and used detailed company-specific information and expert judgment to determine whether workers had been exposed to 21 chemicals and mixtures, including pentachlorophenol and trichlorophenol (Ruder & Yiin, 2011). Duration of work in pentachlorophenol departments was the primary exposure metric. It is likely that the use of work records in this study provided more accurate exposure assignments than self or proxy reports.

One case–control study of childhood leukaemia in California, USA, used home carpet-dust samples to characterize exposure to pentachlorophenol and other persistent organochlorines (Ward et al., 2009). Dust samples were obtained from the room most often used during waking hours for participants who lived in the same residence at time of diagnosis and at the time of sampling (often several years after diagnosis, in 2001–2006). [The Working Group noted that house dust is a major exposure source for young children in older homes, so carpet dust measurements might be a good surrogate for childhood exposure] (Ward et al., 2009). A different study found moderate to high intraclass correlations (0.37–0.95) for pesticides in repeated home-dust samples collected over approximately 2 years (Deziel et al., 2013). However, a study in young children in North Carolina, USA, estimated that dust and soil ingestion contributed only about 6–9% of their total pentachlorophenol exposure, based on dust, diet, and air samples collected in 2003–2005, with the remaining portion from indoor and outdoor air inhalation (43–54% of total exposure), and diet (37–51%) (Wilson et al., 2010).

Studies that used company work records and study-specific job–exposure matrices (JEMs) to assess pentachlorophenol (or total chlorophenol) exposures include a nested case–control study in an international register of workers (Ott et al., 1993; Kauppinen et al., 1994; Kogevinas et al., 1995), and records-based cohort studies of chemical-plant workers in Michigan, USA (Collins et al., 2007, 2009), and Canadian sawmill workers (Hertzman et al., 1997; Heacock et al., 2000; Demers et al., 2006). For JEM-based exposure assignments, exposure intensity scores are assigned for each job (often department- and plant-specific) over time; exposure intensities are then multiplied by job duration and summed across all jobs to calculate a cumulative exposure score for each worker (e.g. Ott et al., 1993; Collins et al., 2007; Cooper & Jones, 2008). The quality of JEM-based exposure assignments thus depends on the accuracy of the intensity score assigned to each job, the variability in personal exposures within each job, and the completeness and validity of the work records linking individual workers to specific jobs or tasks. A wide variety of methods are used to estimate exposure intensity scores, but the scores are most reliable when supported by routine biomonitoring or personal exposure measurements throughout

the duration of exposure. In practice, exposure measurements are often only available for part of the exposure period or not at all, in which case investigators rely on models and/or judgment to assign exposure intensity scores during some or all periods. For example, the Kogevinas et al. (1995) case–control study relied on a team of three industrial hygienists (who were blind to health outcomes) to assign a unitless exposure intensity for each job as the product of judgment-based subscores on innate job tasks, emissions of agents, average daily contact time of the workers with the contaminants, the use of personal protective equipment, and "certain other factors" (Kauppinen et al., 1994). Without direct measurements of pentachlorophenol exposure for the jobs in Kogevinas et al. (1995), non-differential exposure misclassification is likely, resulting in attenuation of epidemiological effect estimates towards a null association.

The studies of Canadian sawmill workers (Hertzman et al., 1997; Demers et al., 2006) and their offspring (Heacock et al., 2000) used JEMs for which exposure intensities were assigned based on hours of annual dermal exposure to chlorophenol, obtained by averaging values gained from interviews of randomly sampled groups of long-term workers (Teschke et al., 1996). Relatively stable intensity estimates with intraclass correlations of 0.78–0.88 were obtained when exposure scores were averaged across raters, whereas scores from individual raters were often discordant regarding the degree of chlorophenol exposure for any job at any particular time (Teschke et al., 1996). Exposure intensities were also validated against several hundred urinary chlorophenate concentrations collected over two seasons in 1986 (Hertzman et al., 1988); the average of the two urine concentrations for each individual was well correlated (r = 0.72) with cumulative exposure scores for total chlorophenols produced by a JEM (Hertzman et al., 1988). The Demers et al. (2006) study refined the previous JEMs by incorporating the percentages of pentachlorophenol and tetrachlorophenol in the specific fungicides used in each plant over time, creating a more specific measure of exposure less prone to attenuation (Friesen et al., 2007).

Occupational exposure to pentachlorophenol is often concomitant with exposure to other polychlorophenols, dibenzodioxins, dibenzofurans, and other chemicals (IARC, 1997, 1999; and Section 1.1.3(b)). This can make it difficult to attribute epidemiological associations with adverse health effects to any one chemical in the mixture, particularly in studies that did not distinguish pentachlorophenol from other chlorophenols, dioxins, or contaminants. Some studies have included quantitative assessments of selected co-exposures, providing a basis for disaggregating their putative effects. For example, the epidemiological study of Canadian sawmill workers used detailed plant records to determine both the pentachlorophenol and tetrachlorophenol content of the products used at any particular time (Demers et al., 2006). Because the formulations changed over time and individual workers worked at different times and in different job tasks, the cumulative exposure scores for the two chemicals were only moderately correlated (r = 0.45) (Demers et al., 2006; as per Cooper & Jones, 2008).

Similarly, cumulative exposures to pentachlorophenol and several dioxins were assessed using study-specific JEMs in an epidemiological study of chemical-plant workers in Michigan, USA (Ramlow et al., 1996; Collins et al., 2009). These studies assigned each job to a pentachlorophenol exposure intensity score of 1–3 based on advice of veteran employees with experience in pentachlorophenol production and industrial hygiene monitoring with sampling primarily in the 1960s and 1970s. TCDD and hexa- to octachlorinated congeners (HxCDD/OCDD) exposure intensities were also assigned values of 0–4 and 0–2, respectively (Ramlow et al., 1996). Later in 2004 and 2005, serum samples were collected from 412 workers and analysed for dioxins

and dibenzofurans; TCDD was elevated among 2,4,5-trichlorophenol workers but not among pentachlorophenol workers (Collins et al., 2007). For the later epidemiological analysis (Collins et al., 2009) a one-compartment pharmacokinetic model was used to calibrate dioxin and dibenzofuran exposure intensities in the JEMs to available serum measurements, and to predict annual and cumulative serum concentrations for each congener (Flesch-Janys et al., 1996; Collins et al., 2009). Although the availability of independent exposure assignments for pentachlorophenol, dioxins, and dibenzofurans would have allowed for mutual adjustment of these co-exposures in epidemiological models, Collins et al. (2009) only evaluated associations with cumulative TCDD-TEQ (a weighted sum of cumulative dioxins and dibenzofuran exposures; EPA, 2010b), with and without exclusion of workers exposed to 2,4,5-trichlorophenol.

Urinary measures of pentachlorophenol and its glucurono-conjugate can be used as a biomarker of short-term exposure. As reviewed in Section 4.1.5, terminal urinary excretion half-lives in humans range from 10 to 20 days, with some evidence of biphasic elimination and more rapid excretion during the first few days (ATSDR, 2001). Other chlorophenols (tetra- and tri-) have been reported to have shorter urinary excretion half-lives (Pekari et al., 1991). Although the short half-lives for chlorophenols limits their utility for chronic exposure assessment, they can be used in validation studies for exposure assignments based on other methods such as JEMs, as in the Canadian sawmill studies (Hertzman et al., 1988).

3. Cancer in Experimental Animals

See Table 3.1.

[In line with IARC (1991), the Working Group noted that a study in mice (United States National Technical Information Service, 1968; Innes et al., 1969) and a study in rats (Schwetz et al., 1978) were inadequate for the evaluation because of some deficiencies in the study design, including the variable combination of small number of animals, dosage used, unknown purity of the compound, and absence of histopathology data. These studies are not included in Table 3.1.]

3.1 Mouse

3.1.1 Oral administration

Groups of 50 male and 50 female B6C3F$_1$ mice (age, 9 weeks) were fed diets containing technical-grade pentachlorophenol (purity, 90.4%) at a concentration of 100 or 200 ppm, or commercial-grade pentachlorophenol (purity, 91%; containing a smaller amount of dioxins and furans than the technical-grade pentachlorophenol) at a concentration of 100, 200, or 600 ppm for 2 years. Two groups of 35 male and 35 female mice were fed control diets. The mice were killed after 112 weeks (NTP, 1989; McConnell et al., 1991). For the most part, mean body weights, food consumption, and survival of mice exposed to pentachlorophenol were comparable to those of controls; however, the survival of females at the lowest dose was significantly reduced after 628 days with the commercial-grade formulation.

In male mice, significant dose-related increase in the incidences of hepatocellular adenoma, hepatocellular carcinoma, and hepatocellular adenoma or carcinoma (combined) was observed with either formulation of pentachlorophenol. The incidence of adrenal pheochromocytoma increased significantly in male mice exposed to both formulations. In female mice exposed to the commercial formulation, there was a significant dose-related increase in the incidence of hepatocellular adenoma, and the incidence of adrenal pheochromocytoma increased significantly at the highest dose. At the highest doses of either formulation, significantly higher incidence of haemangiosarcoma of the spleen [mainly] and/

Table 3.1 Studies of carcinogenicity in experimental animals exposed to pentachlorophenol

Study design Species, strain (sex) Age at start Duration Reference	Route Agent tested, purity Vehicle Dose(s) No. of animals at start No. of surviving animals	Incidence of tumours	Significance	Comments
Full carcinogenicity Mouse, B6C3F$_1$ (M) 9 wk 112 wk McConnell et al. (1991); NTP (1989)	Oral PCP (technical grade), 90.4% Diet 0, 100, 200 ppm, daily 35, 50, 50 12, 24, 22	*Liver* Hepatocellular adenoma: 5/32*, 20/47**, 33/48*** Hepatocellular carcinoma: 2/32*, 10/47, 12/48** Hepatocellular adenoma or carcinoma (combined): 7/32*, 26/47**, 37/48*** *Adrenal gland* Pheochromocytoma: 0/31*, 10/45**, 23/45***	* $P < 0.001$ (trend) ** $P < 0.05$ *** $P < 0.001$ * $P < 0.05$ (trend) ** $P < 0.05$ * $P < 0.001$ (trend) ** $P = 0.015$ *** $P < 0.001$ * $P < 0.001$ (trend) ** $P < 0.05$ *** $P < 0.001$	Strengths: GLP study Impurities: TCP, 0.01%; tetrachlorophenol, 3.8%; HCB, 50 ppm; TCDD, ND; HxCDD, 10.1 ppm; HpCDD, 296 ppm; OCDD, 1386 ppm; PeCDD, 1.4 ppm; HxCDF, 9.9 ppm; HpCDF, 88 ppm; OCDF, 43 ppm
Full carcinogenicity Mouse, B6C3F$_1$ (F) 9 wk 112 wk McConnell et al. (1991); NTP (1989)	Oral PCP (technical grade), 90.4% Diet 0, 100, 200 ppm, daily 35, 50, 50 28, 41, 30	*Liver* Hepatocellular adenoma: 3/33, 8/49, 8/50 Hepatocellular carcinoma, 0/33, 1/49, 1/50 *Vascular system* Haemangiosarcoma: 0/35*, 3/50, 6/50**	NS Tumour incidence: 0/33, 1/49, 1/50 * $P < 0.05$ (trend) ** $P < 0.05$	Strengths: GLP study Impurities: TCP, 0.01%; tetrachlorophenol: 3.8%; HCB: 50 ppm; TCDD, ND; HxCDD, 10.1 ppm; HpCDD, 296 ppm; OCDD, 1386 ppm; PeCDF, 1.4 ppm; HxCDF, 9.9 ppm; HpCDF, 88 ppm; OCDF, 43 ppm

Table 3.1 (continued)

Study design Species, strain (sex) Age at start Duration Reference	Route Agent tested, purity Vehicle Dose(s) No. of animals at start No. of surviving animals	Incidence of tumours	Significance	Comments
Full carcinogenicity Mouse, B6C3F$_1$ (M) 9 wk 112 wk McConnell et al. (1991); NTP (1989)	Oral PCP (commercial grade), 91% Diet 0, 100, 200, 600 ppm, daily 35, 50, 50, 50 25, 28, 29, 35	*Liver* Hepatocellular adenoma: 5/35*, 13/48, 17/48**, 32/49*** Hepatocellular carcinoma: 1/35, 7/48, 7/48*, 9/49* Hepatocellular adenoma or carcinoma (combined): 6/35*, 19/48**, 21/48***, 34/49**** *Adrenal gland* Pheochromocytoma, 0/34*, 4/48, 21/48**, 44/49** Pheochromocytoma (malignant): 1/34, 0/48, 0/48, 3/49	*P < 0.001 (trend) **P < 0.01 ***P < 0.001 *P < 0.05 *P < 0.001 (trend) **P = 0.015 ***P = 0.001 ****P < 0.001 *P < 0.001 (trend) **P < 0.001 NS	Strengths: GLP study Impurities: TCP, 0.007%; tetrachlorophenol: 9.4%; HCB: 65 ppm; TCDD, < 0.04 ppm; HxCDD, 0.19 ppm; HpCDD, 0.53 ppm; OCDD, 0.69 ppm; PeCDF, ND; HxCDF, 0.13 ppm; HpCDF, 0.15 ppm; OCDF, ND
Full carcinogenicity Mouse, B6C3F$_1$ (F) 9 wk 112 wk McConnell et al. (1991); NTP (1989)	Oral PCP (commercial grade), 91% Diet 0, 100, 200, 600 ppm, daily 35, 50, 50, 50 29, 28, 38, 39	*Liver* Hepatocellular adenoma: 1/34*, 3/50, 6/49, 30/48** Hepatocellular carcinoma: 0/34, 1/50, 0/49, 2/48 *Vascular system* Haemangiosarcoma: 0/35*, 1/50, 3/50, 8/49** *Adrenal gland* Pheochromocytoma: 0/35*, 1/49, 2/46, 38/49**	*P < 0.001 (trend) **P < 0.001 NS *P (trend) < 0.001 **P = 0.016 *P (trend) < 0.001 **P < 0.001	Strengths: GLP study Impurities: TCP, 0.007%; tetrachlorophenol: 9.4%; HCB: 65 ppm; TCDD, < 0.04 ppm; HxCDD, 0.19 ppm; HpCDD, 0.53 ppm; OCDD, 0.69 ppm; PeCDF, ND; HxCDF, 0.13 ppm; HpCDF, 0.15 ppm; OCDF, ND

Table 3.1 (continued)

Study design Species, strain (sex) Age at start Duration Reference	Route Agent tested, purity Vehicle Dose(s) No. of animals at start No. of surviving animals	Incidence of tumours	Significance	Comments
Full carcinogenicity Mouse, *Nrf2*$^{+/+}$ (M) 7 wk 60 wk Tasaki et al. (2014)	Oral PCP, 98.6% CRF-1 diet 0, 600, 1200 ppm Ad libitum 15, 15, 20 80%, 27%, 0%	*Liver* Cholangiocarcinoma: 0/15, 0/15, 3/20 Hepatocellular adenoma: 2/15, 1/15, 2/20 Hepatocellular carcinoma, 1/15, 0/15, 0/20	 NS NS NS	
Full carcinogenicity Mouse, *Nrf2*$^{-/-}$ (M) 7 wk 60 wk Tasaki et al. (2014)	Oral PCP, 98.6% CRF-1 diet 0, 600, 1200 ppm Ad libitum 15, 15, 20 53%, 13%, 0%	*Liver* Cholangiocarcinoma, 0/15, 2/15, 6/20* Hepatocellular adenoma, 0/15, 2/15, 4/20* Hepatocellular carcinoma: 1/15, 0/15, 0/20	 *$P < 0.05$ *$P < 0.05$ NS	
Full carcinogenicity Mouse, Tg.AC (F) 14 wk 26 wk Spalding et al. (2000)	Skin PCP, 99% Acetone 0, 0.75, 1.5, 3.0 mg 5×/wk for 20 wk 15, 13, 13, 14 13, 8, 10, 12	Skin papilloma: 1/15, 1/13, 8/13*, 14/14** No. of tumours per total animals per group: 0.07, 0.08, 0.85, 11.6	*[$P < 0.005$, Fisher exact test]; **[$P < 0.0001$, Fisher exact test] NR	Limitations: small number of animals per group

Table 3.1 (continued)

Study design Species, strain (sex) Age at start Duration Reference	Route Agent tested, purity Vehicle Dose(s) No. of animals at start No. of surviving animals	Incidence of tumours	Significance	Comments
Initiation–promotion (tested as promoter) Mouse, B6C3F$_1$ (M) 6 wk 25 wk Umemura et al. (1999)	Oral PCP, 98.6% Diet 0, 300, 600 ppm, daily 20, 20, 20 NR, NR, NR	*Liver* Hepatocellular adenoma, 4/15, 10/15*, 13/18**	*$P < 0.05$, Fisher exact test **$P < 0.01$, Fisher exact test	Mice were given drinking-water containing NDEA at 20 ppm for 13 wk, and after a 4 wk interval, were given basal diet or diet with PCP for 25 wk In another experiment in the same study, when PCP was tested as an initiator followed by drinking-water containing phenobarbital, no hepatocellular tumours were produced
		Hepatocellular carcinoma, 0/15, 2/15, 4/18	NS	
		Hepatocellular adenoma or carcinoma (combined): 4/15, 10/15*, 13/18**	*$P < 0.05$, Fisher exact test **$P < 0.01$, Fisher exact test	
		No. of tumours per total animals per group: 0.33 ± 0.62, 1.27 ± 1.89*, 2.22 ± 3.32*	*$P < 0.05$, Student *t*-test	
Initiation–promotion (tested as promoter) Mouse, B6C3F$_1$ (M) 6 wk 23 wk Umemura et al. (2003a)	Oral PCP, 98.6% Diet 0, 300, 600 ppm, daily 15, 15, 15 NR, NR, NR	*Liver* Hepatocellular adenoma: 1/15, 4/15, 11/15*	*$P < 0.01$, Fisher exact test	Mice were given drinking-water containing NDEA at 20 ppm for 8 wk, and after a 4 wk interval, were given basal diet or diet with PCP for 23 wk
		Hepatocellular carcinoma: 0/15, 1/15, 3/15	NS	
		Cholangioma, 0/15, 1/15, 9/15*	*$P < 0.01$, Fisher exact test	
		Cholangiocarcinoma, 0/15, 0/15, 8/15*	*$P < 0.01$, Fisher exact test	
Initiation–promotion (tested as promoter) Mouse, B6C3F$_1$ (M) 6 wk 25 wk Umemura et al. (2003b)	Oral PCP, 98.6% Diet 0, 600 ppm, daily 20, 20 NR, NR	*Liver* Cholangioma, 0/15, 12/18*	*$P < 0.01$, Fisher exact test	Mice were given drinking-water containing NDEA at 20 ppm for 13 wk, and after a 4 wk interval, were given basal diet or diet with PCP for 25 wk
		Cholangiocarcinoma, 0/15, 11/18*	*$P < 0.01$, Fisher exact test	

Table 3.1 (continued)

Study design Species, strain (sex) Age at start Duration Reference	Route Agent tested, purity Vehicle Dose(s) No. of animals at start No. of surviving animals	Incidence of tumours	Significance	Comments
Full carcinogenicity Rat, F344 (M) 6 wk 2 years Chhabra et al. (1999); NTP (1999)	Oral PCP, 99% Diet 0, 200, 400, 600, 1000 ppm, daily 50, 50, 50, 50, 50 12, 16, 21, 31, 27	*Tunica vaginalis* Malignant mesothelioma, 1/50, 0/50, 2/50, 0/50, 9/50* *Nose* Nasal squamous cell carcinoma, 1/50, 3/50, 1/50, 0/50, 5/50	*$P = 0.014$ (Poly-3 test) NS	Strengths: GLP study The group at 1000 ppm received PCP in the feed for 52 wk and control feed thereafter (stop-exposure group); historical control incidence of nasal squamous cell carcinoma (feeding studies): 5/1341 (0.4 ± 1.0%); range, 0–4%
Full carcinogenicity Rat, F344 (F) 6 wk 2 years Chhabra et al. (1999); NTP (1999)	Oral PCP, 99% Diet 0, 200, 400, 600, 1000 ppm, daily 50, 50, 50, 50, 50 28, 33, 34, 28, 28	Any tumour type	NS	Strengths: GLP study The group at 1000 ppm received PCP in the feed for 52 weeks and control feed thereafter (stop-exposure group)
Co-carcinogenicity Rat, MRC-Wistar (M) 6–8 wk 86–88 wk Mirvish et al. (1991)	Oral PCP (technical grade), 86% Diet 0 (HENU alone), 500 (HENU+PCP), 500 (PCP alone) ppm, daily NR, NR, NR NR, NR, NR	*Bone marrow, lymph node* Acute myelocytic leukaemia, 4/20, 9/15*, 0/5 B-cell lymphoma, 5/20, 2/15, 0/5 *Bone* Osteosarcoma, 5/20, 4/15, 0/5	*[$P < 0.05$, 2-tail Fisher exact test; vs HENU alone] NS NS	Drinking-water containing HENU at 75 mg/L was given 4 days/wk for 40 wk, 2 wk after PCP treatment Impurities: TCDD, 25 µg/kg; and TCDF, 670 µg/kg

Table 3.1 (continued)

Study design Species, strain (sex) Age at start Duration Reference	Route Agent tested, purity Vehicle Dose(s) No. of animals at start No. of surviving animals	Incidence of tumours	Significance	Comments
Co-carcinogenicity Rat, MRC-Wistar (F) 6–8 wk 86–88 wk Mirvish et al. (1991)	Oral PCP (technical grade), 86% Diet 0 (HENU alone), 500 (HENU+PCP), 500 (PCP alone) ppm daily NR, NR, NR NR, NR, NR	*Bone marrow, lymph node* Acute myelocytic leukaemia, 3/19, 3/15, 0/9 B-cell lymphoma, 3/19, 3/15, 0/9 *Bone* Osteosarcoma, 0/19, 1/15, 0/9 *Liver* Adenoma, 1/19, 5/15, 6/9	 NS NS NS NS	Drinking-water containing HENU at 75 mg/L was given 4 days/wk for 40 wk, 2 wk after PCP treatment; no untreated control group Impurities: TCDD, 25 µg/kg; and TCDF, 670 µg/kg

F, female; GLP, good laboratory practice; HCB, hexachlorobenzene; HENU, 2-hydroxyethylnitrosourea; HpCDD, heptachlorodibenzo-*para*-dioxin; HpCDF, heptachlorodibenzofuran; HxCDD, hexachlorodibenzo-*para*-dioxin; HxCDF, hexachlorodibenzofuran; M, male; ND, not detected; NDEA, *N*-nitrosodiethylamine; NR, not reported; NS, not significant; OCDD, octachlorodibenzo-*para*-dioxin; OCDF, octachlorodibenzofuran; PCP, pentachlorophenol; PeCDD, pentachlorodibenzo-*para*-dioxin; ppm, parts per million; TCDD, 2,3,7,8-tetrachlorodibenzo-*para*-dioxin; TCDF, 2,3,7,8-tetrachlorodibenzofuran; TCP, trichlorophenol; vs, versus; wk, week

or liver was also seen in female mice (McConnell et al., 1991; NTP, 1989). [The study complied with the requirements of good laboratory practice (United States Food and Drug Administration, GLP regulations).]

In a study by Tasaki et al. (2014), 50 male wildtype (*Nrf2*$^{+/+}$) and 50 male *Nrf2*-deficient (*Nrf2*$^{-/-}$) mice (age, 7 weeks) were divided into three groups of 15–20 animals and fed diets containing pentachlorophenol (purity, 98.6%) at concentrations of 0, 600, or 1200 ppm for 60 weeks. The survival rates at concentrations of 0, 600, or 1200 ppm were 80%, 27%, and 0%, respectively, in *Nrf2*$^{+/+}$ mice, and 53%, 13%, and 0%, respectively, in *Nrf2*$^{-/-}$ mice. Statistically significant decreases in body-weight gain were observed from week 11 at the higher pentachlorophenol dose for both genotypes, and from week 16 in *Nrf2*$^{-/-}$ mice and from week 36 in *Nrf2*$^{+/+}$ mice treated at the lower dose.

Cholangiocarcinoma, characterized by infiltrative atypical epithelial cells scattered into the stroma or multilayered with mitotic cells, was observed in all treated mice except in *Nrf2*$^{+/+}$ mice treated with the lower dose of pentachlorophenol; the incidence of cholangiocarcinoma in *Nrf2*$^{-/-}$ mice treated with the higher dose of pentachlorophenol was significantly increased. Hepatocellular adenoma or hepatocellular carcinoma was observed in all groups, but only the incidence of hepatocellular adenoma in *Nrf2*$^{-/-}$ mice treated with pentachlorophenol at the higher dose was significantly increased compared with controls (Tasaki et al., 2014).

Groups of 10 male and 10 female *p53*$^{+/-}$ mice (age, 8–11 weeks) were fed diets containing pentachlorophenol (purity, 99%) at a concentration of 0, 100, 200, or 400 ppm for 26 weeks. No significant increase in tumour incidence was observed in exposed mice (Spalding et al., 2000). [This study is not included in Table 3.1.]

3.1.2 Skin application

Groups of 15 female hemizygous Tg.AC mice (age, 14 weeks) were treated with pentachlorophenol (purity, 99%) as a topically applied dose at 0, 0.75, 1.50, or 3.0 mg per mouse daily for 20 weeks. The initial doses were 0 (control), 3.0, 6.0, or 12.0 mg/mouse, but due to toxicity after the first application, the two higher doses were reduced to 0.75 mg and 1.5 mg, respectively. At 26 weeks, the intermediate dose and highest dose significantly increased the incidence of skin papilloma compared with controls (Spalding et al., 2000).

3.1.3 Initiation–promotion studies

Three groups of 20 male B6C3F$_1$ mice (age, 6 weeks) were fed diets containing pentachlorophenol (purity, 98.6%) at a concentration of 0, 600, or 1200 ppm for 13 weeks, with subsequent administration of drinking-water containing phenobarbital at a concentration of 500 ppm for 29 weeks. Three other groups were initiated with drinking-water containing *N*-nitrosodiethylamine (NDEA) at 20 ppm for 13 weeks and, after a 4-week recovery interval, fed diets containing pentachlorophenol at 0, 300, or 600 ppm for 25 weeks. The incidence of hepatocellular adenoma, and incidence and multiplicity of hepatocellular adenoma or carcinoma (combined) in mice treated with pentachlorophenol after NDEA initiation were significantly increased compared with those in mice given NDEA only. In contrast, in mice given pentachlorophenol as an initiator followed by phenobarbital, no significant enhancement of neoplastic lesions occurred (Umemura et al., 1999).

Groups of 15 male B6C3F$_1$ mice (age, 6 weeks) were given drinking-water containing NDEA at 20 ppm for 8 weeks, and after a 4-week interval were fed diets containing pentachlorophenol (purity, 98.6%) at a concentration of 0 (basal diet), 300, or 600 ppm for 23 weeks. Exposure

to pentachlorophenol at 600 ppm significantly promoted the induction of hepatocellular adenoma by NDEA, and also caused significant progression of NDEA-induced cystic biliary hyperplasia to cholangioma and cholangiocarcinoma (Umemura et al., 2003a).

Groups of 20 male B6C3F$_1$ mice (age, 6 weeks) were given drinking-water containing NDEA at 20 ppm for 13 weeks and then, after a 4-week interval, given diets containing pentachlorophenol (purity, 98.6%) at a concentration of 0 or 600 ppm for 25 weeks. In mice initiated with NDEA followed by treatment with pentachlorophenol, the incidences of cholangioma and cholangiocarcinoma were significantly increased compared with mice receiving NDEA only (Umemura et al., 2003b).

Four groups of 10 female CD-1 mice (age, 6 weeks) were treated with a single skin application of 7,12-dimethylbenz[*a*]anthracene in acetone as an initiator. One week later, three groups received pentachlorophenol by skin application at a dose of 2.5, 50, or 1000 µg twice per week for 24 weeks. The fourth group was treated with acetone only for 19 weeks, and served as negative control group. The incidence of skin papilloma was 0/10, 1/10, 3/10, and 3/10 in the groups treated with pentachlorophenol at a dose of 0, 2.5, 50, and 1000 µg, respectively (Chang et al., 2003). [The Working Group judged the study inadequate for the evaluation because of the shorter duration of the study for negative controls compared with the duration for pentachlorophenol-treated groups. This study is not included in Table 3.1.]

3.1.4 Co-carcinogenicity

[Three studies in mice investigated co-carcinogenicity, as described below; these studies are not included in Table 3.1.]

Eight groups of 36 adult female CD-1 mice (age, not reported; average initial weight, 25 g) were fed diets containing 1′-hydroxysafrole at a concentration of 0.14% or 0.27%, or safrole at a concentration of 0.13% or 0.25%, with or without pentachlorophenol (purity, > 99%) at 0.05% for 12 months, and thereafter control diet for 4 months. Concurrent administration of pentachlorophenol with 1′-hydroxysafrole or safrole significantly decreased the incidence and multiplicity of hepatomas of type (a), (b), or mixed types (a) and (b) [hepatocellular tumours], as compared with those induced by 1′-hydroxysafrole or safrole alone (Boberg et al., 1983).

In an intraperitoneal injection study, groups of 23–42 male B6C3F$_1$ mice were given pentachlorophenol (purity, > 99%) at a dose of 0.04 µmol/g bw either on postnatal day 12 or on postnatal days 8 and 12. The mice were then injected with either 1′-hydroxysafrole (0.05, 0.1, or 0.2 µmol/g bw) or NDEA (0.01 or 0.02 µmol/g bw) and killed 10 or 9 months later, respectively. Prior treatment with pentachlorophenol did not affect hepatocarcinogenicity induced by NDEA, but decreased hepatocarcinogenicity induced by 1′-hydroxysafrole (Boberg et al., 1983).

Groups of 35 female CD-1 mice (age, 6 weeks) were fed diets containing *N*-*N*-dimethyl-4-aminoazobenzene at 0.02% or 0.04%, or 4-aminoazobenzene (AB) at 0.018% or 0.035%, with or without pentachlorophenol (purity, > 99%) at 0.05% for 10 months, and thereafter control diet for up to 7–8 months. Co-treatment with pentachlorophenol significantly decreased the incidence and multiplicity of hepatomas of type (a) or mixed types (a) and (b) [hepatocellular tumours] induced by *N*-*N*-dimethyl-4-aminoazobenzene or 4-aminoazobenzene (Delclos et al., 1986).

3.2 Rat

3.2.1 Oral administration

Groups of 50 male and 50 female F344/N rats (age, 6 weeks) were fed diets containing pentachlorophenol (purity, 99%) at a concentration of

0 (control), 200, 400, or 600 ppm for 2 years. A stop-exposure group of 50 male and 50 female rats received diet containing pentachlorophenol at 1000 ppm for 52 weeks, and control feed thereafter for the remainder of the 2-year study. Survival was greater than that of controls in males at 600 ppm and at 1000 ppm, but similar to that of controls in all other exposed groups. Mean body weights were generally lower than those of controls in rats at 400 and 600 ppm. Despite a transitory body-weight reduction, mean body weights of males and females of the stop-exposure group were similar to those of controls by the end of the study (Chhabra et al., 1999; NTP, 1999).

At 2 years, malignant mesothelioma originating from the tunica vaginalis of the testis was present in nine males in the group fed 1000 ppm for 52 weeks (18%) compared with one male in the control group (2%) ($P = 0.014$). The incidence of malignant mesothelioma in historical controls in feeding studies was 40/1354 (3.0 ± 2.3%; range, 0–8%) (Chhabra et al., 1999; NTP, 1999). The range for background incidence of tunica vaginalis mesothelioma is 0.2–5% (Maronpot et al., 2016). [The Working Group considered that the significantly increased incidence in the stop-exposure group of males compared with the matched controls was highly suggestive of a treatment-related effect.] Nasal squamous cell carcinomas were present in five males fed 1000 ppm for 52 weeks (10%) compared with one male in the control group (2%); this was not a significant increase in incidence, but exceeded the range in historical controls for this neoplasm (0–4%; incidence, 5/1341). No carcinogenic activity of pentachlorophenol was seen in male or female rats fed diets containing pentachlorophenol at 200, 400, or 600 ppm for 2 years, or in female rats in the stop-exposure group (Chhabra et al., 1999; NTP 1999). [The study was conducted under the requirements of good laboratory practice (United States Food and Drug Administration, GLP regulations).]

3.2.2 Co-carcinogenicity

Groups of male and female Wistar (MRC-W) rats (age, 8–10 weeks) were fed diets containing pentachlorophenol (technical-grade pentachlorophenol: purity, 86%; containing TCDD at 25 µg/kg and TCDF at 670 µg/kg) for 2 weeks before (and during) treatment with tap water or drinking-water containing 2-hydroxyethylnitrosourea (HENU) [a carcinogen] at a concentration of 75 mg/L (4 days per week) at 0 or 500 ppm for 86–88 weeks. The effective numbers of rats surviving more than 11 weeks were: 20, 15, and 5 in males, and 19, 15, and 9 in females in the groups receiving HENU only, HENU + pentachlorophenol, and pentachlorophenol only, respectively. All survivors were killed at age 94 weeks. HENU alone induced B-cell lymphoma and skeletal osteosarcoma, with higher incidences of both tumour types in males than in females, but incidences of these tumour types were not increased by co-treatment with pentachlorophenol. However, pentachlorophenol acted synergistically with HENU to significantly [$P < 0.05$] increase the incidence of acute myelocytic leukaemia in males (Mirvish et al., 1991).

4. Mechanistic and Other Relevant Data

4.1 Absorption, distribution, metabolism, and excretion

4.1.1 Introduction

Oral absorption of pentachlorophenol is relatively rapid and extensive in all species studied. It distributes throughout the whole body, but preferentially in the viscera. In the blood, pentachlorophenol is extensively bound to plasma proteins, which partly explains its slow elimination. The observed elimination is slowest in humans, faster

in rats, and fastest in mice. Pentachlorophenol is mostly eliminated as glucurono- or sulfo-conjugates, and as tetrachlorohydroquinone (TCHQ) and its conjugates (IARC, 1991). Further oxidation to benzoquinones and their semiquinones has been demonstrated (Lin et al., 1997, 1999). The TCHQ (oxidative) pathway is minor in humans, and about as important as the conjugation pathway in rodents (Reigner et al., 1991, 1992a, c, 1993). For the same exposure dose, mice experience a 4-fold greater amount of protein adducts in liver nuclei than rats, whereas rats experience a 3-fold greater amount in liver cytosol (Lin et al., 1997, 1999). Published physiologically based pharmacokinetic models for pentachlorophenol were not available to the Working Group.

4.1.2 Absorption

(a) Humans

Oral absorption (in a case of acute poisoning) was rapid, with a plateau blood concentration reached by 2–4 hours after ingestion (Haley, 1977; Young & Haley, 1978). About 90% of the ingested dose was recovered in the urine (Braun et al., 1979; Reigner et al., 1992a). Absorption after inhalation is similarly high (Proudfoot, 2003).

Absorption through the skin is well documented qualitatively, but quantitative information is scarce. Although extensive, absorption through skin occurs to a lesser extent and more slowly than after ingestion (Williams, 1982; Proudfoot, 2003). However, in human cadaver skin in vitro, only 1–4% of the dose applied in acetone or soil was recovered in the skin or passed through it (Wester et al., 1993).

(b) Experimental systems

In the rhesus monkey (*Macaca mulatta*), absorption of pentachlorophenol through the skin was approximately 30% and 25% of the dose applied in acetone or soil, respectively, after 24 hours (Wester et al., 1993). After a single oral dose of 10 mg/kg of [^{14}C]-labelled pentachlorophenol, peak plasma concentrations (10–30 µg/g) were attained within 12–24 hours after administration (Braun & Sauerhoff, 1976). The three male monkeys seemed to absorb pentachlorophenol more slowly (absorption rate constant, 0.2 per hour) than the three females (rate constant, 0.4 per hour), but inter-subject variability was of the order of a factor of 2 [thus, the difference was probably not statistically significant.]

In male B6C3F$_1$ mice, a dose of 15 mg/kg of pentachlorophenol administered by gastric intubation was completely absorbed and peak concentrations were seen after 1 or 2 hours (Reigner et al., 1992c).

In male Sprague-Dawley rats, a bolus injection of 1–3 mg (the exact dose was not given) of [^{14}C]-labelled pentachlorophenol in the duodenum resulted in a peak portal-vein plasma concentration after 20 minutes, most of the substance being transported by the portal vein to the liver (Jandacek et al., 2009). In the same strain and sex, after oral administration of pentachlorophenol at 2.5 mg/kg, the peak plasma concentration occurred between 1.5 and 2 hours, with an absorption half-life ranging from 0.25 to 1.5 hours, and a bioavailability of 90% (Reigner et al., 1991). In Fisher 344 rats, the absorption of pentachlorophenol from the gastrointestinal tract after gavage doses of 9.5 and 38 mg/kg was first order with an absorption half-life of about 1.3 hours, and a bioavailability of more than 80% (Yuan et al., 1994). Similar results were obtained by Braun et al. (1977).

The permeability of pork skin [which resembles human skin] to pentachlorophenol has been studied with various solvents, showing that pentachlorophenol in aqueous solutions is fairly well and rapidly absorbed (10% absorption, with a peak at 4 or 5 hours) (Baynes et al., 2002).

4.1.3 Distribution

(a) Humans

Blood and urine levels in occupationally exposed people and the general population have been extensively measured (see also Section 1.4; IARC, 1991; Bader et al., 2007; Carrizo et al., 2008). Pentachlorophenol has also been measured in breast milk and umbilical cord blood (Sandau et al., 2002; Guvenius et al., 2003; Hong et al., 2005; Park et al., 2008). Pentachlorophenol found in the blood is extensively bound to plasma proteins: at least 96% is bound, according to Uhl et al. (1986), and 99.5% according to Reigner et al. (1993). This explains for the most part the long half-life of pentachlorophenol in humans (Reigner et al., 1993). Post-mortem tissues from 21 people from the general population of northern Bavaria, Germany, showed pentachlorophenol (in decreasing order of concentration) in the liver, kidney, brain, spleen, and fat (Grimm et al., 1981; Proudfoot, 2003). In a fatal case of pentachlorophenol poisoning, the highest concentrations of pentachlorophenol were found in the bile and renal tissue, with lower concentrations in the lung, liver, and blood (Ryan et al., 1987; Proudfoot, 2003).

(b) Experimental systems

In two female rhesus monkeys, radioactivity was measured in the major organs 15 days after the oral administration of a single dose of [^{14}C]-labelled pentachlorophenol at 10 mg/kg. About 10% of the administered dose was recovered (the rest was excreted in the urine and faeces). The liver, small intestine, and large intestine contained the largest fractions of radioactivity (1%, 5%, and 2%, respectively) (Braun & Sauerhoff, 1976). In monkeys, about 99% of pentachlorophenol in blood plasma is bound to proteins (Reigner et al., 1993).

In female NMRI mice given a subcutaneous or intraperitoneal injection of [^{14}C]pentachlorophenol at 15–37 mg/kg bw, the highest specific activity was found in the gall bladder and its contents, the wall of the stomach fundus, the contents of the gastrointestinal tract, and the liver. Only traces (less than 0.05%) were detected in exhaled air (Jakobson & Yllner, 1971). In male B6C3F$_1$ mice, plasma protein binding was high (98.8%), but lower than in the other species tested (rat, monkey, human, cow, by increasing order of binding) and the blood to plasma concentration ratio was about 0.6 (Reigner et al., 1992c, 1993). After intravenous injection or stomach intubation with pentachlorophenol at 15 mg/kg, blood plasma kinetics were well described by a one-compartment model (Reigner et al., 1992c).

In rats (strain, not reported), 40 hours after a single oral administration of [^{14}C]pentachlorophenol at 31–40 mg/kg, the highest levels of radioactivity were found in the liver, kidney, and blood (Larsen et al., 1972). Similar results were obtained in female Sprague-Dawley rats after oral administration of a single dose of radiolabelled pentachlorophenol at 10 or 100 mg/kg, with plasma concentration peaking after 4 to 6 hours (Braun et al., 1977). Distribution to tissues was rapid and no distribution phase was observed (Braun et al., 1977; Reigner et al., 1991; Yuan et al., 1994). Plasma protein binding of pentachlorophenol in rats was about 99%, higher than in mice, but lower than in humans (Schmieder & Henry, 1988; Reigner et al., 1993). Modelling studies of the kinetics of pentachlorophenol in rats show that a one-compartment model with zero-order input and kinetic parameters estimated after intravenous administration adequately predicted pentachlorophenol concentrations in the plasma during long-term exposures to drinking-water containing pentachlorophenol (such as during carcinogenicity experiments) (Reigner et al., 1992b; Yuan, 1993, 1995).

4.1.4 Metabolism and modulation of metabolic enzymes

(a) Metabolism

See Fig. 4.1

(i) Humans

Conjugation with glucuronic acid is the major route of metabolism in humans, with about 80–90% of the administered dose (regardless of its value) being found as glucuronide in the urine (Uhl et al., 1986; Reigner et al., 1992a). An earlier study [with pentachlorophenol of unspecified purity] found much less glucuronide in the urine (Braun et al., 1979). [The Working Group noted that the discrepancy is likely due to the analytical method and the choice of volunteers with low blood concentrations of pentachlorophenol before controlled exposure, as discussed by Reigner et al. (1992a).] Dechlorination is a (minor) route of metabolism in humans (Ahlborg et al., 1974) and the formation of TCHQ and its glucuronide represents probably no more than 10–20% of the administered dose. Here also, discrepancies between studies are best explained by differences in analytical methods (Reigner et al., 1992a). Palmitoylpentachlorophenol, a conjugate of pentachlorophenol with palmitic acid, has been found in human abdominal adipose tissue; quantitatively, it is a minor metabolite: for exposures in a typical range of 10–100 µg/day (Reigner et al., 1992a), the level in one individual was of the order of 0.2 µg/g (Ansari et al., 1985). The formation of the metabolites is slow (50% of them are formed in about 5–10 days), mostly because of the high plasma-protein binding (Reigner et al., 1992a) and possible enterohepatic cycling [which the Working Group considered probable] (Braun et al., 1979).

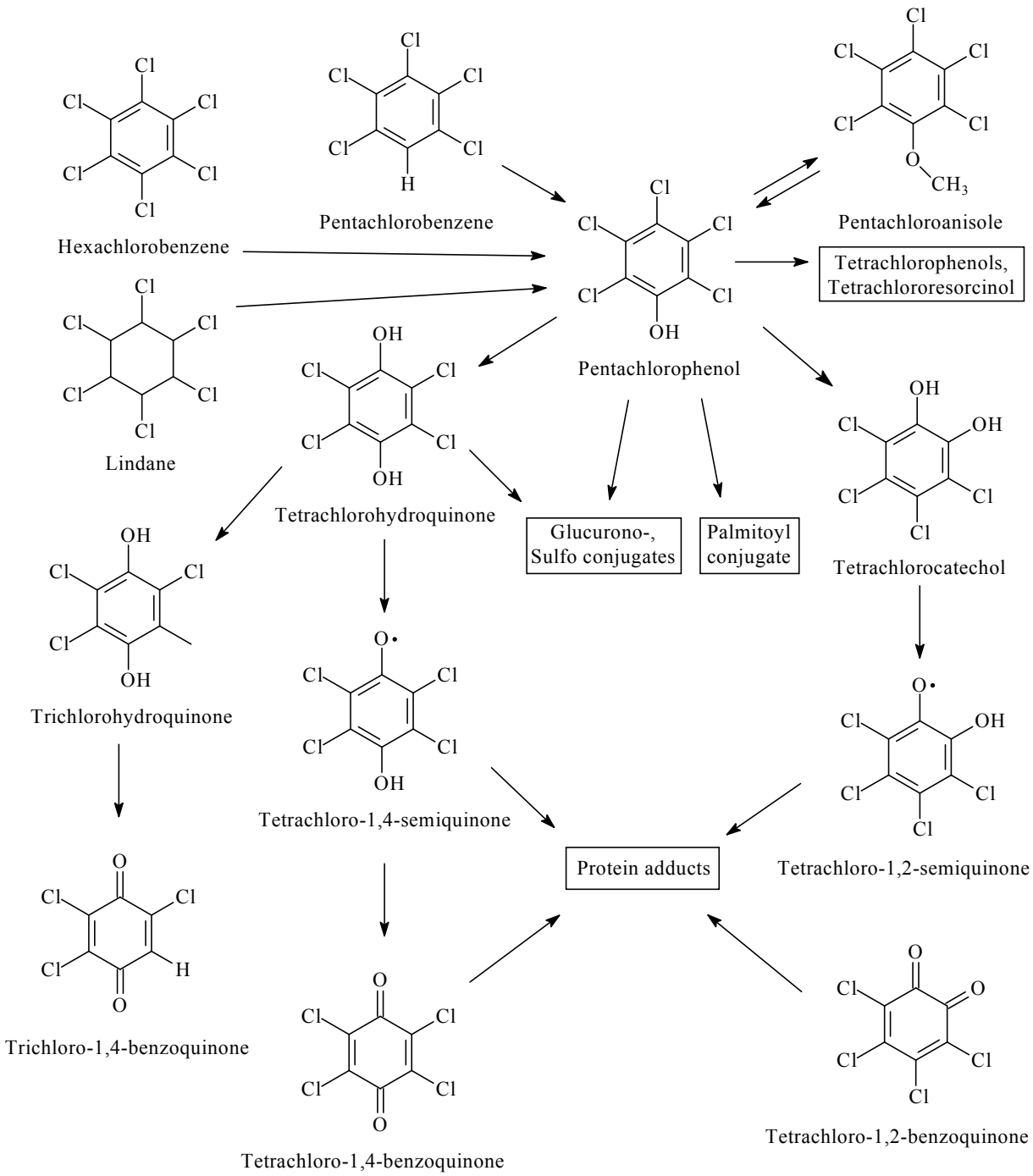
Human liver microsomes in vitro were able to metabolize pentachlorophenol of unspecified purity into TCHQ (Juhl et al., 1985) and glucurono-conjugates (Lilienblum, 1985). Oxidation may involve cytochrome P450 3A4 (Proudfoot, 2003). Pentachlorophenol and other chlorinated phenols are also substrates for purified human hydroxysteroid sulfotransferase hSULT2A1 (Gulcan et al., 2008).

(ii) Experimental systems

In mice, most early studies did not control well for hydrolysis and degradation of the oxidized and conjugated metabolites, making these studies difficult to interpret. The most definitive study, by Reigner et al. (1992c) in male B6C3F$_1$ mice, showed that TCHQ was formed together with glucurono- and sulfo-conjugates of both pentachlorophenol and TCHQ (Reigner et al., 1992c). In B6C3F$_1$ mice treated with pentachlorophenol at a dose of 20 mg/kg bw by gavage, liver protein adducts were formed by reactions with the pentachlorophenol metabolites tetrachloro-1,4-benzoquinone (tetrachloro-*para*-benzoquinone) and tetrachloro-1,2-benzoquinone (tetrachloro-*ortho*-benzoquinone) (Lin et al., 1997). Quantitative time courses were reported.

In rats (mainly Sprague-Dawley), the presence of free pentachlorophenol and TCHQ and their glucurono- or sulfo-conjugates was demonstrated in the urine after pentachlorophenol exposure (Ahlborg et al., 1974; Reigner et al., 1991). The rapid oxidative dechlorination of pentachlorophenol to TCHQ is mediated by liver microsomal enzymes. TCHQ can be further dechlorinated to trichlorohydroquinone (Ahlborg et al., 1980). The metabolites isolated from rat urine and identified were: 2,3,4,5-tetrachlorophenol, 2,3,4,6-tetrachlorophenol, 2,3,5,6-tetrachlorophenol, tetrachlorocatechol (tetrachloro-*ortho*-hydroquinone), tetrachloro-resorcinol, trichlorohydroquinone, TCHQ, and traces of trichloro-1,4-benzoquinone, and tetrachloro-1,4-benzoquinone (Renner & Hopfer, 1990). Rat liver microsomes also convert pentachlorophenol to its glucuronide, but not very efficiently (Lilienblum, 1985). In vitro, pentachlorophenol can be esterified with palmitic acid by rat liver microsomes in the

Fig. 4.1 Metabolism of pentachlorophenol based on human and animal observations



Compiled by the Working Group

presence of coenzyme A (Leighty & Fentiman, 1982). In the same system, oxidative dechlorination of pentachlorophenol forms TCHQ and tetrachlorocatechol, which are oxidized to tetrachloro-1,4-benzoquinone and tetrachloro-1,2-benzoquinone, respectively (van Ommen et al., 1986; Lin et al., 1997, 1999). Five cysteinyl adducts of haemoglobin and albumin have been identified in the blood of rats given pentachlorophenol at a dose of up to 40 mg/kg bw. Those adducts were formed by reactions with the pentachlorophenol metabolites tetrachloro-1,4-benzoquinone and its semiquinones (Waidyanatha et al., 1996).

Pentachlorophenol is a metabolite of hexa- and pentachlorobenzene in rat, mouse, guinea-pig, laying hen, and rainbow trout. It has also been identified as a urinary metabolite of lindane in rats and rabbits (Ahlborg et al., 1980; Umegaki & Ichikawa, 1989).

Pentachlorophenol can be methylated by some fungi and bacteria to form pentachloroanisole (Vodicnik et al., 1980). Pentachloroanisole, in turn, is rapidly demethylated to pentachlorophenol in rats and mice (Yuan et al., 1993).

(b) Modulation of metabolic enzymes

(i) Humans

Pentachlorophenol is a strong inducer of cytochrome P450 enzymes, especially CYP3A, in cultured human hepatoma cells (Dubois et al., 1996). Also in vitro, pentachlorophenol inhibited acetylcholinesterase activity in the membrane of human erythrocytes (Matsumura et al., 1997). It decreased the expression of mRNA of several enzymes (CYP11A, CYP17, CYP19, 3β-hydroxysteroid dehydrogenase, and 17β-hydroxysteroid dehydrogenase) involved in steroidogenesis in the human adrenocortical carcinoma cell line H295R in vitro (Ma et al., 2011).

(ii) Experimental systems

Pentachlorophenol is an inhibitor of *O*-acetyltransferase and sulfotransferase family 1 enzymes (Mulder & Scholtens, 1977; Shinohara et al., 1986) and has been used as such in many experimental systems. In female Wistar rats fed diets containing pentachlorophenol, liver cytochrome P450 was induced (Vizethum & Goerz, 1979).

4.1.5 Excretion

(a) Humans

Renal excretion of unconjugated pentachlorophenol is a minor pathway of elimination in humans, partly because of the extensive binding of pentachlorophenol to plasma proteins, leaving only a small fraction available for renal filtration (Reigner et al., 1992a). After a single oral dose, most of the administered dose is found in the urine as glucurono-conjugates, with a plasma and urinary excretion half-life of about 10–20 days (Uhl et al., 1986; Reigner et al., 1992a, 1993). This leads to significant accumulation in the body after repeated doses: for a given quantity absorbed per day, the quantity found in blood plasma is about six times higher at steady state than for a single dose (Reigner et al., 1992a).

(b) Experimental systems

In monkeys exposed orally to a single dose of [^{14}C]pentachlorophenol at 10 mg/kg, about 70–80% of the radioactivity was recovered in the urine after 15 days and 10–20% in the faeces, with linear kinetics and a half-life values for plasma clearance of about 80 hours for both males and females (Braun & Sauerhoff, 1976). Faecal excretion was steady, indicating that enterohepatic circulation [of the glucuronide, most probably] was occurring. Up to 30% of an oral dose of [^{14}C] pentachlorophenol of 50 mg/kg was excreted in the bile of rhesus monkeys during 1 day (Rozman, et al., 1982). Given the extensive enterohepatic cycling, pentachlorophenol is likely to be mainly

eliminated by glucurono-conjugation, but the sample preparation methods used by Braun & Sauerhoff (1976) did not prevent lysis of the conjugates and did not permit its observation in the urine (Reigner et al., 1993).

In male B6C3F$_1$ mice, after either intravenous or oral administration of pentachlorophenol, the elimination half-life from blood plasma was about 5–6 hours. After 48 hours, only 60–70% of the dose administered (15 mg/kg) was recovered in the urine and faeces. [The Working Group noted that the remainder was most likely retained in the body]. In the urine, 7–9% of the dose administered was excreted as free pentachlorophenol, 3–6% as free TCHQ, 1% as pentachlorophenol glucuronide, 1–3% as tetrachlorohydroquinone glucuronide, 15% as pentachlorophenol sulfate and 15% as tetrachlorohydroquinone sulfate. In the faeces, 6–9% of the dose administered was pentachlorophenol (free and conjugates), and less than 1% was TCHQ (free and conjugates) (Reigner et al., 1992c).

In Sprague-Dawley rats (three male and three females) given a single oral dose of [^{14}C] pentachlorophenol at 10 or 100 mg/kg, urine and faeces were collected at 24-hour intervals, and the animals killed after 8 or 9 days (Braun et al., 1977). Most of the radioactivity (80%), except for females at the higher dose (55%), was recovered from the urine within 8 or 9 days. Most of the remainder (20%) (40% for females at the higher dose) was recovered from the faeces. [The Working Group noted the small number of animals and the variability of the results.] Collection of the expired air at 12-hour intervals from the rats receiving the lower dose showed that less than 1% of the administered dose was excreted as [^{14}C]CO_2. Elimination of radioactivity from the plasma was biphasic with a first half-life of about 15 hours – similar to that found by Larsen et al. (1972) – and a second one that was poorly identified (except in females at the higher dose, for which elimination was monophasic with a half-life of 30 hours). In another study in Sprague-Dawley rats (males only), a biphasic elimination profile from plasma was observed with improved analytical and statistical analyses (Reigner et al., 1991). The first elimination phase had a half-life of 6–8 hours after treatment with pentachlorophenol at a dose of 2.5 mg/kg by intravenous injection or gavage. Those results were coherent with those obtained in Fischer 344 rats after treatment with pentachlorophenol by injection or in the diet at a dose of 5, 9.5, or 38 mg/kg (Yuan et al., 1994). In male Sprague-Dawley rats, a terminal half-life of 35 hours was observed after administration of [^{14}C]pentachlorophenol at a dose of 20 mg/kg by intravenous injection. Irrespective of exposure route, about 60–70% of the 2.5 mg/kg dose was recovered in the urine after 72 hours (pentachlorophenol, 5%; TCHQ, 1%; conjugated pentachlorophenol, 20%; conjugated TCHQ, 30%). After either injection or gavage, 10% of the dose was recovered in faeces after chemical hydrolysis (9% pentachlorophenol and 1% TCHQ), indicating that biliary excretion and [most likely] enterohepatic cycling contribute to elimination (Reigner et al., 1991).

4.2 Mechanisms of carcinogenesis

This section summarizes in the following order the available evidence for the key characteristics of carcinogens (Smith et al., 2016), concerning whether pentachlorophenol induces oxidative stress; is genotoxic; modulates receptor-mediated effects; alters cell proliferation, cell death, or nutrient supply; induces chronic inflammation; and is immunosuppressive. For the other key characteristics of human carcinogens, insufficient data were available for evaluation.

4.2.1 Oxidative stress

(a) Humans

No studies in exposed humans were available to the Working Group.

Michałowicz (2010) reported that pentachlorophenol (0.01 μg/mL and higher) caused small increases in concentrations of reactive oxygen species (ROS) in human lymphocytes isolated from four healthy nonsmoking donors (see Section 4.2.2).

A series of studies examined the role of TCHQ, a known metabolite of pentachlorophenol, in oxidative stress induced by pentachlorophenol (see Section 4.2.2). TCHQ caused DNA strand breaks (Witte et al., 1985) that were suppressed by desferrioxamine, an iron chelator (Carstens et al., 1990). In follow-up studies, desferrioxamine inhibited TCHQ-induced DNA damage by scavenging the reactive tetrachlorosemiquinone radical (Witte et al., 2000). In HepG2 cells, tetrachlorobenzoquinone was genotoxic (Dong et al., 2014). Tetrachlorobenzoquinone also increased phosphorylation of histone γH2AX, and increased 8-hydroxy-2′-deoxyguanosine (8-OHdG) and ROS in these cells. *N*-acetylcysteine attenuated both the oxidative-stress markers and the genotoxicity induced by tetrachlorobenzoquinone.

(b) Non-human mammalian experimental systems

(i) Studies on pentachlorophenol in vivo

Sai-Kato et al. (1995) reported dose-dependent increases in 8-OHdG in the liver but not in the kidney or spleen of mice exposed to pentachlorophenol. Prior exposure to vitamin E, but not to vitamin C or to β-carotene, attenuated the pentachlorophenol-induced hepatic 8-OHdG.

Umemura and colleagues examined the role of oxidative stress in toxicity attributable to pentachlorophenol (purity, 98.6%) in a series of studies by evaluating 8-OHdG as measured by high-performance liquid chromatography–electrochemical detection. In mice treated for 2 and 4 weeks, pentachlorophenol (300, 600, and 1200 ppm in the diet) caused dose-dependent increases in hepatic 8-OHdG, liver weights, hepatotoxicity, and the 5-bromo-2′-deoxyuridine (BrdU) labelling index (Umemura et al., 1996). When given alone for 8 weeks, pentachlorophenol increased hepatic 8-OHdG in a dose-dependent manner (Umemura et al., 1999). In an initiation–promotion study (with diethylnitrosamine as initiator), green tea decreased the number of mice with adenomas and the average number of tumours per mouse only at the highest dose of pentachlorophenol (Umemura et al., 2003a, b). The lowest and the highest doses of pentachlorophenol increased 8-oxodeoxyguanosine (8-OHdG) levels in liver DNA and the labelling index in both hepatocytes and extrabiliary epithelial cells. Green tea decreased the pentachlorophenol-induced increases in 8-OHdG and the increases in labelling indices (Umemura et al., 2003b). The decrease in labelling indices induced by green tea may result from the attenuation of pentachlorophenol-induced hepatotoxicity.

Umemura and colleagues have also evaluated the role of oxidative stress in the toxicity and carcinogenicity of pentachlorophenol using a variety of transgenic mice. In Umemura et al. (2006), mice deficient in nuclear factor erythroid 2-related factor (*Nrf2*$^{-/-}$) and their heterozygote (*Nrf2*$^{-/+}$) and homozygote (*Nrf2*$^{+/+}$) controls were given diets containing pentachlorophenol at 150–1200 ppm for 4 weeks. End-points included measures of oxidative stress (hepatic 8-OHdG and thiobarbituric acid-reactive substances), hepatotoxicity (increased liver weight, serum biochemistry, and cell proliferation), and changes in expression of NAD(P):quinone oxidoreductase 1, UDP-glucuronosyltransferase, and CYP1A2. At the highest dose, pentachlorophenol increased levels of hepatic 8-OHdG and thiobarbituric acid-reactive substances only in the *Nrf2*$^{-/-}$ knockout mice. Increases in hepatocyte proliferation were observed at all doses in the *Nrf2*$^{-/-}$ mice and in the *Nrf2*$^{-/+}$ heterozygotes. Pentachlorophenol increased hepatocyte proliferation in the wildtype mice at all doses except at 150 ppm (Umemura et al., 2006). In a separate

study of *Nrf2*$^{-/-}$ and *Nrf2*$^{+/+}$ mice, long-term exposure to pentachlorophenol increased the incidence of cholangiofibrosis in mice of either genotype (at concentrations of 600 and 1200 ppm *Nrf2*$^{-/-}$, and at 1200 ppm in *Nrf2*$^{+/+}$ mice) (Tasaki et al., 2014; see also Section 3.1).

The guanine-hypoxanthine phosphoribosyl transferase (*gpt*) delta transgenic mouse model was also used to evaluate the role of pentachlorophenol in oxidative stress and genotoxicity (Tasaki et al., 2013). The *gpt* delta animal model can detect point mutations within the *gpt* gene and deletion mutations within the *red/gam* (Spi$^-$) gene (Masumura et al., 2003; Hibi et al., 2011). Tasaki et al. crossed *p53*$^{-/-}$ mice with *gpt* transgenic mice and reported that exposure to pentachlorophenol for 13 weeks increased levels of 8-OHdG and NAD(P):quinone oxidoreductase 1 in the liver in *p53* wildtype and *p53*$^{-/-}$ mice. No increases in the frequency of *gpt* and *red/gam* mutations were observed in either the *p53* wildtype or *p53*$^{-/-}$ mice (Tasaki et al., 2013; see also Table 4.3, Section 4.2.2).

Bordelon et al. (2001) injected mice (age, 15 days) with pentachlorophenol as a single dose of up to 100 mg/kg bw. No 8-OHdG adducts were detected in the liver using [^{32}P]-postlabelling. No signs of toxicity were observed in the infant mice; the median lethal dose (LD_{50}) for pentachlorophenol in adult mice in this study was 50 mg/kg bw.

Lin et al. (2002) reported increased 8-OHdG adduct formation using high-performance liquid chromatography–electrochemical detection in the liver of male rats exposed to pentachlorophenol at 60 mg/kg bw per day by gavage for 27 weeks; no 8-OHdG adducts were detected after a shorter exposure (5 days) at this dose or at 120 mg/kg per day. Two major DNA adducts were detected using [^{32}P]-postlabelling after nuclease P1 adduct enrichment. One co-migrated with adducts formed by the metabolite tetrachloro-1,4-benzoquinone. This adduct appeared to be formed in parallel with 8-OHdG in the chronically exposed rats only, at levels 10 times lower than those of 8-OHdG adducts (Lin et al., 2002). In another study in male rats, 8-OHdG lesions and chromosomal aberrations were not induced in the liver after exposure to an intraperitoneal dose of pentachlorophenol at 10 mg/kg per day for 5 days, but the frequency of sister-chromatid exchange was significantly increased (Daimon et al., 1997) (see also Table 4.3, Section 4.2.2).

(ii) Studies on metabolites of pentachlorophenol in vivo

In mice treated with pentachlorophenol (purity, not reported; 40 mg/kg bw) or TCHQ (20 mg/kg bw) by intraperitoneal administration and necropsied 6 hours after exposure, glutathione (GSH) levels in the liver were depleted by 65% by TCHQ, but were unaltered by pentachlorophenol (Wang et al., 1997). In rats given a single intraperitoneal injection of pentachlorophenol (40 mg/kg bw) or TCHQ (15 mg/kg bw), with or without a 2-hour pretreatment with vitamin E (100 mg/kg bw), there was an increase in urinary levels of 8-epi-prostaglandin F2α, a major F2-isoprostane that is increased by free-radical mediated arachidonic acid oxidation (Wang et al., 2001). The increase in 8-epi-prostaglandin F2α was associated with increases in serum alanine aminotransferase and aspartate aminotransferase, and was attenuated by co-administration of vitamin E. TCHQ was more effective than pentachlorophenol in all cases (Wang et al., 2001).

Mice fed diet containing TCHQ (300 mg/kg bw per day) for 2 weeks had increased hepatic 8-OHdG (measured by liquid chromatography–electrochemical detection) (Dahlhaus et al., 1994). No increases in oxidative stress were observed in mice given a single intraperitoneal dose of TCHQ (20 or 50 mg/kg bw), 6 or 24 hours after exposure (Dahlhaus et al., 1994; see also Section 4.2.2).

(iii) Studies on pentachlorophenol metabolites in vitro

In splenocytes isolated from male ICR mice and exposed to pentachlorophenol (purity, > 98%; 25, 50, and 100 μM) or TCHQ (12.5, 25, and 50 μM), ROS were increased by TCHQ in a dose-dependent manner as measured using dichlorodihydrofluorescein diacetate (DCFH-DA). Viability began decreasing at 15 minutes, falling to 50–60% at the lowest dose, and 20–40% at the higher doses at 6 hours (Chen et al., 2014).

Siraki et al. (2004) evaluated a variety of *para*-benzoquinones, including tetrachloro-*para*-benzoquinone [tetrachloro-1,4-benzoquinone], in rat primary hepatocytes and pheochromocytoma (PC12) cells. Tetrachloro-*para*-benzoquinone induced ROS at concentrations that were 10 times lower than those for the half-maximal response (EC_{50}) for GSH depletion in rat hepatocytes or the PC12 cells. Of the 14 benzoquinone derivatives, tetrachloro-*para*-benzoquinone was the most potent for cytotoxicity and ROS formation. The potency of tetrachloro-*para*-benzoquinone for GSH depletion was similar to that of five other benzoquinone derivatives.

In mouse embryonic fibroblast NIH 3T3 cells exposed to TCHQ (5–50 μM) for 30 minutes, cell viability was significantly decreased in a dose-dependent manner and this was attenuated by co-treatment with *N*-acetylcysteine. In the same cells, apoptosis was observed after exposure to TCHQ (50 μM) for 8 hours (Wang et al., 1997; see Section 4.2.4).

TCHQ induced 8-OHdG adducts in Chinese hamster V79 lung fibroblasts (Dahlhaus et al., 1995, 1996; see also Section 4.2.2). Dahlhaus et al. (1996) observed that pentachlorophenol and tetrachloro-*ortho*-hydroquinone (also named tetrachlorocatechol) did not induce 8-OHdG, whereas 8-OHdG was increased by tetrachloro-*para*-hydroquinone, tetrachloro-*para*-benzoquinone [tetrachloro-1,4-benzoquinone], and tetrachloro-*ortho*-benzoquinone [tetrachloro-1,2-benzoquinone]. Tetrachloro-*para*-hydroquinone is the main metabolite of pentachlorophenol, while tetrachloro-*para*-benzoquinone and tetrachloro-*ortho*-hydroquinone are minor metabolites in rats and humans (Juhl et al., 1985).

(c) Non-mammalian experimental systems

In various species of fish, exposure to pentachlorophenol increased oxidative stress, decreased the glutathione/oxidized glutathione (GSH/GSSG) ratio, and altered genes and proteins involved in the response to oxidative stress (Thomas & Wofford, 1984; Zhang et al., 2008; Luo et al., 2009). Pentachlorophenol (purity, > 98%) was shown to be an uncoupler of oxidative phosphorylation in zebrafish embryos (Xu et al., 2014). No effect of pentachlorophenol (3.75–75 μM) on lipid peroxidation was seen in the digestive gland from mussels (Milowska et al., 2003). Pietsch et al. (2014) demonstrated effects of pentachlorophenol or TCHQ on ROS, superoxide dismutase, and cell viability in rainbow trout liver RTL-W1 cells that were shown to metabolize pentachlorophenol to TCHQ.

In yeast, pentachlorophenol increased concentrations of superoxide dismutase in *Humicola lutea* 110 (Angelova et al., 1995).

The antioxidants butylated hydroxytoluene and butylated hydroxyanisole increased toxicity and delayed cell growth in *Pseudomonas fluorescens* bacteria co-treated with pentachlorophenol (Trevors et al., 1981).

(d) Acellular systems

Naito et al. (1994) reported 8-OHdG in calf thymus DNA co-exposed to TCHQ and Cu(II) (20 μM) (see Section 4.2.2). DNA damage was attenuated by copper chelators and H_2O_2 scavengers, suggesting that Cu(I) and hydrogen peroxide (H_2O_2) were involved in the mechanism of DNA damage. Incubation of TCHQ with H_2O_2 produced hydroxyl radicals (·OH), which could not be inhibited by the presence of several iron chelators. [The Working Group noted that

TCHQ can react directly with H_2O_2 to produce hydroxyl radicals in a reaction independent of the classic Fenton system (Zhu et al., 2000; Zhu & Shan, 2009)]. However, in *Escherichia coli*, the presence of copper can enhance the cytotoxicity of pentachlorophenol (Zhu & Chevion, 2000; Zhu et al., 2001).

4.2.2 Genetic and related effects

Studies on pentachlorophenol have been carried out in exposed humans, in human cells in vitro, in other mammals in vivo, and in non-mammalian systems, as summarized in Table 4.1, Table 4.2, Table 4.3, Table 4.4, Table 4.5, and Table 4.6. If purity was not reported in the study, pentachlorophenol was considered to be of technical grade (approximately 90% pentachlorophenol and 10% contaminants).

(a) Humans

(i) Exposed humans

See Table 4.1.

Several studies of genetic effects in humans occupationally exposed to pentachlorophenol were available. Bauchinger et al. (1982) (also reported in Schmid et al., 1982) reported increases in chromosomal aberrations, but not in sister-chromatid exchanges, in 22 male workers in a pentachlorophenol-producing factory (14 workers exposed to Na-PCP and 8 to pentachlorophenol). All workers were smokers, and duration of exposure ranged from 1 to 30 years. The matched control group was of 22 unexposed workers (9 smokers) from similar employment settings; however, pentachlorophenol was measured in the blood and urine of pentachlorophenol-factory workers but not in the controls. Increases in the frequencies of chromosome-type aberrations (i.e. dicentric chromosomes and acentric fragments) were not influenced by smoking habits. There was no effect on the frequency of sister-chromatid exchange when smoking was controlled for.

Ziemsen et al. (1987) also measured chromosomal aberrations and sister-chromatid exchange in 20 workers exposed for 3–34 years during production of wood preservatives that consisted of pentachlorophenol and Na-PCP. Exposure was estimated by measurement of serum concentration of pentachlorophenol. No association was found between frequency of chromosomal aberrations or sister-chromatid exchange in peripheral lymphocytes and duration of employment, age, smoking status, type of exposure (pentachlorophenol or Na-PCP), or serum concentration of pentachlorophenol.

Another small study reported no significant increase in the frequency of chromosomal aberrations in six workers from a pentachlorophenol wood-treatment plant; four unmatched controls were used for comparisons (Wyllie et al., 1975). Exposure was estimated by measurement of concentration of pentachlorophenol in the serum and urine.

(ii) Human cells in vitro

See Table 4.2.

Several studies in human cells in vitro reported using the comet assay to detect DNA strand breaks (Michałowicz, 2010; Michałowicz & Majsterek, 2010; Stang & Witte, 2010; Tisch et al., 2005; Ozaki et al., 2004; Jin et al., 2012). Michałowicz (2010) reported a significant, dose-dependent increase in percentage DNA damage as measured by the alkaline comet assay in primary lymphocytes exposed to pentachlorophenol (purity, 99.5%) at 0.2, 1.0, or 5.0 µg µg/mL for 1 hour. These concentrations also increased levels of ROS detectable by the fluorescent probe 6-carboxy-2′,7′-dichlorodihydrofluorescein diacetate (H_2DCF-DA), but cell viability was only decreased at ≥125 µg/mL. Michałowicz & Majsterek (2010) repeated these findings using repair enzymes to detect oxidized DNA bases in the comet assay. Stang & Witte, (2010) reported that pentachlorophenol (purity, not reported) induced dose-dependent DNA

Table 4.1 Genetic and related effects of pentachlorophenol in exposed humans

End-point	Tissue	Cell type if specified	Description of exposure and controls	Mean exposure level	Response, significance[a]	References
Chromosomal aberrations	Blood,	Lymphocytes	22 male workers at a PCP plant (8: PCP; 14: Na-PCP) and 22 male controls	< 0.1 to > 0.5 mg/m^3 (TWA)	+ (P = 0.004)	Bauchinger et al. (1982); Schmid et al. (1982)
Sister-chromatid exchange					–	
Chromosomal aberrations	Blood	Lymphocytes	20 workers at PCP wood-preservative production plant	180 µg/m^3	–	Ziemsen et al. (1987)
Sister-chromatid exchange					–	
Chromosomal aberrations	Blood	NR	6 PCP wood-treatment plant workers and 4 unexposed controls; Idaho	1887.9 ng/m^3 for 5 mo	–	Wyllie et al. (1975)

[a] +, positive; –, negative

mo, month; Na-PCP, sodium pentachlorophenate ; NR, not reported; PCP, pentachlorophenol; TWA, time-weighted average

Table 4.2 Genetic and related effects of pentachlorophenol in human cells in vitro

End-point	Tissue, cell line	Results[a]		Concentration (LEC or HIC)	Comments	References
		Without metabolic activation	With metabolic activation			
DNA strand breaks, alkaline comet assay	Lymphocytes (primary)	+	NT	0.2 µg/mL	Purity, 99.5%	Michałowicz (2010)
DNA strand breaks, comet assay + Fpg and Endo III enzymes	Lymphocytes (primary)	+	NT	0.2 µg/mL	Purity, 99.5%	Michałowicz & Majsterek (2010)
DNA strand breaks, high-throughput comet assay	Lymphocytes (primary)	–	+	0.5 mM [133 µg/mL]	Purity, NR	Stang & Witte (2010)
DNA strand breaks, high-throughput comet assay	Liver, HepG2	+	NT	1 mM [266 µg/mL]	Purity, NR	Stang & Witte (2010)
	Fibroblast, NHDF-p	–	+	1.25 mM [333 µg/mL]		
	Cervical carcinoma, HeLa	–	+	1.15 mM [306 µg/mL		
DNA strand breaks, comet assay and microgel electrophoresis	Cervical carcinoma, HeLa	–	NT	50 µM [13.5 µg/mL]	Purity, NR	Jin et al. (2012)
Chromosomal aberrations, sister-chromatid exchange	Nasal mucosal epithelial cells (primary)	+	NT	1.2 M [3.2×10^5 µg/mL]	Purity, > 99.5%	Tisch et al. (2001, 2005)
	Lymphocytes (primary)	–	NT	90 µg/mL	Na-PCP, technical grade; purity, 85%	Ziemsen et al. (1987)

[a] +, positive; –, negative; the level of significance was set at $P < 0.05$ in all cases

Endo III, endonuclease III; Fpg, formamidopyrimidine DNA glycosylase; HIC, highest ineffective concentration; LEC, lowest effective concentration; Na-PCP, sodium pentachlorophenate; NR, not reported; NT, not tested

damage in a high-throughput comet assay in HepG2 cells without S9, and in primary lymphocytes, fibroblasts, and HeLa cells (and in CHO V79 cells, described below) in the presence of S9. Pentachlorophenol (purity, not reported) gave negative results in a separate study in HeLa cells (Jin et al., 2012), and DNA damage induced by pentachlorophenol (purity, > 99%) in the human promyelocytic leukaemia cell line HL-60 was attributed to high toxicity (51% viable cells) (Ozaki et al., 2004). Concentration-dependent induction of DNA damage in primary mucosal epithelial cells isolated from human nasal conchae was induced by pentachlorophenol (purity, > 99.5%) (Tisch et al., 2001, 2005).

Technical-grade Na-PCP (purity, 85%; up to the cytotoxic concentration of 90 µg/mL) did not increase the frequency of chromosomal aberrations or sister-chromatid exchange in primary lymphocytes from healthy donors, exposed in vitro (Ziemsen et al., 1987).

(b) Experimental systems

(i) Non-human mammals in vivo

See Table 4.3.

Studies that also reported on 8-OHdG and other end-points relevant to oxidative stress (Sai-Kato et al., 1995; Daimon et al., 1997; Tasaki et al., 2013) are discussed in Section 4.2.1.

No increase in the frequency of micronucleus formation was observed in mouse or rat bone marrow after intraperitoneal injection of pentachlorophenol (purity, 91.6%) every 24 hours for 3 days. The highest dose in mice (150 mg/kg bw) and rats (75 mg/kg bw) was lethal (NTP, 1999).

(ii) Non-human mammalian cells in vitro

See Table 4.4.

Pentachlorophenol (purity, > 99.5%) did not induce forward (Jansson & Jansson, 1986) or reverse (Helleday et al., 1999) *Hprt* mutations in Chinese hamster V79 lung fibroblasts. Pentachlorophenol (purity, not reported; 6.66 µg/mL) did not induce DNA strand breaks (or 8-OHdG) in Chinese hamster V79 cells (Dahlhaus et al., 1996). However, significant DNA strand breakage was detected by the comet assay in another study in Chinese hamster V79 cells treated with pentachlorophenol at a higher concentration (266 µg/mL) and with S9 (Stang & Witte, 2010). In Chinese hamster ovary cells, DNA strand breaks were not detected after exposure to pentachlorophenol at 10 µg/mL (Ehrlich, 1990), but a marginal induction of chromosomal aberrations (80 µg/mL; only with S9) and sister-chromatid exchange (30 µg/mL; only without S9) was reported at slightly higher concentrations of pentachlorophenol (purity, 91.6%) (NTP, 1999).

(iii) Non-mammalian experimental systems in vivo

See Table 4.5.

In zebrafish, analytical-grade pentachlorophenol induced point mutations in the *Tp53* gene (Yin et al., 2006) and DNA adduct formation (Fang et al., 2015).

Pentachlorophenol produced chromosomal aberrations and/or micronuclei in freshwater fish (Farah et al., 2003, 2006) (purity, 99%), catfish (Ahmad et al., 2002) (purity, 99%), snails (Pavlica et al., 2000), and mussels (Pavlica et al., 2000; Villela et al., 2006), but not in frogs exposed as larvae (Venegas et al., 1993). Pentachlorophenol induced DNA strand breaks in mussels in vivo (Pavlica et al., 2001; Villela et al., 2006) and in vitro (Milowska et al., 2003), as well as in earthworms (Klobučar et al., 2011).

Pentachlorophenol did not induce nondisjunction or chromosome loss in *Drosophila melanogaster* (Ramel & Magnusson, 1979).

In the onion, pentachlorophenol (purity, 99%) induced chromosomal aberrations in one study (Ateeq et al., 2002), but not in another (Venegas et al., 1993). Micronucleus formation was observed in the onion (Repetto et al., 2001).

Table 4.3 Genetic and related effects of pentachlorophenol in non-human mammals in vivo

End-point	Species, strain (sex)	Tissue	Results[a]	Dose (LED or HID)	Route, duration, dosing regiment	Comments	References
DNA adducts (8-OHdG, HPLC-ECD)	Mouse, B6C3F$_1$ (M)	Liver	+	60 mg/kg	Gavage, single dose/6 h	Purity, 98.6%	Sai-Kato et al. (1995)
DNA adducts,^{32}P-postlabelling	Rat, F344/Du Crj (M)	Liver	–	10 mg/kg bw	i.p., 5 days	Purity, NR	Daimon et al. (1997)
Sister-chromatid exchanges	Rat, F344/Du Crj (M)	Liver	+				
Chromosomal aberrations			–				
Mouse spot test	Mouse, *p53*$^{+/+}$ or *p53*$^{-/-}$ C57BL/6 *gpt delta* (M)	Liver	–	6000–12 000 ppm	p.o., 13 wk		Tasaki et al. (2013)
Micronucleus formation	Mouse, B6C3F$_1$ (M)	Bone marrow (PCE)	–	150 mg/kg bw	i.p., 1×/day, 3 days	Purity, 91.6% HID was lethal	NTP (1999)
Micronucleus formation	Rat, F344/N, (M)	Bone marrow (PCE)	–	75 mg/kg bw	i.p., 1×/day, 3 days	Purity, 91.6% HID was lethal	NTP (1999)

[a] +, positive; –, negative; the level of significance was set at $P < 0.05$ in all cases

bw, body weight; h, hour(s); HID, highest ineffective dose; i.p., intraperitoneal; HPLC-ECD, high-performance liquid chromatography–electrochemical detection; LED, lowest effective dose; M, male; NR, not reported; 8-OHdG, 8-hydroxy-2′-deoxyguanosine; PCE, polychromatic erythrocytes; p.o., oral; ppm, parts per million; wk, week

Table 4.4 Genetic and related effects of pentachlorophenol in non-human mammalian cells in vitro

End-point	Cell line	Results[a]		Concentration (LEC or HIC)	Comments	References
		Without metabolic activation	With metabolic activation			
DNA strand breaks, alkaline elution assay	Chinese hamster ovary	–	NT	10 µg/mL	Purity, NR	Ehrlich (1990)
DNA strand breaks, alkaline elution assay	Chinese hamster fibroblast V79	–	NT	25 µM [6.66 µg/mL]	Purity, NR	Dahlhaus et al. (1996)
DNA strand breaks, high-throughput comet assay	Chinese hamster fibroblast V79	–	+	1 mM [266 µg/mL]	Purity, NR	Stang & Witte (2010)
Hprt mutation	Chinese hamster fibroblast V79	–	NT	50 µg/mL	Purity, > 99.5%	Jansson & Jansson (1986)
Hprt mutation	Chinese hamster fibroblast V79	–	NT	35 µg/mL (V79SPD8 clone), 40 µg/mL (V79Sp5 clone)	Purity, NR	Helleday et al. (1999)
Chromosomal aberrations	Chinese hamster ovary	–	(+)	80 µg/mL	Purity, 91.6%	Galloway et al. (1987); NTP (1989, 1999)
Sister-chromatid exchange		(+)	–	30 µg/mL		

[a] +, positive; –, negative; (+), positive result in a study of limited quality; the level of significance was set at $P < 0.05$ in all cases

HIC, highest ineffective concentration; LEC, lowest effective concentration; NR, not reported; NT, not tested

Table 4.5 Genetic and related effects of pentachlorophenol in non-mammalian experimental systems in vivo

End-point	Species, strain, tissue	Results[a]	Concentration (LEC or HIC)	Comments	Reference
Tp53 gene mutation	*Tuebingen* zebrafish, liver	+	5 µg/L (10 days)	Purity, > 98%	Yin et al. (2006)
DNA adducts (8-OHdG, ELISA)	*Danio rerio* zebrafish, AB strain embryos	+	30 µg/L (6 days post fertilization)	Purity, > 99% 8-OHdG lesions in larvae	Fang et al. (2015)
Chromosomal aberrations	*Channa punctatus*, kidney	+	0.6 ppm [600 µg/L] (96 h)	Purity, 99%	Farah et al. (2006)
Micronucleus formation	*Channa punctatus*, erythrocytes	+	0.2 ppm [200 µg/L] (96 h)	Purity, 99%	Farah et al. (2003)
Micronucleus formation	*Heteropneustes fossilis*, erythrocytes	+	0.1 ppm [100 µg/L] (96 h)	Purity, 99%	Ahmad et al. (2002)
Micronucleus formation	*Caudiverbera caudiverbera* larvae, erythrocytes	–	1.5 ppm [1500 µg/L] (6 days)	Purity, NR	Venegas et al. (1993)
Micronucleus formation	*Planorbarius corneus*, haematocytes	+	100 µg/L (7 days)	Technical grade	Pavlica et al. (2000)
DNA strand breaks, comet assay	*Dreissena polymorpha*, haematocytes	+	80 µg/L (7 days)	Technical grade	Pavlica et al. (2001)
Micronucleus formation	*Dreissena polymorpha*, haematocytes	+	10 µg/L (up to 14 days)	Technical grade	Pavlica et al. (2000)
DNA strand breaks, comet assay	*Limnoperna fortune*, haematocytes	+	100 µg/L (2 h)	Purity, NR	Villela et al. (2006)
Micronucleus formation		+	10 µg/L (24 or 48 h)		
DNA strand breaks, comet assay	*Eisenia fetida,* coelomocytes	+	0.125 µg/cm^2 (24 h)	Purity, NR	Klobučar et al. (2011)
Aneuploidy, nondisjunction and loss of sex chromosomes	*Drosophila melanogaster*	–	400 ppm [400 µg/mL]	Purity, NR	Ramel & Magnusson (1979)
Chromosomal aberrations	*Allium cepa* (onion)	–	1.5 ppm [1.5 µg/mL] (6 days)	Purity, NR	Venegas et al. (1993)
Chromosomal aberrations	*Allium cepa* (onion)	+	0.5 ppm [0.5 µg/mL]	Purity, 99%	Ateeq et al. (2002)
Micronucleus formation	*Allium cepa* (onion)	+	5 µM [1.33 µg/mL]	Purity, NR	Repetto et al. (2001)

[a] +, positive; –, negative; the level of significance was set at $P < 0.05$ in all cases

h, hour(s); HIC, highest ineffective concentration; LEC, lowest effective concentration; NR, not reported; 8-OHdG, 8-hydroxy-2′-deoxyguanosine; PCR, polymerase chain reaction; ppm, parts per million

(iv) Non-mammalian experimental systems in vitro

See Table 4.6.

Pentachlorophenol gave positive results in lower eukaryotic non-mammalian systems. Pentachlorophenol induced forward gene conversion (Fahrig, 1974; Fahrig et al., 1978), mutation (Fahrig et al., 1978), and mitotic recombination (Waters et al., 1982) in various strains of *Saccharomyces cerevisiae*.

In prokaryotic non-mammalian systems, pentachlorophenol did not induce reverse mutations in *Salmonella typhimurium* strains TA97a, TA98, TA100, TA1535, TA1537, or YG1024 in nearly all studies identified (Waters et al., 1982; Donnelly et al., 1990; George et al., 1991; Markiewicz et al., 1996; Donnelly et al., 1998; Gichner et al., 1998; NTP, 1999). Two studies reported positive results with exogenous S9 in TA98 (Nishimura & Oshima, 1983; Gopalaswamy & Nair, 1992).

Pentachlorophenol did not induce reverse mutations or DNA damage in two strains of *Escherichia coli* (Waters et al., 1982). DNA strand breaks were detected using the Microscreen prophage-induction assay in *Escherichia coli* after exposure to pentachlorophenol (purity, 92%) (DeMarini et al., 1990). Results were positive with exogenous S9 and marginally positive in the absence of S9. DNA damage was also detected in two strains of *Bacillus subtilis*, one wildtype (Ozaki et al., 2004) and one recombination-deficient (Waters et al., 1982); Ozaki et al. used pentachlorophenol with a purity of > 99%.

(v) Acellular systems

See Table 4.6.

Van Ommen et al. (1986) reported the formation of both DNA and protein adducts in calf thymus DNA and microsomal proteins from rats after exposure to pentachlorophenol, but Witte et al. (1985) did not detect adduct formation in calf thymus or bacteriophage DNA in the absence of metabolic activation.

Dai et al. reported the formation of pentachlorophenol–DNA adducts with calf thymus DNA (Dai et al., 2005) or excess deoxyguanosine (Dai et al., 2003) in the presence of peroxidase. Adducts were detected using liquid chromatography-mass spectrometry with nuclear magnetic resonance spectral analysis. The oxidation of pentachlorophenol by the peroxidases (horseradish and myeloperoxidase) yielded chlorophenoxyl radicals that formed oxygen adducts that were specific to the C8 of deoxyguanosine; adducts were not formed with the three other deoxynucleosides. These chlorophenoxyl radicals were also able to self-pair to form an electrophilic 1,4-benzoquinone; this derivative can also react with deoxyguanosine to form 4′′-hydroxy-1,N^2-benzetheno-deoxyguanosine adducts (Dai et al., 2005). These chlorophenoxyl radicals were specific to pentachlorophenol oxidation by peroxidases; when the same experiment was conducted using rat liver microsomes, different DNA adducts formed from the electrophilic benzoquinone metabolites were observed (Dai et al., 2003).

(c) Genetic and related effects of pentachlorophenol metabolites

See Table 4.7.

Several studies investigated the genetic and related effects of the major metabolites of pentachlorophenol, including TCHQ, tetrachlorocatechol (also named tetrachloro-*ortho*-hydroquinone), tetrachloro-1,2-benzoquinone (tetrachloro-*ortho*-benzoquinone), and tetrachloro-1,4-benzoquinone (tetrachloro-*para*-benzoquinone) (see also Section 4.2.1).

(i) TCHQ

TCHQ induced DNA damage measured by the comet assay in the human fibroblast GM 5757 cell line (Witte et al., 2000; Stang & Witte, 2010), and by alkaline elution in Chinese hamster ovary cells (Ehrlich, 1990). TCHQ induced mutations at the *Hprt* locus (but not at the Na/K-ATPase

Table 4.6 Genetic and related effects of pentachlorophenol in non-mammalian and acellular systems in vitro

End-point	Species, strain	Results[a]		Concentration (LEC or HIC)	Comments	Reference
		Without metabolic activation	With metabolic activation			
Mitotic gene conversion	*Saccharomyces cerevisiae* D4	+	NT	0.19 mM [50.6 µg/mL]	Purity, NR Vehicle, DMSO	Fahrig (1974)
Mitotic gene conversion	*Saccharomyces cerevisiae* MP-1	+	NT	400 µg/mL	Purity, 99% Survival, 59%	Fahrig et al. (1978)
Forward mutation	*Saccharomyces cerevisiae* MP-1	+	NT	400 µg/mL	Purity, 99% Survival, 59%	Fahrig et al. (1978)
Mitotic recombination	*Saccharomyces cerevisiae* D3	+	+	10 mg/plate	Technical grade	Waters et al. (1982)
Reverse mutation	*Salmonella typhimurium* TA100	–	–	0.04 µmol/plate [11 µg/plate]	Purity, NR	Nishimura & Oshima (1983)
Reverse mutation	*Salmonella typhimurium* TA98	–	+	0.04 µmol/plate [11 µg/plate]	Purity, NR	Nishimura & Oshima (1983)
Reverse mutation	*Salmonella typhimurium* TA98	NT	–	50 µg/plate	Purity, NR	Donnelly et al. (1990)
Reverse mutation	*Salmonella typhimurium* TA98, TA100	–	–	100 µg/plate		George et al. (1991)
Reverse mutation	*Salmonella typhimurium* TA98	–	+	100 µg/plate	Purity, NR	Gopalaswamy & Nair (1992)
Reverse mutation	*Salmonella typhimurium* TA98	–	–	100 µg/plate	Purity, NR	Markiewicz et al. (1996)
Reverse mutation	*Salmonella typhimurium* TA97a, TA98 and TA100	–	–	200 µg/plate	Purity, > 98%	Donnelly et al. (1998)
Reverse mutation	*Salmonella typhimurium* YG1024	–	–	200 µM [53.3 µg/mL]	Purity, NR	Gichner et al. (1998)
Reverse mutation	*Salmonella typhimurium* TA98, TA100, TA1535, TA1537	–	–	30 µg/plate	Purity, 91.6%	Haworth et al. (1983); NTP (1989, 1999)
Reverse mutation	*Salmonella typhimurium* TA98, TA100, TA1535, TA1537, TA1538	–	–	10mg/plate	Technical grade	Waters et al. (1982)
Prophage λ induction	*Escherichia coli* WP2s (λ)	+	+	12.71 µM [3.4 µg/mL]	Purity, 92%	DeMarini et al. (1990)
Differential toxicity	*Escherichia coli* p3478 (polA-)	–	NT	10 mg/plate	Technical grade	Waters et al. (1982)

Table 4.6 (continued)

End-point	Species, strain	Results[a]		Concentration (LEC or HIC)	Comments	Reference
		Without metabolic activation	With metabolic activation			
Reverse mutation	*Escherichia coli* WP2	–	–	10 mg/plate	Technical grade	Waters et al. (1982)
Differential toxicity	*Bacillus subtilis* M45 (*recA*-)	+	NT	10 mg/plate	Technical grade	Waters et al. (1982)
Differential toxicity	*Bacillus subtilis* M45 (*recA*–, *recA*+)	+	NT	3 µg/plate (*recA*–), 6 µg/plate (*recA*+)	Purity, > 99%	Ozaki et al. (2004)
DNA adducts, covalent binding	Calf thymus DNA	–	NT	100 mM [26.6×10^3 µg/mL]	Purity, NR	Witte et al. (1985)
DNA adducts, covalent binding	Calf thymus DNA	NT	+	100 µM [26.63 µg/mL]	Purity, NR	van Ommen et al. (1986)
C8-dG O-adduct, LC-MS	Bacteriophage PM2 DNA	–	NT	100 mM [26.6×10^3 µg/mL]	Purity, NR	Witte et al. (1985)
C8-dG O-adduct, LC-MS	2′-Deoxyguanosine	+	–	100 µM [26.63 µg/mL]	Purity, NR Horseradish peroxidase/ H_2O_2 Alternative adduct formed in presence of S9	Dai et al. (2003)
DNA strand breaks, quantitative gel electrophoresis	Calf thymus DNA	+	NT	100 µM [26.63 µg/mL]	Purity, NR In the presence of horseradish peroxidase/ H_2O_2.	Dai et al. (2005)

[a] +, positive; –, negative; the level of significance was set at $P < 0.05$ in all cases

C8-dGO, C-8-2′-deoxyguanosine; DMSO, dimethyl sulfoxide; HIC, highest ineffective concentration; LC-MS, liquid chromatography-mass spectrometry; LEC, lowest effective concentration; NR, not reported; NT, not tested; S9, 9000 × g supernatant

Table 4.7 Genetic and related effects of metabolites of pentachlorophenol

End-point	Tissue, cell line	Results[a]	Concentration (LEC or HIC)	Comments	References
Tetrachlorohydroquinone					
DNA strand breaks, comet assay	Human fibroblasts, GM 5757	+	6.5 µM [1.6 µg/mL]	Purity, NR	Witte et al. (2000)
DNA strand breaks, high throughput comet assay	Human fibroblasts, NHDF-p	+	NR	Purity, "grade II"	Stang & Witte (2010)
DNA strand breaks, alkaline elution assay	Chinese hamster ovary	+	2 µg/mL	Purity, NR	Ehrlich (1990)
DNA strand breaks, alkaline elution assay	Chinese hamster fibroblast, V79	+	25 µM [6.2 µg/mL]	Purity, NR	Dahlhaus et al. (1995)
Hprt mutation Na/K-ATPase locus, ouabain-resistant mutants	Chinese hamster fibroblast, V79	+ –	20 µM [5 µg/mL] 60 µM [15 µg/mL]	Purity, > 99%	Jansson & Jansson (1991)
Micronucleus formation	Chinese hamster fibroblast, V79	+	10 µM [2.5 µg/mL]	Purity, > 99%.	Jansson & Jansson (1992)
DNA adducts, covalent binding	Calf thymus DNA	+	50 mM [12.5 µg/mL]	Purity, NR	Witte et al. (1985)
DNA adducts, covalent binding	Calf thymus DNA	–	200 µM [50 µg/mL]	Purity, NR. Positive with 20 µM Cu(II)	Naito et al. (1994)
DNA strand breaks, quantitative gel electrophoresis	Bacteriophage PM2 DNA	+	5 µM [1.3 µg/mL]	Purity, NR	Witte et al. (1985)
DNA strand breaks, ^{32}P-labelled DNA fragments, electrophoresis	Plasmid DNA	–	200 µM [50 µg/mL]	Purity, NR Positive with 20 µM Cu(II)	Naito et al. (1994)
*Tetrachlorocatechol (tetrachloro-*ortho*-hydroquinone)*					
DNA strand breaks, comet assay + Fpg and Endo III	Human lymphocytes (primary)	+	0.02 µg/mL	Purity, 99%	Michałowicz & Majsterek (2010)
DNA strand breaks, alkaline comet assay	Human lymphocytes (primary)	+	0.2 ppm [0.2 µg/mL]	Purity, 99.5%	Michałowicz (2010)
Aldehydic DNA lesions, aldehyde reactive slot-blot assay (ASB assay)	Human breast cancer, MCF-7	+	500 µM [124 µg/mL]	Only positive with prior GSH depletion	Lin et al. (2005)
Na/K-ATPase locus, ouabain resistant mutant; *Hprt* mutation	Chinese hamster fibroblasts, V79	–	120 µM [30 µg/mL]	Purity, > 99%	Jansson & Jansson (1991)
Aldehydic DNA lesions, ASB assay	Calf thymus DNA	–	100 µM [25 µg/mL]	Positive with 20 µM Cu(II) + 100 µM NAD(P)H	Lin et al. (2005)
Tetrachlorobenzoquinone					
DNA strand breaks, comet assay	Human liver, HepG2	+	6.25 µM [1.5 µg/mL]	Isomer of TCBQ not specified; purity, NR	Dong et al. (2014)

Table 4.7 (continued)

End-point	Tissue, cell line	Results[a]	Concentration (LEC or HIC)	Comments	References
DNA strand breaks for γ-H2AX; micronucleus formation	Human liver, HepG2	+	12.5 µM [3 µg/mL]	Isomer of TCBQ not specified; purity, NR	Dong et al. (2014)
DNA strand breaks, alkaline elution assay	Chinese hamster fibroblast, V79	–	25 µM [6.2 µg/mL]	TC*o*BQ; purity, NR	Dahlhaus et al. (1996)
DNA strand breaks, alkaline elution assay	Chinese hamster fibroblast, V79	+	25 µM [6.2 µg/mL]	TC*p*BQ; purity, NR	Dahlhaus et al. (1996)
DNA adducts, Cl_2BQ-dG, HPLC-MS-NMR	2′-Deoxyguanosine	+	0.062 mmol/20 mL [3.1 mM] [762 µg/mL]	Isomer of TCBQ, not specified	Nguyen et al. (2005)

[a] +, positive; –, negative; the level of significance was set at $P < 0.05$ in all cases

Cl_2BQ-dG, dichlorobenzoquinone-deoxyguanosine; GSH, glutathione; HIC, highest ineffective concentration; HPLC-MS-NMR, high-performance liquid chromatography-mass spectrometry-nuclear magnetic resonance; LEC, lowest effective concentration; NR, not reported; TCBQ, tetrachlorobenzoquinone; TCoBQ, tetrachloro-*ortho*-benzoquinone (tetrachloro-1,2-benzoquinone); TCpBQ, tetrachloro-*para*-benzoquinone (tetrachloro-1,4-benzoquinone)

gene locus) (Jansson & Jansson, 1991), micronuclei (Jansson & Jansson, 1992), 8-OHdG adducts, and DNA strand breaks (Dahlhaus et al., 1996; 1995; see Section 4.2.1) in Chinese hamster V79 lung fibroblasts. TCHQ induced DNA adducts in calf thymus DNA and DNA strand breaks in bacteriophage PM2 DNA (Witte et al., 1985). Naito et al. (1994) also reported DNA strand breaks in plasmid DNA and DNA adducts in calf thymus DNA, but only after co-exposure to Cu(II) (20 μM) plus TCHQ.

(ii) Tetrachlorocatechol

Tetrachlorocatechol (also named tetrachloro-*ortho*-hydroquinone) induced oxidized base damage (Michałowicz & Majsterek, 2010) and DNA strand breaks (Michałowicz, 2010) in human primary lymphocytes. Tetrachlorocatechol induced aldehydic DNA lesions, or abasic (apurinic/apyrimidinic) sites, in human breast cancer MCF-7 cells depleted of GSH, and in calf thymus DNA with the addition of Cu(II) and NAD(P)H (Lin et al., 2005). However, in V79 Chinese hamster lung fibroblasts, tetrachlorocatechol did not induce mutations at *Hprt* or the Na/K-ATPase gene loci (Jansson & Jansson, 1991), and did not increase the frequency of DNA strand breaks or 8-OHdG adducts (Dahlhaus et al., 1996; see Section 4.2.1).

(iii) Tetrachloro-1,2-benzoquinone and tetrachloro-1,4-benzoquinone

Both tetrachloro-1,2-benzoquinone (tetrachloro-*ortho*-benzoquinone) and tetrachloro-1,4-benzoquinone (tetrachloro-*para*-benzoquinone) formed 8-OHdG adducts in Chinese hamster V79 lung fibroblast cells, but only tetrachloro-1,4-benzoquinone (the metabolite of TCHQ) induced DNA damage (Dahlhaus et al., 1996). In HepG2 cells, tetrachloro-1,4-benzoquinone increased DNA strand breaks (as measured by the comet assay), histone γ-H2AX phosphorylation, 8-OHdG adducts, and micronucleus formation (Dong et al., 2014). Nguyen et al. (2005) reported the formation of tetrachlorobenzoquinone adducts to 2′-deoxyguanosine; it was not specified whether the *ortho* or *para* form of tetrachlorobenzoquinone was used.

4.2.3 Receptor-mediated effects

(a) Exposed humans

No data were available to the Working Group.

(b) Human and other mammalian cells in vitro

The literature on receptor-mediated effects was sparse; however, high-throughput data (discussed in Section 4.3) suggest interaction with several nuclear receptor subtypes, including estrogen receptors and the aryl hydrocarbon receptor (AhR).

Pentachlorophenol exhibited antagonism for estrogen receptors in human HELN cells expressing estrogen-receptor subtypes ERα and ERβ (Lemaire et al., 2006). Other studies in fish, discussed below, indicated predominantly anti-estrogenic activity (Petit et al., 1997; Lemaire et al., 2006; Zhao et al., 2006a, b). However, pentachlorophenol was shown to be estrogenic in the human MCF-7 cell proliferation assay in a single study (Suzuki et al., 2001). In this study, pentachlorophenol at concentrations in the nanomolar range was estrogenic, and when tested as a binary mixture with estradiol (E2), synergistic effects were detected (Suzuki et al., 2001). [The Working Group noted that the divergent results were most likely the consequence of the different cell types and assay methods used, together with effects of pentachlorophenol that are unrelated to binding with and activation of estrogen receptors.]

(c) Non-human mammals in vivo

The developmental neurotoxicity of pentachlorophenol was associated with decreases in circulating thyroxine (T4) in the dam and the pups. Decreases in plasma T4 were also observed in rats exposed perinatally to pentachlorophenol (Kawaguchi et al., 2008). Ewe lambs or their dams

were fed pentachlorophenol at a dose of 1 mg/kg bw per day from conception to age 67 weeks (Beard & Rawlings, 1999). Serum levels of free T4 and total T4 were decreased in the offspring when measured on weeks 65–66; smaller decreases were observed for triiodothyronine (T3). In addition, exposure to pentachlorophenol blunted the T4 and T3 increases in response to endogenous thyroid-stimulating hormone (Beard & Rawlings, 1999). The decrease in T4 was associated with increased scrotal circumference, seminiferous tubule atrophy, and reduced epididymal sperm density (Beard et al., 1999). A multigenerational study in minks exposed to pentachlorophenol at 1 mg/kg per day reported decreased serum T4 concentrations in the F_2 males and F_3 males and females (Beard & Rawlings, 1998).

(d) Non-mammalian experimental systems

In cultures of juvenile goldfish (*Carassius auratus*) hepatocytes, pentachlorophenol failed to induce an estrogenic effect as measured by vitellogenin concentrations in the media and was cytotoxic at very low concentrations (< 1.21 µg/mL) (Zhao et al., 2006a, b). Co-culturing pentachlorophenol with 17β-estradiol in this in-vitro model significantly reduced the estrogenic activity of 17β-estradiol, with a potency similar to that of the anti-estrogen tamoxifen (Zhao et al., 2006a). Similarly, the anti-estrogenic effects of pentachlorophenol were corroborated by results from a reporter-gene assay in yeast expressing rainbow trout estrogen-receptor, in which pentachlorophenol inhibited estrogen-dependent cell growth (Petit et al., 1997).

Pentachlorophenol (1 and 10 µg/L) increased mRNA expression of thyroid hormone receptors α and β (Thrα and Thrβ) in zebrafish embryo cultures (Cheng et al., 2015). In contrast, *Thrβ* gene expression was decreased by exposure to pentachlorophenol (27 µg/L) in the brain of male but not female zebrafish (age, 4 months) (Yu et al., 2014). In a study in vitro on purified transthyretin from Japanese quail, treatment with pentachlorophenol displaced radiolabelled T3 from transthyretin, but was without effect on thyroid hormone receptor (Ishihara et al., 2003) suggesting that the effects of pentachlorophenol are limited to displacement of thyroid hormones from serum carrier proteins.

4.2.4 Altered cell proliferation or death

(a) Humans

No data were available to the Working Group.

In the HepG2 human hepatoma cell line, TCHQ and pentachlorophenol altered the expression of several apoptosis-relevant genes, including *BCL-2*. *BAX*, heat shock protein (HSP) expression, and cellular apoptosis susceptibility (CAS) gene while PCP altered *BCL-2* and *BAX* expression but not HSP and CAS (Wang et al., 2001). TCHQ -induced apoptosis and DNA laddering, but cell death induced by pentachlorophenol appeared to be more characteristic of necrosis. TCHQ, but not pentachlorophenol, induced apoptosis and DNA fragmentation, and decreased *CAS* gene expression in human T-24 bladder cells. Neither compound exhibited these effects in Chang human liver cells (with HeLa markers) (Wang et al., 2000). In both cell lines, TCHQ, but not pentachlorophenol, decreased BCL-2/BAX protein expression.

Both pentachlorophenol and TCHQ markedly increased apoptotic cell number and induced DNA fragmentation in Jurkat human T cells, although TCHQ was more potent (Wispriyono et al., 2002). TCHQ but not pentachlorophenol increased the phosphorylation of all mitogen-activated protein kinases (MAPKs) examined [i.e. extracellular signal-regulated protein kinase (ERK), p38, and c-Jun NH(2)-terminal kinase (JNK)]. Apoptosis by pentachlorophenol or TCHQ was mildly (but significantly) suppressed by a MAPK/ERK kinase inhibitor (U0126), markedly suppressed by a p38 inhibitor (SB203580), and almost completely suppressed when both inhibitors were given at the same

time. LL-Z1640–2, an inhibitor of JNK phosphorylation, did not affect apoptosis induced by either TCHQ or pentachlorophenol.

A study in vitro reported that pentachlorophenol at 60 µg/mL induced a slowdown of cell proliferation in human lymphocytes from normal healthy donors (Ziemsen et al., 1987).

(b) Experimental systems

Chen et al. (2015) reviewed effects of pentachlorophenol and TCHQ in mice, rats, and in mammalian cells in vitro, noting that TCHQ induced apoptosis/necrosis both in vivo and in vitro. Antioxidants attenuated cytotoxicity, apoptosis/necrosis, and other effects induced by pentachlorophenol and/or TCHQ. In addition, a role for MAPK in pentachlorophenol/TCHQ-triggered cytotoxicity was shown by the finding that higher doses of TCHQ could lead to necrosis of freshly isolated splenocytes through marked increases in ROS and sustained ERK activation (Chen et al., 2014).

In studies detailed in Section 4.2.1, increased hepatocyte cell proliferation was reported in B6C3F$_1$ male mice exposed to pentachlorophenol at 600 or 1200 ppm for 8 weeks (Umemura et al., 1999). Liver weights were increased in mice exposed to pentachlorophenol (600 ppm for 2 or 4 weeks) (Umemura et al., 1996, 2003a). Pentachlorophenol (600 ppm in the diet for 2 weeks) increased cell proliferation in epithelial cells of intrahepatic bile ducts as well as hepatocytes in exposed B6C3F$_1$ mice (Umemura et al., 2003b). Furthermore, hepatic cell proliferation caused by pentachlorophenol was enhanced in *Nrf2*-deficient mice (*Nrf2*$^{-/-}$ or *Nrf2*$^{+/-}$) compared with *Nrf2*$^{+/+}$ mice, whereas the effects of pentachlorophenol on relative liver weights was diminished in *Nrf2*$^{-/-}$ and *Nrf2*$^{+/-}$ mice compared with *Nrf2*$^{+/+}$ mice (Umemura et al., 2006).

In an initiation–promotion study on skin tumours, dermally administered pentachlorophenol and TCHQ (2.5, 50, or 1000 µg, twice per week for 25 weeks, 1 week after initiation with dimethylbenz[*a*]anthracene) enhanced mice skin epidermal hyperplasia and proliferating cell nuclear antigen labelling index in the epidermis, with TCHQ showing greater effects (Chang et al., 2003).

In male B6C3F$_1$ mice treated with pentachlorophenol (300 or 600 ppm in the diet), there was a dose-related inhibition of gap-junctional intercellular communication in hepatocytes, associated reductions in connexin32 (Cx32) plaques in the plasma membrane, and increased cell proliferation index. These effects were attenuated by pre-and co-treatment with green tea extract (Sai et al., 2000).

Pentachlorophenol, but not TCHQ, inhibited gap-junctional intracellular communication in rat liver epithelial cells (WB cells) (Sai et al., 1998). Pentachlorophenol treatment of v-myc-transfected rat liver epithelial cells inhibited gap-junctional intercellular communication and associated apoptosis induced by serum deprivation (Sai et al., 2001).

In vitro, cell proliferation was enhanced in pentachlorophenol-treated AML 12 mouse hepatocyte cells (Dorsey et al., 2004, 2006). TCHQ affected proliferation and differentiation in two stroma-free murine bone marrow culture models, a multipotent progenitor cell line (factor-dependent cell Paterson-, FDCP-mix), and primary lineage-depleted bone marrow cells (Henschler et al., 2001).

4.2.5 Inflammation and immunosuppression

(a) Exposed humans

Exposure to pentachlorophenol has been associated with inflammation as well as cellular and humoral immunodeficiency in several cohort studies (Klemmer et al., 1980; Cooper & Macauley, 1982; Daniel et al., 1995, 2001), but not in a case–control study (Colosio et al., 1993). In cohort studies, increased prevalence rates for inflammation and low-grade infections of the skin and subcutaneous tissue, mucous

membranes of the eyes and upper respiratory tract (Klemmer et al., 1980) and more frequent respiratory tract infections (Daniel et al., 2001) have been documented in workers occupationally exposed to pentachlorophenol. T-lymphocyte dysfunction and increased circulating concentrations of cytokines including interleukin-8 (IL-8) have also been documented in workers (n = 188) exposed to pentachlorophenol (Daniel et al., 1995), whereas exposure to pentachlorophenol for more than 6 months was negatively associated with circulating concentrations of IL-2, soluble IL-2R, IL-6, IL-10, interferon-gamma (IFN-γ), tumour necrosis factor-α (TNF-α), transforming growth factor-β2 (TGF-β2), soluble IL-1R antagonist, and soluble intercellular adhesion molecule-1 (ICAM-1) (Daniel et al., 2001). Exposure to pentachlorophenol was associated with a blunted proliferative response to mitogens in those with the highest exposure. Pentachlorophenol exposure has also been linked with pancreatitis in a single study (Cooper & Macauley, 1982). In the only available case–control study (Colosio et al., 1993), no effect was observed on serum immunoglobulins, complement fractions, autoantibodies, or on absolute or differential counts of peripheral blood mononuclear cells.

Human lymphocytes were collected from people living in log homes treated with pentachlorophenol as a preservative, and compared with cells collected from a control group of people not living in log homes (McConnachie & Zahalsky, 1991). Exposed individuals had lower proliferative response to a variety of antigens. In addition, there was an increase in natural-killer cell activity, but only in exposed females.

(b) Human cells in vitro

A variety of studies used isolated human lymphocytes to evaluate the effects of pentachlorophenol on markers of immune response.

In one study in vitro, the lytic function of human natural killer cells was decreased by exposure to pentachlorophenol (10 μM) for 24 hours or more. Lower concentrations of pentachlorophenol required longer incubations to produce similar effects (Nnodu & Whalen; 2008). Similar results were also found in another study that showed that pentachlorophenol (5 μM) decreases the lytic effects of natural killer cells (Reed et al., 2004).

In a study using human peripheral blood lymphocytes treated with pentachlorophenol for 1, 2, and 6 days, pentachlorophenol (10 μM) decreased natural-killer cell binding function (34.6%), and CD11a (21.7%) and CD56 (26.2%) cell-surface proteins (Hurd et al., 2012), indicative of immune suppression. In another study, pentachlorophenol (40–200 μM; either technical or analytical grade) increased cell proliferation in response to antigen, although higher concentrations decreased cell proliferation in isolated lymphocytes from healthy donors (Lang & Mueller-Ruchholtz, 1991). In addition, lymphokine production and immunoglobulin secretion was significantly decreased by both technical- and analytical-grade pentachlorophenol.

(c) Mammalian experimental systems

In mice, a single oral dose of pentachlorophenol (0, 10, 30, or 100 mg/kg) activated the interferon signalling gene network in the liver within 24 hours (Kanno et al., 2013). No effect on inflammation was observed in Mexican hairless dogs treated topically for 7 days with pentachlorophenol (Kimura et al., 1998).

Palmitoylpentachlorophenol, a putative metabolite of pentachlorophenol, induced pancreatic toxicity in rats after a single exposure at 100 mg/kg by gavage (Ansari et al., 1987). The pancreatic lesions observed consisted of focal, spotty vacuolization, loss of pancreatic acini, and acute inflammatory infiltrate.

Several studies evaluated and compared the immunosuppressive effects of technical- and analytical-grade pentachlorophenol in rodents (Kerkvliet et al., 1982a, b, 1985a, b; White & Anderson, 1985; Holsapple et al., 1987; Blakley

et al., 1998). A more recent study by Chen et al. (2013) observed no significant immunosuppressive effects of pentachlorophenol in mice. Others have observed cytokine changes in mice exposed to TCHQ but not to pentachlorophenol, with no changes in immune function (Chang et al., 2003). Elevated serum tumour necrosis factor-α (TNF-α) was observed in mice treated with TCHQ for 25 weeks, but not at earlier time points or in those treated with pentachlorophenol. Neither pentachlorophenol- nor TCHQ-treated mice exhibited changes in serum interleukin-1β (IL-1beta) levels. [The Working Group noted that the immunosuppressive effects of technical-grade pentachlorophenol may be attributable to dioxin contaminants.]

A few studies examined the effects of technical-grade pentachlorophenol in cattle and pigs (Forsell et al., 1981; Hillam & Greichus, 1983; Hughes et al., 1985). No observed effects occurred in lactating cattle exposed to pentachlorophenol for 135 days (Forsell et al., 1981). Technical-grade pentachlorophenol induced a broad spectrum of toxicity in bull calves (Hughes et al., 1985). Histological lesions reported were cortical atrophy in the thymus and squamous metaplasia and hyperkeratous changes in the Meibomian gland of the eyelid. These effects were not observed in animals receiving the purified pentachlorophenol. Pigs exposed to pentachlorophenol at 5, 10, or 15 mg/kg bw for 30 days had decreased lymphocyte counts, and decreased serum gamma globulin and IgG (Hillam & Greichus, 1983).

A pentachlorophenol metabolite, TCHQ, interacts with murine haematopoietic progenitor cells, stimulating the formation of macrophages (Henschler et al., 2001).

(d) Non-mammalian experimental systems

In goldfish (*Carassius auratus*), pentachlorophenol (0.053 and 0.13 mg/L in the water for 14 days) decreased serum IgM concentrations (Chen et al., 2004). In macrophages isolated from goldfish, pentachlorophenol (1–50 µg/mL) decreased *IL-1β* and *TNF-α* mRNA expression and suppressed IgM production in co-cultured B cells at cytotoxic concentrations (Chen et al., 2005).

Technical-grade pentachlorophenol and, to a lesser extent, analytical-grade pentachlorophenol inhibited the respiratory burst of the isolated leukocytes from *Fundulus heteroclitus* (Atlantic killifish) (Roszell & Anderson, 1993). In contrast, analytical-grade pentachlorophenol (0.1–1 µg/L for 14 days) had no effect on immune function in rainbow trout (Shelley et al., 2009).

Treatment with pentachlorophenol (100–1000 ppm) enhanced the resistance of pathogenic bacteria to antibiotics (Chandra & Sankhwar, 2011).

4.3 Data relevant to comparisons across agents and end-points

High-throughput screening data generated by the Toxicity Testing in the 21st Century (Tox21) and Toxicity Forecaster (ToxCast™) research programmes of the government of the USA (Kavlock et al., 2012; Tice et al., 2013) were considered in the assessment of the five chemicals reviewed in *IARC Monographs* Volume 117 (pentachlorophenol, 2,4,6- trichlorophenol, 3,3′,4,4′-tetrachloroazobenzene, aldrin and dieldrin) as well as two metabolite isomers of 2,4,6-trichlorophenol (2,4,5- trichlorophenol and 2,3,6- trichlorophenol). The United States Environmental Protection Agency (EPA) has systematically analysed concentration–response sample-assay pairs from ToxCast and Tox21. The resulting concentration–response models and activity calls have been publicly released via the interactive Chemical Safety for sustainability (iCSS) ToxCast Dashboard (EPA, 2015a, b). Summary matrix files, the ToxCast data analysis pipeline (tcpl) R package and connected database (invitrodb_v1) are also available (EPA, 2015c).

The tcpl R package and associated database enables access to all of the underlying concentration–response data, the analysis decision logic and methods, concentration–response model outputs, activity calls, and activity caution flags.

The Tox21 and ToxCast research programmes have tested more than 8000 and 1800 chemicals, respectively. ToxCast, specifically, has tested 1000 chemicals across the full assay battery in conjunction with ToxCast Phase I and II. The remaining 800 chemicals were tested as part of an endocrine profiling effort that resulted in a subset of assays being tested. For the present volume of the *IARC Monographs*, one chemical had no testing data (3,3′,4,4′-tetrachloroazobenzene), one was tested only in Tox21 assay components, and the remaining chemicals were tested in both ToxCast and Tox21 assays.

Data on the current publicly released ToxCast assay battery, including the Tox21 assays run at the United States National Institutes of Health (NIH), comprise 1192 assay end-points derived from 762 assay components (i.e. readouts) and 359 assays (i.e. experiments). The 359 assays were sourced from 12 vendors or collaborators spanning diverse technological and biological space, including more than 350 gene targets. Roughly a third of the final assay end-points were analysed from biochemical (cell-free) assay formats, with the remainder being cell-based (cell lines, primary cells, and co-cultures) or whole embryo (zebrafish larvae). The biochemical assays have no xenobiotic metabolism capacity, while the cell-based assays have a variable biotransformation capability varying from very limited to moderate. Thus, chemical effects requiring biotransformation to active metabolites may be missed in some or all of the assays in vitro. Relatively uniform testing concentration ranges were used, from low nanomolar up to approximately 100–200 micromolar. Compounds of very low relative molecular mass generally have only low affinity for biomolecular interactions due to limited free energy for binding (Hopkins et al., 2004). Hence screening in vitro at the concentrations used in ToxCast and Tox21 may be insufficient to detect molecular interactions of receptor-type interactions. These compounds of very low relative molecular mass may also have high vapour pressure, which could lead to loss of sample during testing and, thus, failure to reach effective active concentrations.

The Tox21 and ToxCast assays in vitro were selected to cover a broad range of potential toxicity mechanisms and are not specifically focused on carcinogenesis. Therefore, the Working Group of *IARC Monograph*s Volume 112 mapped the assay end-points available at that time to the key characteristics of human carcinogens (IARC, 2017; Smith et al., 2016). The consensus assignments resulted in 263 assay end-points mapped to 7 of 10 "key characteristics" (IARC, 2017). Subsequently, the Working Groups for *IARC Monograph*s Volumes 113, 115, and the present Volume 117 updated these "mappings," including reviewing the additional assay end-points added to Tox21 and ToxCast data since the initial determination. As a result, 25 assay end-points were added to the initial 263 that were mapped to key characteristics, resulting in 288 in total. The assay end-points used, the activity call, and the mapping to "key characteristics" are available as supplemental material to the present volume (Annex 1). The key characteristics listing number of assays included and a brief description are given below.

1. *Is electrophilic or can be metabolically activated*: 31 assay end-points consisting of CYP biochemical activity, and aromatase, which regulates conversion of androgens to estrogens. [The Working Group noted that these assays largely indicate inhibition of CYP activity, and do not directly measure metabolic activation or electrophilicity.]
2. *Is genotoxic*: 10 assay end-points consisting of cellular TP53 induction and DNA repair-sensitive cellular assays. [The Working Group

noted that *TP53* activation can occur in response to a variety of cell stresses in addition to DNA damage.]

3. *Alters DNA repair or causes genomic instability*: 0 assay end-points
4. *Induces epigenetic alterations*: 14 assay end-points including biochemical assays targeting histone deacetylases and other enzymes modifying chromatin, as well as assays for cellular transcription factors involved in epigenetic regulation. [The Working Group noted these end-points have not been extensively validated with reference compounds for epigenetic alterations.]
5. *Induces oxidative stress*: 18 assay end-points, all cellular assays, targeting nuclear erythroid-related factor 2/antioxidant response element (NRF2/ARE), other stress-related transcription factors, and protein upregulation in response to ROS.
6. *Induces chronic inflammation*: 45 assay end-points, mostly using primary human cells, measuring protein expression levels indicative of inflammatory responses, including cytokines, cell adhesion molecules, and nuclear factor kappa-light-chain-enhancer of activated B cells (NFκB).
7. *Is immunosuppressive*: 0 assay end-points.
8. *Modulates receptor-mediated effects*: 93 assay end-points targeting nuclear receptors (e.g. AhR, androgen receptor, estrogen receptor, farnesoid X receptor, peroxisome proliferator-activated receptor, pregnane X receptor, retinoic acid receptor, among others) in cellular assays for transactivation, receptor dimerization, and nuclear translocation, as well as biochemical radioligand-binding assays and coregulatory recruitment assays.
9. *Causes immortalization*: 0 assay end-points.
10. *Alters cell proliferation, cell death, or nutrient supply*: 88 assay end-points measuring cell cycle markers, proliferation, cytotoxicity, and mitochondrial toxicity, using a wide variety of assay formats in cell lines, primary human cells, and developing zebrafish larvae.

For each chemical, the results of the in-vitro assays that represent each "key characteristic" can be compared with the results for a larger compendium of substances with similar in-vitro data, so that a particular chemical can be aligned with other chemicals with similar toxicological effects. Nonetheless, the available assays do not cover the full spectrum of relevant targets, and metabolic capacity in many of the assays is limited, which could account for any absence of bioactivity. Conversely, the presence of bioactivity alone does not definitively imply that the agent exhibits that key characteristic, as the assay data are considered along with other information, both in vivo and in vitro.

Each chemical was assigned an "active" or "inactive" call within each assay end-point based on the normalized concentration–response data in the ToxCast database using methods published previously (Sipes et al., 2013). ToxCast/Tox21 tested a broad range of screening concentrations designed to identify whether compounds elicited bioactivity and at what potency. In the analysis by the Working Group, each "active" was given a value of 1, and each "inactive" was given a value of 0. Thus, by assigning all active compounds a value of 1, the "potency" estimates from the concentration–response data were not explicitly used for all subsequent analyses.

A brief summary of potentially significant outcomes for each of the substances relevant to the present volume follows (see also Table 4.8).

4.3.1 Specific effects across the "key characteristics" based on data from high-throughput screening in vitro

A summary is given below for each relevant compound (see also Table 4.8).

Table 4.8 Summary of activity of compounds reviewed in *IARC Monographs* Volume 117 and tested in ToxCast high-throughput screening assays

Key characteristic (No. of assay end-points)	No. of active end-points / No. of end-points tested					
	Pentachlorophenol	2,4,6-Trichlorophenol	2,4,5-Trichlorophenol	2,3,6-Trichlorophenol	Aldrin	Dieldrin
Characteristic (1) *Is electrophilic or can be metabolically activated* (31 end-points)						
CYP inhibition (29 end-points)	0/9	0/9	1/9	NT	0/9	2/9
Aromatase inhibition (2 end-points)	1/2	0/2	0/2	0/1	0/2	1/2
Characteristic (2) *Is genotoxic* (10 end-points)						
P53 activation (9 end-points)	6/8	0/8	1/8	0/6	3/8	0/8
DNA damage (1 end-point)	0/1	0/1	0/1	0/1	0/1	0/1
Characteristic (4) *Induces epigenetic alterations* (14 end-points)						
DNA binding (7 end-points)	5/7	1/7	3/7	0/7	1/7	0/7
Transformation catalyst (7 end-points)	0/6	0/6	0/6	NT	0/6	0/6
Characteristic (5) *Induces oxidative stress* (18 end-points)						
Oxidative stress (7 end-points)	0/5	0/5	3/5	0/1	4/5	1/5
Oxidative stress marker (6 end-points)	4/6	3/6	4/6	1/6	3/6	3/6
Metalloproteinase (5 end-points)	NT	NT	NT	NT	1/5	NT
Characteristic (6) *Induces chronic inflammation* (45 end-points)						
NFκB (2 end-points)	1/2	0/2	0/2	0/2	2/2	0/2
Cell adhesion (14 end-points)	0/14	0/14	0/14	NT	0/14	0/14
Cytokines (29 end-points)	0/29	0/29	1/29	NT	0/29	1/29
Characteristic (8) *Modulates receptor-mediated effects* (93 end-points)						
ER (18 end-points)	2/18	2/18	4/18	0/6	4/18	4/18
AHR (2 end-points)	2/2	1/2	0/2	1/2	0/2	0/2
Other nuclear receptors (29 end-points)	3/29	0/29	6/29	0/20	4/29	3/29
RAR (6 end-points)	2/6	0/6	3/6	0/4	2/6	3/6
PPAR (12 end-points)	5/12	3/12	3/12	2/8	1/12	1/12
PXR (7 end-points)	4/7	1/7	2/7	1/6	3/7	3/7
AR (12 end-points)	3/12	0/12	2/12	0/9	1/12	3/12
FXR (7 end-points)	2/7	0/7	0/7	0/3	2/7	3/7

Table 4.8 (continued)

Key characteristic (No. of assay end-points)	No. of active end-points / No. of end-points tested					
	Pentachlorophenol	**2,4,6-Trichlorophenol**	**2,4,5-Trichlorophenol**	**2,3,6-Trichlorophenol**	**Aldrin**	**Dieldrin**
Characteristic (10) ***Alters cell proliferation, cell death, or nutrient supply*** (88 end-points)						
Cytotoxicity (49 end-points)	18/41	2/40	14/40	0/21	20/40	10/40
Mitochondrial toxicity (14 end-points)	1/10	1/10	2/10	1/2	2/10	1/10
Cell cycle marker (21 end-points)	5/18	1/18	7/18	0/6	4/18	2/18
Proliferation (4 end-points)	0/4	0/4	0/4	NT	0/4	0/4

AHR, aryl hydrocarbon receptor; AR, androgen receptor; CYP, cytochrome; ER, estrogen receptor; FXR, farnesoid X receptor; NT, not tested; PPAR, peroxisome proliferator-activated receptor; PXR, pregnane X receptor; RAR, retinoic acid receptor; TCoBQ, tetrachloro-*ortho*-benzoquinone (tetrachloro-1,2-benzoquinone); TCpBQ, tetrachloro-*para*-benzoquinone (tetrachloro-1,4-benzoquinone)

(a) Pentachlorophenol

Pentachlorophenol (CAS No. 87-86-5) was tested across the full assay suite of ToxCast and Tox21, with data available on 870 assay end-points. The results for the 255 assay end-points mapped to key characteristics are summarized in Table 4.8. The assays with most activity were related to TP53 in human liver or intestinal cell lines, transcription factor activation indicative of DNA-binding, transcription factors that are markers of oxidative stress (in particular NRF2), a variety of receptor-mediated effects, and cytotoxicity and cell cycle markers. The activity across multiple nuclear receptor assays is difficult to interpret because of inconsistency across assay platforms (e.g. Attagene (ATG) vs Nova screen (NVS) vs Tox21). However, two assays for anti-estrogenic activity were consistent, and corroborate data on receptor-mediated effects (Section 4.2.3). In addition, pentachlorophenol showed activity in many cytotoxicity assays in cell lines as well as in primary human cells, which may have confounded results either directly through cell death or indirectly through generation of lipid peroxidation products. Finally, it cannot be ruled out that the activity in the AhR assay might be related to dioxin contamination.

(b) 2,4,6-Trichlorophenol and metabolites

2,4,6-Trichlorophenol (CAS No. 88-06-2) and one of its metabolites, 2,4,5-trichlorophenol (CAS No. 95-95-4) were tested across the full assay suite of ToxCast and Tox21, with data available on 883 assay end-points for both compounds. Another metabolite, 2,3,6-trichlorophenol (CAS No. 933-75-5), was tested in a more limited suite of assays, with data available on 276 assay end-points. The results for the assay end-points mapped to key characteristics are summarized in Table 4.8. Of the three isomers, 2,4,5-trichlorophenol was the most active, specifically in assays related to transcription-factor activation indicative of DNA binding, oxidative stress responses, as well as transcription factors that are markers of oxidative stress, a variety of receptor-mediated effects, and cytotoxicity and cell cycle markers. 2,4,6-Trichlorophenol was less active, but many of its effects overlapped with those of 2,4,5-trichlorophenol. 2,3,6-Trichlorophenol was the least active. Of particular note, were assays related to oxidative stress, since in several cases the "inactive" calls were for earlier time points in assays that gave "active" calls at later time points. Such a time delay is consistent with the need for metabolic activation. In addition, 2,4,5-trichlorophenol was active in all the oxidative stress assays in which 2,4,6-trichlorophenol was active. The activity across multiple nuclear-receptor assays was difficult to interpret because most active calls were for ATG assays, while many of the NVS binding assays and the corresponding Tox21 assays gave inactive calls for the same receptor. In addition, 2,4,5-trichlorophenol, which had the most activity across these assays, also exhibited the most activity across cytotoxicity assays in cell lines as well as in primary human cells. Thus it is possible that the results for modulation of nuclear receptors may have been confounded either directly through cell death or indirectly through generation of lipid peroxidation products.

(c) 3,3′,4,4′-Tetrachloroazobenzene

3,3′,4,4′-Tetrachloroazobenzene (CAS No. 14047-09-7) was not tested.

(d) Aldrin and dieldrin

Aldrin (CAS No. 309-00-2) and dieldrin (CAS No. 60-57-1) were tested across the full assay suite of ToxCast and Tox21, with data available on 879 and 878 assay end-points, respectively. The results for the assay end-points mapped to key characteristics are summarized in Table 4.8. Both compounds were active in assays related to oxidative stress responses, as well as transcription factors that are markers of oxidative stress, a variety of receptor mediated

effects, and cytotoxicity and cell cycle markers. Of particular note were assays related to oxidative stress, since several of the "inactive" calls were for earlier time points in assays that gave "active" calls or were active at later time points, or were active for aldrin. Aldrin and dieldrin were active in three out of six assays for transcription factor markers of oxidative stress, two of which were common to the agents. The activity across multiple nuclear-receptor assays were difficult to interpret because most of the activity was in ATG assays, whereas the corresponding NVS binding assays and the corresponding Tox21 assays for the same receptors were either inactive or active for the opposite direction (antagonism vs agonism). In addition, aldrin, and to a lesser extent dieldrin, also exhibited the most activity across cytotoxicity assays in cell lines as well as primary human cells. Thus it is possible that the results for modulation of nuclear receptors may have been confounded either directly through cell death or indirectly through generation of lipid peroxidation products.

4.3.2 Integrating effects across end-points and chemicals

To integrate the data across individual assay end-points into the cumulative score for each key characteristic, the toxicological prioritization index (ToxPi) approach (Reif et al., 2010) and associated software (Reif et al., 2013; Filer et al., 2014) were used. In the Working Group's analyses, the ToxPi score provides a measure of the relative potential for a chemical to be associated with a "key characteristic". ToxPi is a dimensionless index score that integrates multiple different assay results and displays them visually. Within each subset of end-points ("slice"), data are translated into ToxPi slice-wise scores for all compounds as detailed below and in the publications describing the approach and the associated software package (Reif et al., 2013). Within each individual slice for a given chemical, the distance from the origin represents the relative chemical-elicited activity of the component assays (i.e. slices extending farther from the origin were associated with "active" calls on more assays). The overall score for a chemical, visualized as a radial ToxPi profile, is the aggregation of all slice-wise scores.

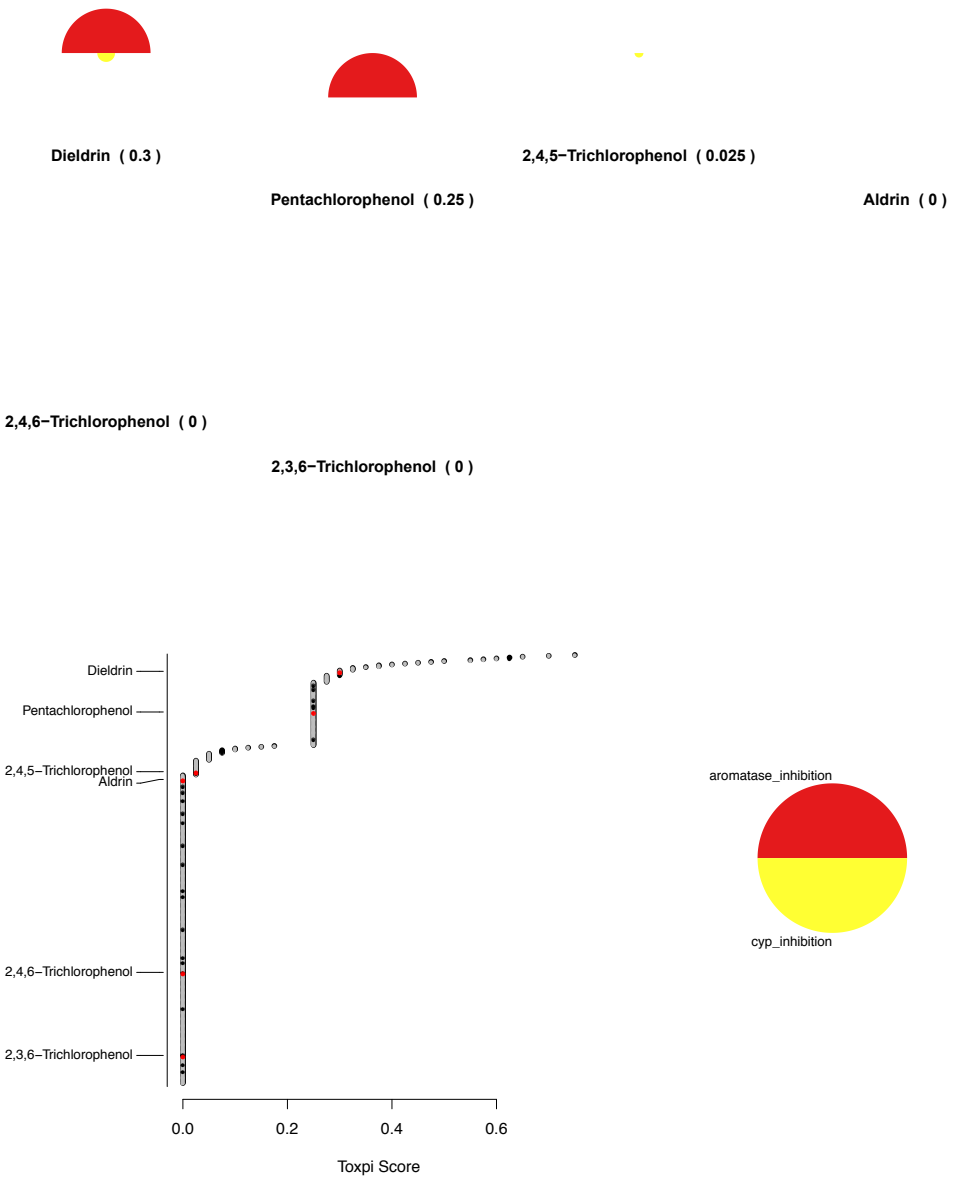
The relative effects of pentachlorophenol, 2,4,6-trichlorophenol (and its metabolite isomers 2,4,5-trichlorophenol and 2,3,6-trichlorophenol), aldrin, and dieldrin were compared with those of 489 (out of more than 800 total) chemicals previously evaluated by the *IARC Monographs* for which Tox21/ToxCast assay end-point data were available (not including chemicals in the present Volume 117 that have been evaluated previously). Of these 489 chemicals, 30 are classified in Group 1 (*carcinogenic to humans*), 47 are in Group 2A (*probably carcinogenic to humans*), 163 are in Group 2B (*possibly carcinogenic to humans)*, 248 are in Group 3 (*not classifiable as to its carcinogenicity to humans*), and 1 is in Group 4 (*probably not carcinogenic to humans).*

The results are presented in a dot plot as a rank order of all compounds in the analysis arranged in the order of their relative activity. The relative positions of pentachlorophenol, 2,4,6-trichlorophenol (and its metabolite isomers 2,4,5-trichlorophenol and 2,3,6-trichlorophenol), aldrin, and dieldrin (i.e. all chemicals evaluated in Volume 117) in the ranked list are also shown on the *y*-axis. The legend key (lower right graphic in each plot) lists components of the ToxPi chart as subcategories that comprise assay end-points in each characteristic. The ToxPi profile and numeric score for each of the chemicals evaluated in Volume 117 are shown above the ranking chart.

Specific observations across chemicals are as follows:

- Characteristic (1) *Is electrophilic or can undergo metabolic activation* (Fig. 4.2): Dieldrin and pentachlorophenol ranked the

Fig. 4.2 ToxPi rankings using ToxCast assay end-points mapped to metabolic activation

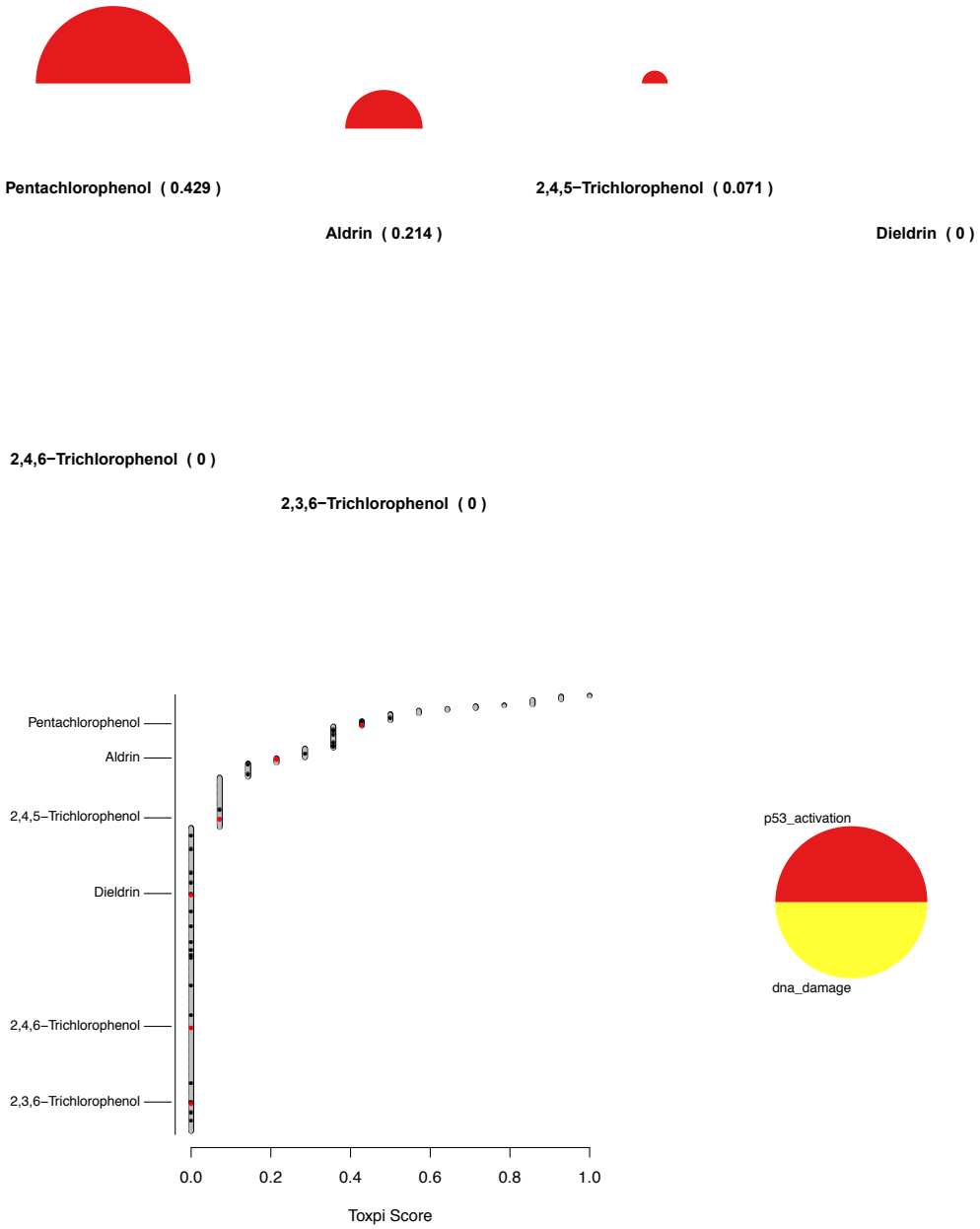


Across the top, the ToxPi shapes and scores for characteristic 1 (is electrophilic or can undergo metabolic activation) are shown from the six chemicals pentachlorophenol, 2,4,6-trichlorophenol (and its metabolite isomers 2,4,5-trichlorophenol and 2,3,6-trichlorophenol), aldrin, and dieldrin tested in the ToxCast programme that are in the present *IARC Monographs* Volume 117. On the lower left, the relative ranks of these chemicals (red dots) are shown (*y*-axis) with respect to their ToxPi scores (*x*-axis) compared with the 489 chemicals previously evaluated by IARC (grey dots, with chemicals classified in Group I [carcinogenic to humans] as black dots). On the lower right, the subcategories of the ToxPi chart, as well as their respective colour coding are shown.

highest among the chemicals in Volume 117, with the other chemicals being evaluated having minimal activity. However, even for dieldrin and pentachlorophenol, the ToxPi score was in the lower half of the range across all the chemicals evaluated by IARC. The highest ranking chemical is malathion, with a ToxPi score of 0.75.

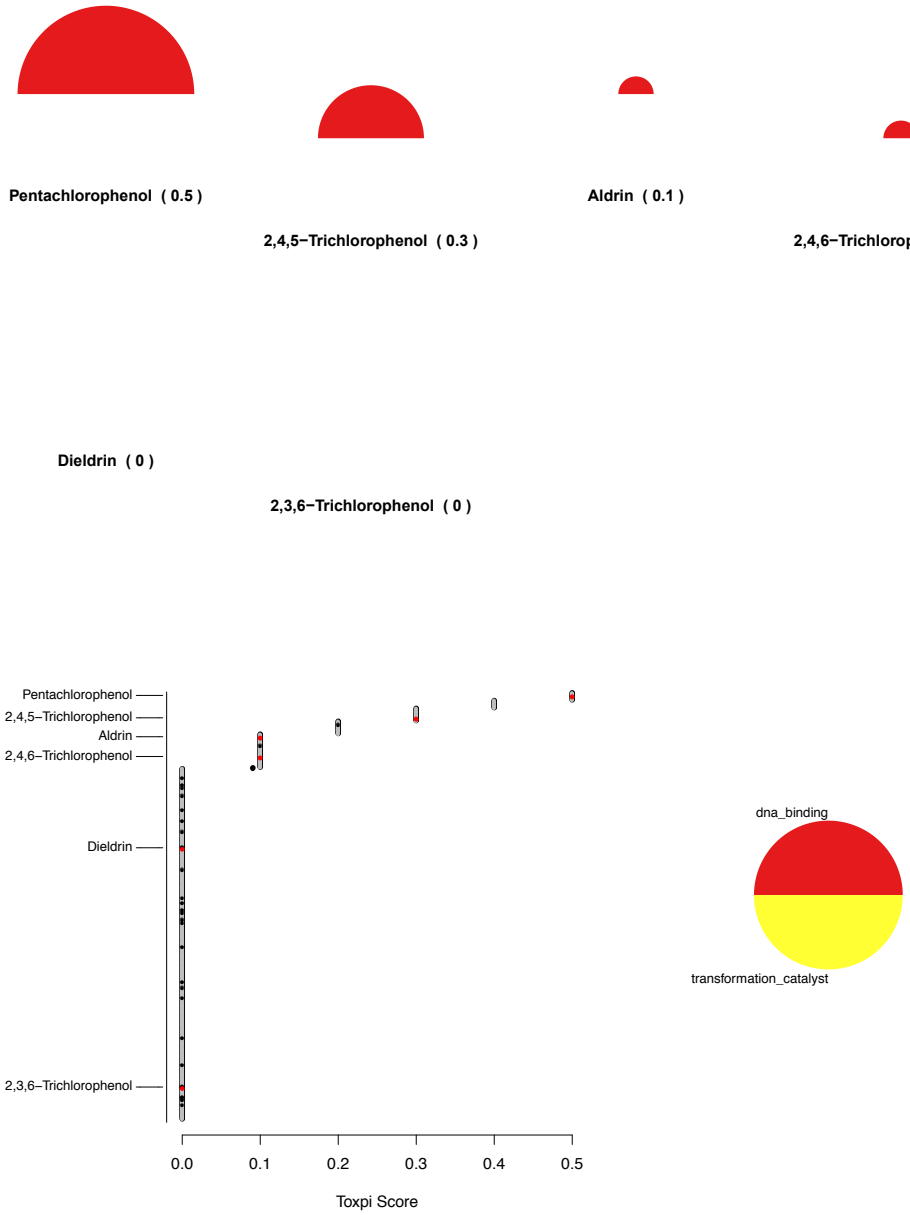
- Characteristic (2) *Is genotoxic* (Fig. 4.3): Pentachlorophenol and aldrin ranked the highest among the chemicals in Volume 117, with the other chemicals being evaluated having minimal activity. However, all the ToxPi scores for chemicals evaluated in this volume were in the lower half of the range across all the chemicals evaluated by IARC. The highest ranking chemical is Michler's ketone, with a ToxPi score of 1.0.
- Characteristic (4) *Induces epigenetic alterations* (Fig. 4.4): Pentachlorophenol and 2,4,5-trichlorophenol ranked the highest among the chemicals in Volume 117, with the other chemicals being evaluated having minimal activity. In addition, pentachlorophenol had the highest ranking ToxPi score of 0.5, jointly with eight other chemicals previously evaluated by IARC. Seven of these other eight chemicals additionally had the same ToxPi shape, with all the activity related to DNA binding, rather than a transformation catalyst.
- Characteristic (5) *Induces oxidative stress* (Fig. 4.5): Aldrin and 2,4,5-trichlorophenol ranked the highest among the chemicals in Volume 117, but dieldrin, pentachlorophenol, and 2,4,6-trichlorophenol also showed activity. Aldrin was ranked sixth, and 2,4,5-trichlorophenol ranked twenty-third overall among IARC chemicals, with chlordane having the highest score of 0.58. From the ToxPi shape, it is clear that most of the chemicals showed activity for oxidative stress markers, but aldrin and 2,4,5-trichlorophenol had relatively high activity in measures of stress responses.
- Characteristic (6) *Induces chronic inflammation* (Fig. 4.6): Aldrin and pentachlorophenol ranked the highest among the chemicals in Volume 117, with the other chemicals being evaluated having minimal activity. The highest ranked chemical was tris(2,3-dibromopropyl) phosphate with a ToxPi score of 0.83, more than double the score for any other chemical evaluated by IARC.
- Characteristic (8) *Modulates receptor-mediated effects* (Fig. 4.7): Pentachlorophenol, dieldrin, 2,4,5-trichlorophenol, and aldrin were all highly ranked in terms of activity in assay end-points mapped to receptor-mediated effects, with pentachlorophenol having the second highest ToxPi score among chemicals evaluated by IARC. Aldrin is at the top 95th percentile of ToxPi scores, with a ranking of 26 out of 495 compounds. Moreover, the relative promiscuity of these compounds is evident from the shape of the ToxPi, which shows relatively high activity across multiple categories of receptors. The overall highest ranking chemical is kepone (chlordecone), with a ToxPi score of 0.582, only slightly higher than that for pentachlorophenol.
- Characteristic (10) *Alters cell proliferation, cell death, or nutrient supply* (Fig. 4.8): 2,4,5-trichlorophenol, aldrin, and pentachlorophenol ranked the highest among the chemicals in Volume 117, all above the top 95th percentile rankings. These chemicals also had similar ToxPi shapes, with most of the activity related to cytotoxicity and cell cycle markers, less activity in mitochondrial toxicity, and none in proliferation. Dieldrin had a somewhat lower score (but similar shape), and there was minimal activity for 2,4,6-trichlorophenol and 2,3,6-trichlorophenol. The highest ranked chemical overall is 3,3′,5,5′-tetrabromobisphenol A, with a

Fig. 4.3 ToxPi rankings using ToxCast assay end-points mapped to genotoxicity



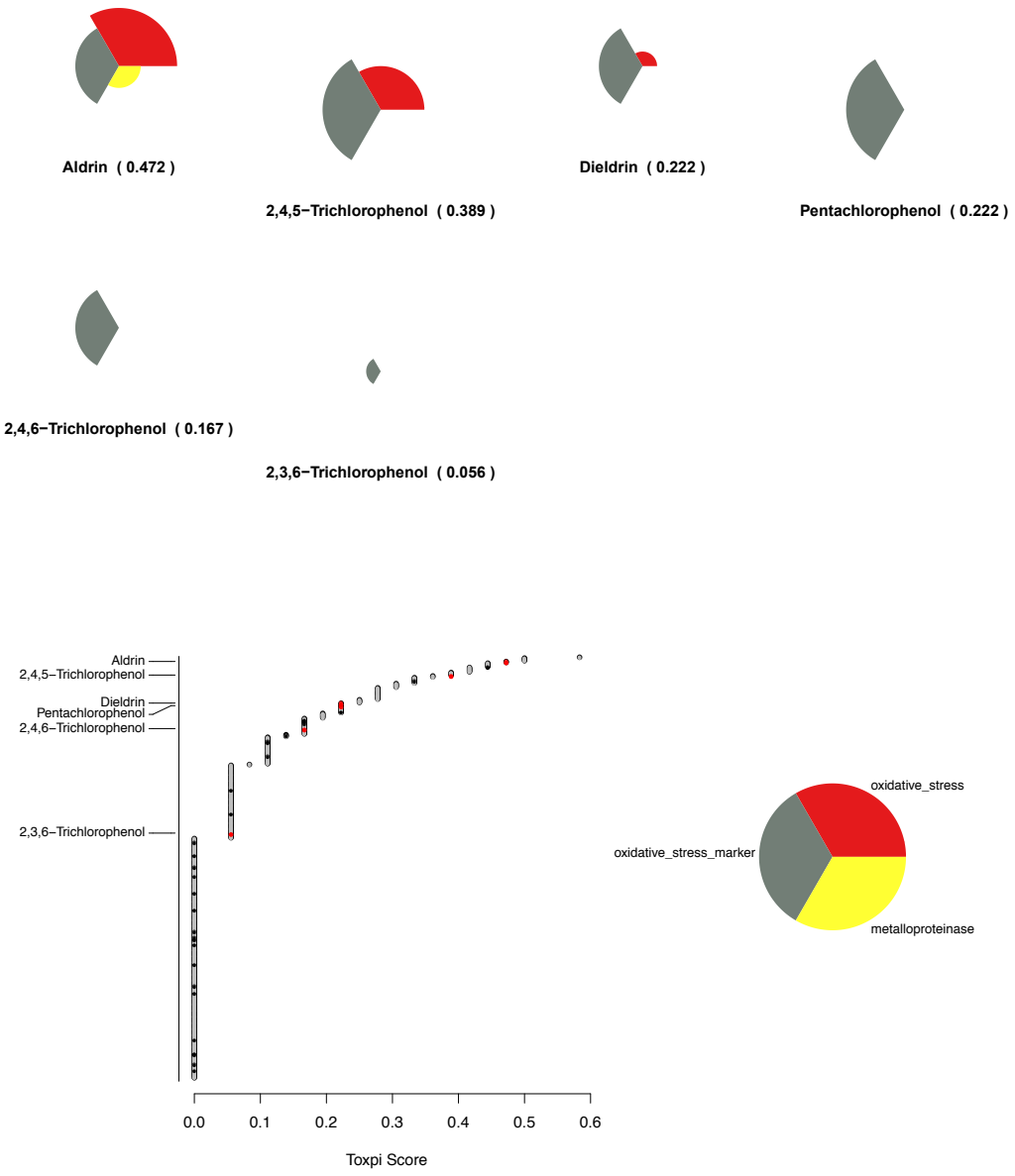
Across the top, the ToxPi shapes and scores for characteristic 2 (is genotoxic) are shown from the six chemicals pentachlorophenol, 2,4,6-trichlorophenol (and its metabolite isomers 2,4,5-trichlorophenol and 2,3,6-trichlorophenol), aldrin, and dieldrin tested in the ToxCast programme that are in the present *IARC Monographs* Volume 117. On the lower left, the relative ranks of these chemicals (red dots) are shown (*y*-axis) with respect to their ToxPi scores (*x*-axis) compared with the 489 chemicals previously evaluated by IARC (grey dots, with chemicals classified in Group I [carcinogenic to humans] as black dots). On the lower right, the subcategories of the ToxPi chart, as well as their respective colour coding are shown.

Fig. 4.4 ToxPi rankings using ToxCast assay end-points mapped to epigenetic alterations



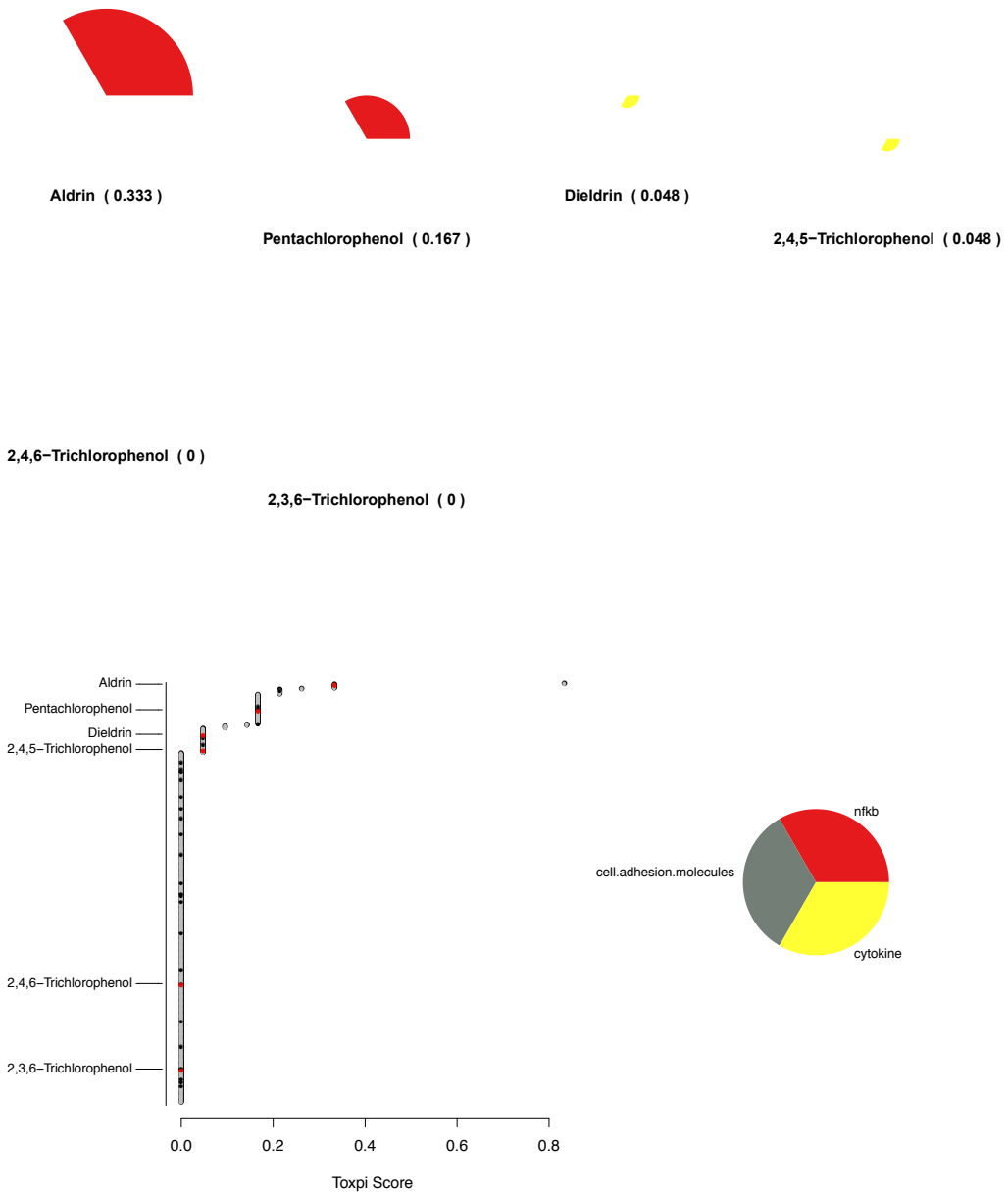
Across the top, the ToxPi shapes and scores for characteristic 4 (induces epigenetic alterations) are shown from the six chemicals pentachlorophenol, 2,4,6-trichlorophenol (and its metabolite isomers 2,4,5-trichlorophenol and 2,3,6-trichlorophenol), aldrin, and dieldrin tested in the ToxCast programme that are in the present *IARC Monographs* Volume 117. On the lower left, the relative ranks of these chemicals (red dots) are shown (*y*-axis) with respect to their ToxPi scores (*x*-axis) compared with the 489 chemicals previously evaluated by IARC (grey dots, with chemicals classified in Group I [carcinogenic to humans] as black dots). On the lower right, the subcategories of the ToxPi chart, as well as their respective colour coding are shown.

Fig. 4.5 ToxPi rankings using ToxCast assay end-points mapped to oxidative stress markers



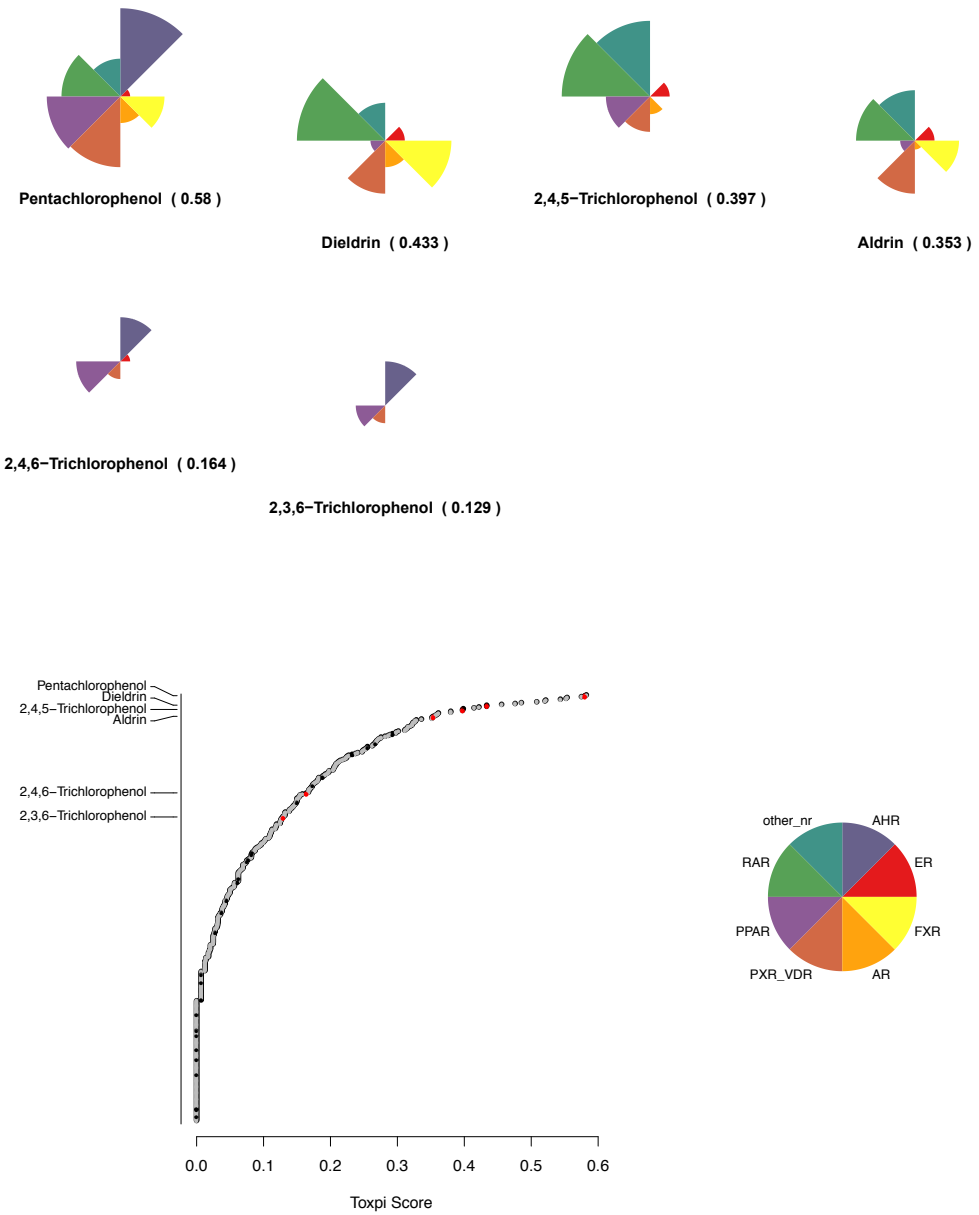
Across the top, the ToxPi shapes and scores for characteristic 5 (induces oxidative stress) are shown from the six chemicals pentachlorophenol, 2,4,6-trichlorophenol (and its metabolite isomers 2,4,5-trichlorophenol and 2,3,6-trichlorophenol), aldrin, and dieldrin tested in the ToxCast programme that are in the present *IARC Monographs* Volume 117. On the lower left, the relative ranks of these chemicals (red dots) are shown (*y*-axis) with respect to their ToxPi scores (*x*-axis) compared with the 489 chemicals previously evaluated by IARC (grey dots, with chemicals classified in Group I [carcinogenic to humans] as black dots). On the lower right, the subcategories of the ToxPi chart, as well as their respective colour coding are shown.

Fig. 4.6 ToxPi rankings using ToxCast assay end-points mapped to chronic inflammation



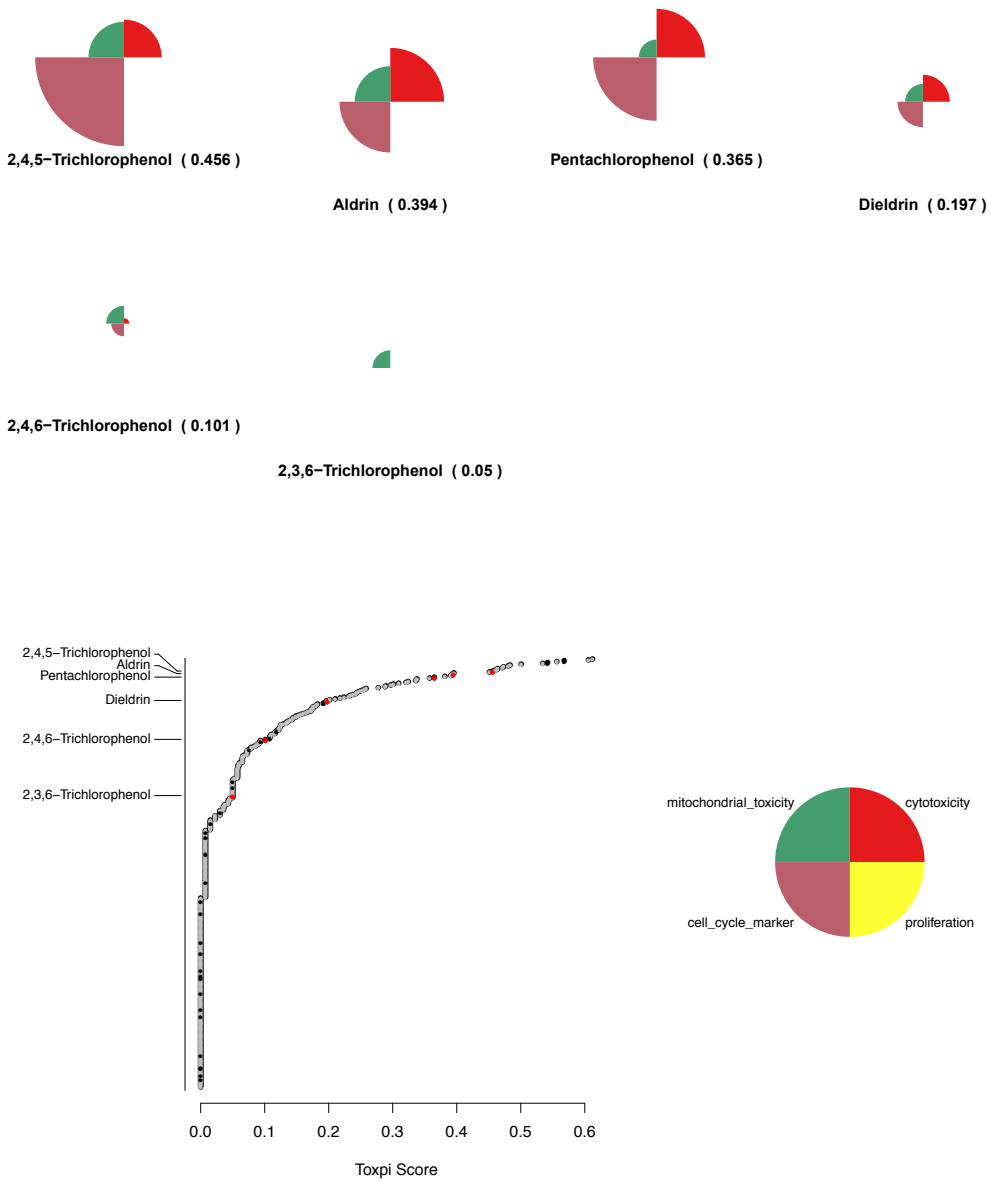
Across the top, the ToxPi shapes and scores for characteristic 6 (induces chronic inflammation) are shown from the six chemicals pentachlorophenol, 2,4,6-trichlorophenol (and its metabolite isomers 2,4,5-trichlorophenol and 2,3,6-trichlorophenol), aldrin, and dieldrin tested in the ToxCast programme that are in the present *IARC Monographs* Volume 117. On the lower left, the relative ranks of these chemicals (red dots) are shown (*y*-axis) with respect to their ToxPi scores (*x*-axis) compared with the 489 chemicals previously evaluated by IARC (grey dots, with chemicals classified in Group I [carcinogenic to humans] as black dots). On the lower right, the subcategories of the ToxPi chart, as well as their respective colour coding are shown.

Fig. 4.7 ToxPi rankings using ToxCast assay end-points mapped to modulation of receptor-mediated effects



Across the top, the ToxPi shapes and scores for characteristic 7 (modulates receptor-mediated effects) are shown from the six chemicals pentachlorophenol, 2,4,6-trichlorophenol (and its metabolite isomers 2,4,5-trichlorophenol and 2,3,6-trichlorophenol), aldrin, and dieldrin tested in the ToxCast programme that are in the present *IARC Monographs* Volume 117. On the lower left, the relative ranks of these chemicals (red dots) are shown (*y*-axis) with respect to their ToxPi scores (*x*-axis) compared with the 489 chemicals previously evaluated by IARC (grey dots, with chemicals classified in Group I [carcinogenic to humans] as black dots). On the lower right, the subcategories of the ToxPi chart, as well as their respective colour coding are shown.

Fig. 4.8 ToxPi rankings using ToxCast assay end-points mapped to cell proliferation, death, or nutrient supply



Across the top, the ToxPi shapes and scores for characteristic 10 (alters cell proliferation, cell death, or nutrient supply) are shown from the six chemicals pentachlorophenol, 2,4,6-trichlorophenol (and its metabolite isomers 2,4,5-trichlorophenol and 2,3,6-trichlorophenol), aldrin, and dieldrin tested in the ToxCast programme that are in the present *IARC Monographs* Volume 117. On the lower left, the relative ranks of these chemicals (red dots) are shown (*y*-axis) with respect to their ToxPi scores (*x*-axis) compared with the 489 chemicals previously evaluated by IARC (grey dots, with chemicals classified in Group I [carcinogenic to humans] as black dots). On the lower right, the subcategories of the ToxPi chart, as well as their respective colour coding are shown.

score of 0.61, and also a similar shape in that cytotoxicity and cell cycle markers make the greatest contribution, with additional contribution from mitochondrial toxicity.

Whereas examining each chemical's activity individually gives a sense of "absolute" activity, this comparison across chemical provides important context with respect to "relative" activity. Overall, this comparison across chemicals demonstrates that several chemicals evaluated in the present volume – pentachlorophenol, aldrin, dieldrin, and 2,4,5-trichlorophenol, a metabolite of 2,4,6-trichlorophenol – rank very highly with respect to assays mapped to the key characteristics of cytotoxicity, receptor modulation and, to a lesser extent, oxidative stress. However, the results of receptor modulation need to be interpreted with caution, since in some cases the results are not consistent across assay platforms for the same receptor, and because they can be confounded by cytotoxicity.

4.4 Susceptibility

No studies in humans were available to the Working Group.

One study in experimental animals examined the role of oxidative stress in the carcinogenicity of pentachlorophenol, using *Nrf2* knockout mice (Tasaki et al., 2014). Alterations in the Nrf2 pathway in mice affected development of cholangiocarcinoma after dietary exposure to pentachlorophenol at 1200 ppm. The wildtype mice did not develop cholangiocarcinomas.

4.5 Other adverse effects

4.5.1 Humans

Several epidemiological studies have examined non-cancer health effects in populations exposed to pentachlorophenol. Several studies have reported haematological effects in populations exposed to pentachlorophenol (Roberts, 1983; McConnachie & Zahalsky, 1991; Colosio et al., 1993). These effects range from aplastic anaemia to increased activation of T cells, increased incidence of autoimmunity, and immunosuppression and B-cell dysregulation. Neurological effects, such as nausea, lethargy, and peripheral neuropathies, have also been reported (Jorens & Schepens, 1993). Reported hepatic effects include increases in serum bile acids (Colosio et al., 1993). Begley et al. (1977) found depressed creatinine clearance and phosphorus reabsorption values in 18 workers exposed to pentachlorophenol, suggesting reduced glomerular filtration rate and tubular function. A few small case reports describing acute poisonings to pentachlorophenol identified a wide range of symptoms, including fever, hepatotoxicity and neurological symptoms (Wood et al., 1983; Walls et al., 1998). Chloracne was also a common finding in workers exposed to pentachlorophenol (Lambert et al., 1986; O'Malley et al., 1990; Leet & Collins, 1991).

Dahlgren et al. (2003) reported increases in the prevalence of bronchitis and asthma in a population of residents near a wood treatment plant who had sustained prolonged low-level exposure to pentachlorophenol and other wood-processing waste chemicals. These results may suggest impacts on the immune system.

Dimich-Ward et al. (1996) followed children of fathers who had worked in British Columbia sawmills for 1 year or more. The population consisted of 19 675 children of 9512 fathers. The study found an increased risk of congenital anomalies of the eye, with no associations for low birth weight, prematurity, still births, or neonatal deaths.

4.5.2 Experimental systems

In rats and mice, the liver is a target organ for pentachlorophenol, with a range of effects reported, including increased liver weight,

hepatocellular hypertrophy, and vacuolization (Kerkvliet et al., 1982a, b; Umemura et al., 1996; NTP, 1999). Necrosis, periportal fibrosis, and hepatocellular degeneration were seen at high doses of pure or technical-grade pentachlorophenol in rodents (Kerkvliet et al., 1982a, b; NTP, 1999). Mild to moderate renal toxicity (e.g. increased kidney weights and blood urea nitrogen) has been observed in rodents with long-term exposure to pure or technical-grade pentachlorophenol (Kimbrough & Linder, 1978; Nishimura et al., 1980; Blakley et al., 1998) but is infrequently accompanied by histopathological changes in the kidney.

5. Summary of Data Reported

5.1 Exposure data

Technical-grade pentachlorophenol is composed of approximately 90% pentachlorophenol and 10% contaminants, including other chlorophenols and various dioxin and furan congeners (primarily hexa-, hepta-, and octa- congeners). Pentachlorophenol and its salts have been widely used as herbicide, algicide, defoliant, wood preservative, germicide, fungicide, and molluscicide. Pentachlorophenol has been classified as a persistent organic pollutant under the Stockholm Convention, which requires parties to take measures to eliminate its production and use. Pentachlorophenol is banned for most uses in North America and Europe, but exceptions exist for heavy duty wood preservation, such as treating utility poles. Continued use in other parts of the world has been reported, such as for cleaning fish ponds to control schistosomiasis vectors in Asia.

Occupational exposure to pentachlorophenol has been measured in workers involved in the manufacture of pentachlorophenol and other chlorophenols, sawmill workers, agricultural workers, workers involved in treating wood products, electrical-utility workers, and waste-incinerator workers. Pentachlorophenol exposures were generally highest in workers directly involved in treating wood or who had direct contact with the treated product, with mean urinary concentrations often exceeding 100 µg/L. The general population may be exposed to pentachlorophenol from proximity to treated wood products, from contaminated food and waters, from incinerator emissions, and from contact with leather and textiles treated with chlorophenols. Median urinary concentrations of pentachlorophenol measured between the 1970s and 2000s in the general population ranged from < 1 to 25 µg/L.

5.2 Human carcinogenicity data

In its evaluation of the epidemiological studies reporting on cancer risks associated with exposure to pentachlorophenol, the Working Group identified four reports from occupational cohorts and seven reports from population-based case–control studies. It was noted that interpretation of the results of all studies with respect to the carcinogenicity of pentachlorophenol was complicated by contamination with dioxin and furan, as well as co-exposures to other chlorophenols. Of particular interest was the contaminant 2,3,7,8-tetrachlorodibenzo-*para*-dioxin (TCDD), an IARC Group 1 carcinogen, which is not found in significant levels in pentachlorophenol; however, a number of the other higher chlorinated dioxins of substantially lower potency are characteristic of the pattern of contamination, including a range of hexachlorodibenzo-*para*-dioxin (HxCDD), heptachlorodibenzo-*para*-dioxin (HpCDD), and octachlorodibenzo-*para*-dioxin (OCDD) congeners. The studies that the Working Group found most informative were cohort studies that dealt with this issue by using high-quality exposure assessment techniques. These techniques included estimation of cumulative dermal

exposure to pentachlorophenol in a cohort study of Canadian sawmill workers, and measurement of the profile of dioxin congeners in serum to differentiate between chemicals in a cohort study of chemical-company workers. Three or more independent studies reported results for evaluation of risk of non-Hodgkin lymphoma (NHL), multiple myeloma, kidney, soft tissue sarcoma, and cancer of the lung, while cancer of the liver was reported in only one study. The cohort study of sawmill workers was considered to be a key investigation because of its relatively large size and high-quality exposure assessment, and the analysis of both mortality and incidence. Although considerably smaller and including only mortality follow-up, the chemical-company and National Institute for Occupational Safety and Health (NIOSH) cohort studies were both considered informative due to the quality of the exposure assessment and the length of follow-up.

5.2.1 NHL and other haematopoietic cancers

An elevated risk of NHL after exposure to pentachlorophenol was reported in all four cohort studies, and in three independent case–control studies, two from Sweden and one from New Zealand. In most studies, the increased risks for the most highly exposed workers were statistically significant and at least 2-fold. In the study from Canada, a statistically significant trend with estimated cumulative dermal exposure to pentachlorophenol was observed. In the chemical-company cohort analyses, risk in the subcohort exposed to pentachlorophenol (but not 2,4,5-trichlorophenol) was significantly elevated. In addition, a statistically significant risk was observed in the entire cohort in those with high exposure to the HxCDD, HpCDD, and OCDD congeners that can be considered as markers of exposure to pentachlorophenol as used in industry. An elevated but not statistically significant risk was observed for exposure to TCDD, although TCDD levels were lower in the pentachlorophenol subcohort than in the 2,4,5-trichlorophenol subcohort. A non-significantly increased risk of mortality due to NHL was found in the NIOSH study of pentachlorophenol-manufacturing workers exposed to pentachlorophenol but not trichlorophenol. All three case–control studies reported excess risks of NHL with exposure to pentachlorophenol, although there was less clarity on the extent to which the risk can be attributed solely to exposure to pentachlorophenol in these studies due to the use of job titles or self-reported exposure.

The Canadian sawmill study found a similar statistically significant trend in incidence of multiple myeloma with increasing cumulative dermal exposure to pentachlorophenol, and non-significant excess risks were observed in both the NIOSH cohort and in New Zealand fencing workers, but not in the chemical-company cohort.

Because of the consistent associations observed in several studies in different countries, and the observation of either exposure–response trends or the highest risk in the highest exposure category in two occupational cohort studies with high-quality exposure assessments, the Working Group concluded that the data demonstrated a causal association between NHL and exposure to pentachlorophenol, such that chance, bias and confounding can be ruled out with reasonable confidence. While the numbers were small in studies of multiple myeloma, which is now classified as a subtype of NHL, the increased risks observed in three studies lend support to this conclusion.

5.2.2 Other cancers

For other cancer sites, the results observed were generally not statistically significant or not consistent across studies. Elevated risk of cancer of the kidney was reported in three cohort studies, with a significant trend in Canadian sawmill workers; however, the numbers of cases

were small in all studies. Excess risk of cancer of the lung was observed in the pentachlorophenol-only subcohort in the NIOSH study, but there was no excess in either the Canadian sawmill workers or chemical-company cohorts. A statistically significant excess of soft tissue sarcoma was observed in one case–control study in Sweden, but no excess was observed in either the Canadian cohort or a New Zealand case–control study. Mortality from cancer of the liver was investigated in the Canadian cohort and, although numbers were small, a substantial excess risk was observed; however, there was no other support for this finding.

Overall, the Working Group concluded that there was scarce and inconsistent evidence of carcinogenicity after exposure to pentachlorophenol for these other cancer sites.

5.3 Animal carcinogenicity data

In mice, there were six studies of carcinogenicity with pentachlorophenol: five feeding studies, and one skin application study in transgenic females. The five feeding studies included two studies in males and females, two studies in transgenic males, and one study in transgenic males and females. There were three initiation–promotion studies with pentachlorophenol tested as a promoter in males. There were three co-carcinogenicity studies in males or females.

In mice, in one feeding study cited in one report, technical-grade pentachlorophenol increased the incidence of hepatocellular adenoma, hepatocellular carcinoma, hepatocellular adenoma or carcinoma (combined), and pheochromocytoma of the adrenal gland in males; and of haemangiosarcoma of the vascular system in females. In the same report, in a second feeding study, commercial-grade pentachlorophenol (with a smaller concentration of dioxins and furans compared with technical-grade pentachlorophenol) increased the incidence of hepatocellular adenoma, hepatocellular carcinoma, hepatocellular adenoma or carcinoma (combined), and pheochromocytoma of the adrenal gland in males; and of haemangiosarcoma of the vascular system, hepatocellular adenoma, and pheochromocytoma of the adrenal gland in females.

In one feeding study in male transgenic mice, there was an increase in the incidence of hepatocellular adenoma and cholangiocarcinoma of the liver. In the skin application study in female transgenic mice, there was an increase in the incidence of skin papilloma.

In three initiation–promotion studies in mice, pentachlorophenol by oral administration (feeding) promoted the development of hepatocellular adenoma or carcinoma (combined) in one study, hepatocellular adenoma in two studies, and cholangioma and cholangiocarcinoma of the liver in two studies.

In rats, there was one feeding study and one co-carcinogenicity study in males and in females. In the feeding study, pentachlorophenol increased the incidence of malignant mesothelioma of the tunica vaginalis of the testis in males. In the co-carcinogenicity study, pentachlorophenol increased the incidence of acute myelocytic leukaemia in males.

5.4 Mechanistic and other relevant data

Absorption of pentachlorophenol via oral and dermal exposure is rapid and extensive in all species studied, including humans, monkeys, mice, and rats. Pentachlorophenol distributes widely in the body via blood circulation. Pentachlorophenol is extensively bound to plasma proteins, with the greatest binding in humans, which leads to slow direct elimination of the parent compound. Metabolism involves both conjugation to glucurono- or sulfo-conjugates subsequently excreted in the urine, as well as oxidation to reactive metabolites,

including benzoquinones and semiquinones. Both pathways are active across the species studied, but the oxidation pathway is predominant in rodents while the conjugation pathway predominates in humans. Pentachlorophenol is also a strong inducer of cytochrome P450 enzymes, particularly CYP3A, and is an inhibitor of *O*-acetyltransferase and sulfotransferase enzymes. Excretion half-life is 10–20 days in humans and shorter in other mammalian species, such as monkeys (~80 hours), rats (~35 hours), and mice (~6 hours). There is *strong* evidence of metabolic activation to electrophilic benzoquinones and redox-cycling semiquinones.

In addition, there were data available on other key characteristics of carcinogens to evaluate whether pentachlorophenol induces oxidative stress, is genotoxic, modulates receptor-mediated effects, induces inflammation, is immunosuppressive, and alters cell proliferation, cell death, or nutrient supply.

There is *strong* evidence that pentachlorophenol induces oxidative stress and genotoxicity that can operate in humans. No studies of oxidative stress in exposed humans were available. Numerous studies in human cells, in mammalian systems in vivo or in vitro, and in non-mammalian experimental systems have reported increases in reactive oxygen species, oxidative stress markers, and DNA adducts associated with oxidative damage. Moreover, many studies across different species and experimental systems also demonstrated that these effects can be attenuated with co-exposure to a variety of antioxidants. These effects have been observed with treatment using either pentachlorophenol or metabolites such as tetrachlorohydroquinone (TCHQ) and tetrachlorobenzoquinone. TCHQ is the most studied metabolite, and appears to be more potent than pentachlorophenol, consistent with the need for metabolic activation of pentachlorophenol to induce oxidative stress. In addition, studies in *Nrf2*-knockout mice demonstrated that dysregulation of antioxidant expression increased pentachlorophenol-induced oxidative damage, cholangiofibrosis, and cholangiocarcinomas. In addition, multiple studies demonstrated genotoxicity consistent with oxidative damage in the form of 8-hydroxy-2′-deoxyguanosine (8-OHdG) formation in the livers of mice (and to a lesser extent, rats) treated in vivo. However, in a study using transgenic mice, pentachlorophenol exposure increased 8-OHdG, but did not induce *gpt* reporter gene mutations in the liver of *Tp53* wildtype or *Tp53*$^{-/-}$ mice. Pentachlorophenol also caused DNA strand breaks in multiple human cell types. Pentachlorophenol did not induce reverse mutations in the Ames test, whereas positive results were found in yeast and other bacterial assays that are more sensitive to oxidative DNA damage. Studies in acellular systems also reported DNA damage and/or adducts caused by pentachlorophenol in the presence of metabolic activation. Positive results have been reported for pentachlorophenol metabolites such as TCHQ, including mutation, micronucleus formation, and DNA strand breaks in multiple experimental systems. Evidence for induction of chromosomal aberrations, micronucleus formation, and sister-chromatid exchange, which includes studies in exposed humans and in multiple experimental mammalian systems, is mixed.

There is *strong* evidence that pentachlorophenol modulates receptor-mediated effects that can operate in humans with respect to anti-estrogenic activity. There are consistent results from studies in vitro using complementary techniques, including in human cells and in high-throughput screening data from Tox21. Several studies in mammals reported modulation of thyroid hormones after developmental exposures to pentachlorophenol, while the results of studies in vitro were ambiguous.

There is *strong* evidence that pentachlorophenol alters cell proliferation, cell death, or nutrient supply that can occur in humans. Pentachlorophenol and TCHQ induce apoptosis

in multiple experimental systems in vitro and in vivo, including in several human cell lines. Pentachlorophenol increases cell proliferation in mouse hepatocytes, intrahepatic bile duct epithelia, and skin, and alters proliferation and differentiation in mouse bone marrow culture, but decreased cell proliferation in one study in human lymphocytes in vitro. In several different experimental systems in vitro and in vivo, inhibition of gap-junction intercellular communication was observed after treatment with pentachlorophenol.

There is *moderate* evidence that pentachlorophenol induces chronic inflammation and is immunosuppressive. One study in exposed humans suggested increases in the frequency of mild infections and inflammation in skin, eye membrane and mucosa. Multiple studies in human cells and mammalian systems in vitro and in vivo suggest disruption of cytokines and/or deficiencies in cellular or humoral immunity as a result of treatment with pentachlorophenol. However, dioxin contamination present in technical-grade pentachlorophenol may have contributed to observations of immune suppression, as some effects were not observed with analytical-grade pentachlorophenol.

In the ToxCast/Tox21 high-throughput testing programmes of the United States government, pentachlorophenol was active for multiple assay end-points measuring markers of oxidative stress and *TP53* activation, consistent with the strong evidence for oxidative stress and associated genotoxicity discussed above. Pentachlorophenol was also active for many assay end-points related to modulation of receptor-mediated effects; however, these effects may be related to cytotoxicity, which was also observed across many assay end-points in cell lines and primary human cells.

There were no data on cancer susceptibility in humans. In experimental animals, one study in *Nrf2*-knockout mice suggested that dysregulation of antioxidant expression can increase susceptibility to pentachlorophenol-induced carcinogenicity.

Pentachlorophenol has been associated with haematological effects in some human studies, and effects on thyroid function, reproduction, toxicity in liver, and kidney in experimental animals.

6. Evaluation

6.1 Cancer in humans

There is *sufficient evidence* in humans for the carcinogenicity of pentachlorophenol. Pentachlorophenol causes non-Hodgkin lymphoma.

6.2 Cancer in experimental animals

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

6.3 Overall evaluation

Pentachlorophenol is *carcinogenic to humans* (*Group 1*).

6.4 Rationale

The Working Group attributed the cancers observed in studies in humans and experimental animals to exposure to pentachlorophenol, and not to impurities in pentachlorophenol, based on the following considerations:

- Measured impurities in pentachlorophenol are dominated by higher chlorinated dioxins and furans, which are much less potent than 2,3,7,8-tetrachlorodibenzo-*para*-dioxin (TCDD).
- The pattern of excess cancers observed in studies of occupational exposure to

pentachlorophenol differed from those observed in studies with high exposure to dioxins (i.e. excesses of all cancers combined, cancer of the lung, and soft tissue sarcoma, in addition to non-Hodgkin lymphoma).

- The pattern of excess cancers observed in experimental animals was similar for technical-grade pentachlorophenol (purity, 90.4%), commercial-grade pentachlorophenol (purity, 91%; with lower content of dioxin and furan), and analytical-grade pentachlorophenol (purity, ≥ 98%).
- Mechanistic studies with technical- and analytical-grade pentachlorophenol observed a wide spectrum of effects that differed from those observed with dioxins and furans.

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