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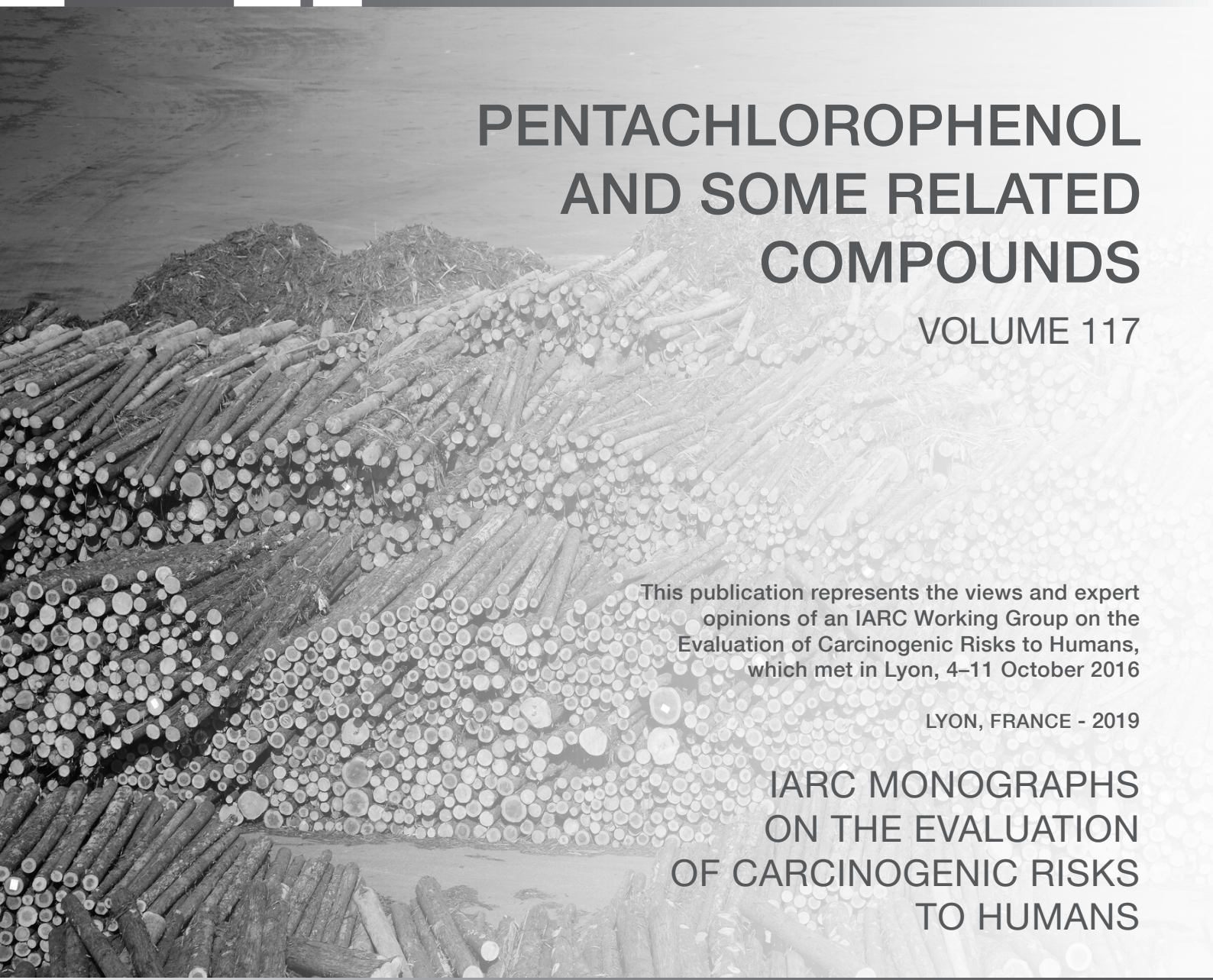

PENTACHLOROPHENOL AND SOME RELATED COMPOUNDS

VOLUME 117

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International Agency for Research on Cancer

World Health Organization

2,4,6-TRICHLOROPHENOL

1. Exposure Data

1.1 Identification of the agent

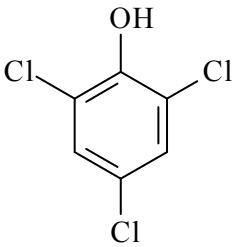
1.1.1 Nomenclature

Chem. Abstr. Serv. Reg. No.: 88-06-2

Chem. Abstr. Serv. Name: 2,4,6-Trichlorophenol

IUPAC Systematic Name: 2,4,6-Trichlorophenol

Synonyms: 2,4,6-TCP, Trichlorfenol



Molecular formula: $C_6H_3Cl_3O$

Relative molecular mass: 197.46

1.1.2 Chemical and physical properties of the pure substance

Description: Colourless to yellow crystals with a strong phenolic odour (Budavari, 1996; IARC, 1999; NTP, 2016)

Boiling-point: 246 °C (Lide, 1997; IARC, 1999)

Melting-point: 69 °C (Lide, 1997; IARC, 1999)

Solubility: Soluble in water (438–1200 mg/L at 25 °C) (Choudhary et al., 2013); soluble in acetone, acetic acid, diethyl ether, benzene, carbon tetrachloride, toluene, and ethanol (Lewis, 1993; Lide, 1997; IARC, 1999; NTP, 2016)

Vapour pressure: 133 Pa at 76.5 °C (United States National Library of Medicine, 1997; IARC, 1999)

Octanol/water partition coefficient: log K_{ow}, 3.69 (NTP, 2016)

Conversion factor: 1 ppm = 8.08 mg/m^3, at normal temperature (25 °C) and pressure (1 atm)

Dissociation constant (pK_a): 6.23 at 25 °C (NTP, 2016).

1.1.3 Technical products and impurities

(a) Trade names

Omal, Dowicide 2S, Phenaclor (NTP, 1979; ATSDR, 1999)

(b) Impurities

Technical-grade 2,4,6-trichlorophenol (2,4,6-TCP) has been found to contain 2,3,7-trichlorodibenzo-*para*-dioxin, 1,3,6,8-tetrachlorodibenzo-*para*-dioxin, 1,3,7,9-tetrachlorodibenzo-*para*-dioxin, 2,3,7,8-tetrachlorodibenzofuran, and other tetra-, penta-, and hexachlorodibenzofurans (WHO, 1989; INERIS, 2005). In the USA, 1,3,6,8-tetrachlorodibenzo-*para*-dioxin and 2,3,7-trichlorodibenzo-

para-dioxin were found in a commercial sample of 2,4,6-TCP at levels of 49 and 93 mg/kg, respectively (Firestone et al., 1972). In a Swedish sample of 2,4,6-TCP, 2,3,7,8-tetrachlorodibenzofuran was found at 1.5 mg/kg, penta-, hexa-, and heptachlorodibenzofurans at 17.5, 36, and 4.8 mg/kg, respectively, and polychlorinated dibenzo-*para*-dioxins (PCDDs) at < 3 mg/kg (Rappe et al., 1979).

1.2 Production and use

1.2.1 Production process

2,4,6-TCP was prepared by Laurent in 1836 by the chlorination of phenol, and this method has been used in the USA. In Japan, 2,4,6-TCP is co-produced during the manufacture of *ortho*- or *para*-chlorophenol, in a process also involving the chlorination of phenol (IARC, 1979). Distillation allows separation of 2,4,6-TCP from 2,3,4,6-tetrachlorophenol and pentachlorophenol, which are also formed during the reaction (INERIS, 2005).

1.2.2 Production volume

Commercial production of technical-grade 2,4,6-TCP in the USA was first reported in 1950 (IARC, 1979). In 1975, production was discontinued by the only manufacturer in the USA because of the high cost of removing PCDDs (NTP, 2016). In the USA, imports of 2,4,6-TCP totalled 2200 lb [~1000 kg] in 1976, 600 lb [~272 kg] in 1978, and 550 lb [~250 kg] in 1980 (IARC, 1979; NTP, 2016). In 2000, the United States Environmental Protection Agency (EPA) reported that 2,4,6-TCP was no longer used commercially (EPA, 2000).

In 2009, 2,4,6-TCP was produced by one manufacturer each in China, India, and Europe, and was available from 27 suppliers worldwide, including 16 suppliers in the USA (NTP, 2016).

In 2016, several companies were registered as manufacturing 2,4,6-TCP (mostly analytical grade): USA (11 companies), Canada (1), Germany (1), Switzerland (2), United Kingdom (2), China (1), Hong Kong Special Administrative Region, China (1), and Japan (2) (Chem Sources, 2016).

1.2.3 Use

2,4,6-TCP has been used primarily in various pesticide formulations and as a wood preservative. It has also been used as a fungicide, glue preservative, insecticide, bactericide, defoliant, herbicide, and anti-mildew agent for textiles (NTP, 2016). According to reports from New Zealand and Sweden, chlorophenols including 2,4,6-TCP were used from the 1970s until the late 1980s for the treatment of pelts (Glover et al., 1975; Pearce et al., 1988; Mikoczy et al., 1994). 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).

2,4,6-TCP is an intermediate for the synthesis of several chemicals such as pentachlorophenol, 2,3,4,6-tetrachlorophenol, and their sodium salts (INERIS, 2005).

Although most uses of 2,4,6-TCP were cancelled in the USA, 2,4,6-TCP continues to be used in the synthesis of some fungicides (NTP, 2016).

1.3 Analytical methods

Analytical methods for 2,4,6-TCP in different media have been described elsewhere (ATSDR, 1999; INERIS, 2005).

1.4 Occurrence and exposure

1.4.1 Occupational exposure

Occupational exposure to 2,4,6-TCP may occur in workers involved in the manufacture of 2,4,6-TCP and other chlorophenols, formulations containing 2,4,6-TCP, and chemicals that use 2,4,6-TCP as an intermediate (e.g. higher chlorinated phenols, phenolic resins, dyes, and drugs). 2,4,6-TCP is a common by-product in manufacturing pentachlorophenol, 2,4-dichlorophenol, tetrachlorophenol, and their salts, so workers exposed to those substances may also be exposed to 2,4,6-TCP (Kogevinas et al., 1995).

Occupational exposure also occurs in workers who apply formulations containing 2,4,6-TCP (e.g. sawmill workers), and workers exposed to 2,4,6-TCP as a by-product or contaminant (e.g. hazardous-waste incinerator workers) (ATSDR, 1999). Exposure may also occur in workers using 2,4,6-TCP as a biocide for treating textiles and leathers, or in workers handling the treated materials (de Souza Silveira et al., 2012; Karci, 2014). For example, 2,4,6-TCP was widely adopted for use as a fungicide for cured lamb pelts in New Zealand (Glover et al., 1975). Exposure to 2,4,6-TCP often occurs concurrently with other chlorophenol compounds, such as pentachlorophenol, and with PCDDs and polychlorinated dibenzofurans (PCDFs) (see Section 1.1.3).

(a) Air

In a Finnish sawmill that had regularly used 2,3,4,6-tetrachlorophenol containing 10–20% 2,4,6-TCP and 5% pentachlorophenol since the 1940s, median area air concentrations of 2,4,6-TCP ranged from 13 to 18 μg/m^3 for workers involved in outdoor vat-dipping, spraying lumber bundles, and trough-dipping lumber, to 68 μg/m^3 for workers involved in machine-stacking of lumber. Exposure of short duration to 2,4,6-TCP at a median air concentration of 610 μg/m^3 could occur inside kilns during drying. No 2,4,6-TCP was detected near workers who were trimming, grading, and packaging lumber (Kauppinen & Lindroos, 1985).

(b) Biological markers

Data on concentrations of 2,4,6-TCP in the urine have been collected in several studies in humans (Table 1.1). 2,4,6-TCP has been measured in the urine of hazardous- and municipal-waste incinerator workers, sawmill workers, and harbour workers involved in river dredging. Mean concentrations were typically < 4 μg/g creatinine. Urinary concentrations of 2,4,6-TCP ranged from 0.1 to 5.5 μg/g of creatinine in harbour workers and controls in Europe (Radon et al., 2004), from < 3 to 3.1 μg/g of creatinine in sawmill workers in Finland (Kontsas et al., 1995), and from 0.04 to 8.73 μg/g of creatinine in hazardous-waste incinerator workers in Europe (Domingo et al., 2001; Agramunt et al., 2003; Mari et al., 2013). No information on urinary concentrations of 2,4,6-TCP in textile or leather workers was found.

1.4.2 Community exposure

The general population may be exposed to 2,4,6-TCP as a result of proximity to 2,4,6-TCP-treated wood products, from dermal contact with 2,4,6-TCP-treated leathers and textiles, from use of wood preservatives that may contain 2,4,6-TCP, or from food and water contaminated with 2,4,6-TCP. Air exposure to 2,4,6-TCP may occur from the incineration of chlorinated compounds in municipal and hazardous waste, coal, and wood (ATSDR, 1999). 2,4,6-TCP can also be formed inadvertently when water containing phenol or some aromatic acids is treated with hypochlorite, such as during the bleaching process in pulp and paper mills, and during the disinfection of drinking-water sources (NTP, 2016; ToxNet, 2016).

Table 1.1 Concentrations of 2,4,6-trichlorophenol in urine samples from occupationally exposed workers

Country, year	Occupation	Work task or type of worker	No. of workers	Exposure[a]		Reference
				Level	Range	
Germany, 1997	Harbour workers	River dredging	83	Median, 0.36	0.1–3.8	Radon et al. (2004)
Germany, 1997	Harbour workers	Office workers	80	Median, 0.30	0.1–5.5	Radon et al. (2004)
Germany, 1999–2000	Hazardous-waste incinerator workers	Baseline, pre-employment	28	Mean, 0.86	0.04–8.73	Domingo et al. (2001); Schuhmacher et al. (2002)
Germany, 1999–2001	Hazardous-waste incinerator workers	Plant workers	19	Annual mean, 1.1–3.5	NR	Domingo et al. (2001); Schuhmacher et al. (2002)
Germany, 1999–2002	Hazardous-waste incinerator workers	Laboratory workers	3	Annual mean, 0.15–1.0	NR	Domingo et al. (2001); Schuhmacher et al. (2002)
Germany, 1999–2003	Hazardous-waste incinerator workers	Administrative worker	1	Annual mean range, 0.3–0.6	NR	Domingo et al. (2001); Schuhmacher et al. (2002)
Spain, 1999–2011	Hazardous-waste incinerator workers	Plant workers, including incinerator operators, boiler maintenance, furnace maintenance, control panel, and waste-gas-washing operators	16	Annual mean range, 0.3–3.5	NR	Agramunt et al. (2003); Mari et al. (2009); Mari et al. (2013)
Spain, 1999–2012	Hazardous-waste incinerator workers	Laboratory workers	5	Annual mean range, 0.05–1.00	NR	Agramunt et al. (2003); Mari et al. (2009); Mari et al. (2013)
Spain, 1999–2013	Hazardous-waste incinerator workers	Administrative workers	5	Annual mean range, 0.1–1.4	NR	Agramunt et al. (2003); Mari et al. (2009); Mari et al. (2013)
Germany, NR	Municipal waste incinerator	Municipal waste workers	53	Median, 0.85	0.30–3.86	Angerer et al. (1992)
Germany, NR	Municipal waste incinerator	Unexposed	248	Median, 0.6	< 1.2–10.6	Angerer et al. (1992)
Finland, NR	Sawmill workers	Tasks involving contact with chlorophenols	35	NR	One sample, 3.1; remainder, < 3	Kontsas et al. (1995)
Finland, NR	Sawmill workers	Unexposed	17	NR	All, < 3	Kontsas et al. (1995)
Finland, NR	Sawmill workers	Moving lumber that had been dipped in chlorophenol solution	7	Mean, 5.04 µmol/L [995 µg/L]		Pekari et al. (1991)

[a] Urinary concentrations are presented in µg/g creatinine unless otherwise indicated

NR, not reported

Compiled by the Working Group

(a) Water

2,4,6-TCP in water biodegrades in 8–14 days and absorbs readily to solids and sediments (ToxNet, 2016). 2,4,6-TCP concentrations in water were higher downstream (< 3.2 µg/L) than upstream (≤ 0.08 µg/L) from a Finnish pulp and paper mill (Oikari et al., 1985). 2,4,6-TCP was detected in 54% of surface water samples collected from Chinese rivers; the median concentration of 2,4,6-TCP was 2.0 ng/L, with substantially higher concentrations observed in rivers in northern China (maximum, 28 650 ng/L) than in southern China (Gao et al., 2008). In Poland, mean concentrations of 2,4,6-TCP ranged from 0.06 to 0.89 µg/L in river-water samples, and from 0.09 to 0.83 µg/L in drinking-water samples (Michałowicz et al., 2011). In river-water samples in the Republic of Korea, the median concentration of 2,4,6-TCP was 3.6 ng/L, and the maximum was 22 ng/L (Sim et al., 2009).

(b) Sediment and soil

Release of 2,4,6-TCP to soil may occur from disposal of manmade wastes, atmospheric deposition, and accidental releases (ATSDR, 1999). In river-sediment samples in the Republic of Korea, 2,4,6-TCP concentrations ranged from < 0.15 to 3.8 ng/g dry weight (Sim et al., 2009).

(c) Air

2,4,6-TCP exists as a vapour in the air and is degraded, with a half-life of 24 days, by reaction with photochemically produced hydroxyl radicals (ToxNet, 2016). In Portland, Oregon, USA in 1984, 2,4,6-TCP was detected in the air in five out of seven measured rain events, with a mean concentration (in samples in which 2,4,6-TCP was detected) of 0.15 ng/m^3 in the air samples and 1.4 ng/L in the precipitation samples (Leuenberger et al., 1985).

(d) Residues in food, and dietary intake

2,4,6-TCP has been measured at concentrations of up to 0.042 µg/g in coffee (Spadone et al., 1990). 2,4,6-TCP concentrations in red wine varied from 13 to 42 ng/L and were correlated with 2,4,6-TCP concentrations in the cork of the bottle (Ozhan et al., 2009), while oak barrels used to age wine and other spirits contained 2,4,6-TCP at concentrations ranging from 0.3 to 0.8 µg/g (Pizarro et al., 2006). 2,4,6-TCP has been measured at concentrations of up to 0.075 µg/g in semi-bleached-paper dishes and napkins (Ozaki et al., 2004).

(e) Household exposure

No measurements of 2,4,6-TCP in samples collected in homes were available to the Working Group.

(f) Biological markers

2,4,6-TCP has been measured in the urine in the general population (Table 1.2). The proportion of samples with detectable concentrations of 2,4,6-TCP ranged from 0% to 88%. Median concentrations were < 5 µg/L.

In the National Health and Nutrition Examination Survey (NHANES) of 1999–2004 in the USA, children aged < 15 years had urinary concentrations of 2,4,6-TCP ranging from 0.16 to 1772 µg/g of creatinine (Xu et al., 2011). In the NHANES and Center for the Health Assessment of Mothers and Children of Salinas (CHAMACOS) cohorts of pregnant women, urinary concentrations of 2,4,6-TCP ranged from 0.4 to 142 µg/L (Castorina et al., 2010). In one study in the USA, < 5% of breast-milk samples contained 2,4,6-TCP at detectable levels when the limit of detection was 1.2 µg/L (Ye et al., 2006).

Table 1.2 Concentrations of 2,4,6-trichlorophenol in urine samples from the general population

Country, year	Age (years)	No. of samples	Exposure		Comments	Reference
			Level	Range, % detects		
Republic of Korea, 2009	18–69	1865	Median, 0.47 µg/g creatinine	< 0.05–127 µg/g creatinine, 88% detects	Higher in rural residents	Kim et al. (2014)
USA, 1988–94	20–59	867	Median, < 2 µg/g creatinine	< 2–28 µg/g creatinine, 9.5% detects		Hill et al. (1995)
USA, 1999–2002	NR	523	Median, 1.4 µg/L	< 0.6–142 µg/L, 56% detects	Pregnant women, 13 weeks gestation; California agricultural area; CHAMACOS cohort	Castorina et al. (2010)
USA, 1999–2002	NR	479	Median, 4.5 µg/L	0.4–62 µg/L, 74% detects	Pregnant women, 26 weeks gestation; California agricultural area; CHAMACOS cohort	Castorina et al. (2010)
USA, 1999–2002	NR	223	Median, 1.8 µg/L	< 1.3–68 µg/L, 60% detects	Pregnant women NHANES	Castorina et al. (2010)
USA, NR	2–6	197	Median, < 1 µg/g creatinine	< 1–34 µg/g creatinine, 21% detects		Hill et al. (1989)
USA, 2003–2010	6 to > 60	10 423	Median, < 1 µg/g creatinine	95th percentile, 0.9–5.20 µg/g creatinine, < 50% detects	NHANES	NHANES (2015)
Canada, 1993	36–76	31	NR	All < 2 µg/g creatinine	Sport fish consumers from three great lakes	Anderson et al. 1998
Germany, 1998	18–69	692	Median, 0.3 µg/g creatinine	0.2–4.1 µg/g creatinine	General population of Germany	Becker et al. (2003)

CHAMACOS, Center for the Health Assessment of Mothers and Children of Salinas; NHANES, National Health and Nutrition Examination Survey; NR, not reported
Compiled by the Working Group

1.5 Regulations and guidelines

Occupational exposure limits for 2,4,6-TCP in air included an 8-hour average air concentration of 0.5 mg/m^3 in Denmark and Sweden, and short-term air concentrations of 1.0 mg/m^3 in Denmark and 1.5 mg/m^3 (for 15 minutes) in Sweden (IFA, 2016).

The World Health Organization (WHO) has established an international drinking-water guideline for 2,4,6-TCP of 200 µg/L (WHO, 1993).

The United States EPA has established ambient water quality criteria of 1.4 µg/L on the basis of seafood (fish or shellfish) and water consumption, 2.4 µg/L on the basis of seafood consumption only, and 2.0 µg/L on the basis of organoleptic-effect criteria (NTP, 2016).

In the USA, there are additional restrictions and requirements regarding transportation, presence in ambient air and hazardous waste, and releases to the environment (ATSDR, 1999). For example, 2,4,6-TCP is listed as a hazardous air pollutant under the Clean Air Act, and as a hazardous substance under the Clean Water Act (NTP, 2016), triggering a variety of requirements regarding pollutant monitoring, emissions control, record keeping, and reporting by major source.

The United States EPA has classified 2,4,6-TCP as Group B2, a "probable human carcinogen" (EPA, 1999). Under the harmonized classification and labelling system of the European Union, 2,4,6-TCP is "suspected of causing cancer (Carc. 2)" [H351] and has been determined to be "very toxic to aquatic life (Aquatic Acute 1)" [H400] and "very toxic to aquatic life with long lasting effects (Aquatic Chronic 1)" [H410], to be "harmful if swallowed (Acute Tox. 4)" [H302], to "cause serious eye irritation (Eye Irrit. 2)" [H319], and to "cause skin irritation (Skin Irrit. 2)" [H315] (ECHA, 2016).

2. Cancer in Humans

While many studies have examined the risk of cancer among workers exposed to 2,4,5-trichlorophenol, with a focus on contamination by 2,3,7,8-tetrachlorodibenzo-*para*-dioxin (TCDD), very few studies have provided results for the 2,4,6 isomer of trichlorophenol (2,4,6-TCP). The Working Group reviewed all the available epidemiological studies with relevant results for the evaluation of 2,4,6-TCP. All studies focused on occupational exposure. One case–control study nested in an occupational cohort (Kogevinas et al., 1995) and several case–control studies provided pertinent data. Studies in New Zealand, where 2,4,6-TCP was used for the treatment of sheep pelts (Glover et al., 1975), are reviewed below (Smith et al., 1984; Pearce et al., 1986b, 1988). Two case–control studies in Sweden reported associations between exposure to phenoxy herbicides or chlorophenols and soft tissue sarcoma and non-Hodgkin lymphoma (NHL) (Eriksson et al., 1981; Hardell et al., 1981), but did not present specific results for 2,4,6-TCP and were not considered further. 2,4,6-TCP has been used in tanneries, as has pentachlorophenol, but cohort studies of tannery workers did not specify which chlorophenol was in use; these studies were therefore not reviewed by the Working Group.

2.1 Cohort studies

See Table 2.1.

The IARC international register of workers exposed to phenoxy herbicides, chlorophenols, and dioxins included some workers exposed to 2,4,6-TCP (Saracci et al., 1991; Kogevinas et al., 1995). The pooled cohort consisted of 21 183 workers from 24 cohorts in 11 countries in Europe, North America, and Oceania. Work history records, detailed company exposure questionnaires, and company reports were used

Table 2.1 Epidemiological studies of cancer and exposure to 2,4,6-trichlorophenol

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, United Kingdom 1939–1992 Nested case–control	Cases: 32 NHL; 11 STS; cohort was identified from the 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 reviewed by industrial hygienists to estimate cumulative exposure to 21 chemicals	NHL STS	2,4,6-TCP (ever use) 2,4,6-TCP (ever use)	2 1	0.8 (0.08–8.04) 5.0 (0.31–79.94)	Matching factors: sex, age, country of residence at time of employment, country of cohort	Strengths: large study; objective exposure assessment methods; estimates of exposure to PCP, phenoxy herbicides, dioxins and furans; cancer incidence data Limitations: no quantitative exposure information; exposures to several compounds highly correlated; low power
Smith et al. (1984) New Zealand 1976–1980 Case–control	Cases: 82; male cases reported to the national cancer registry Controls: 92; one cancer control per case, matched by year of registration and age from the registry Exposure assessment method: questionnaire; work in pelt departments in meat works or in tanneries where 2,4,6-TCP was used; telephone interview	STS	Pelt department workers in meat works Tannery workers Pelt department or tannery workers	4 3 6	[4.7 (0.26–85.6)] – [7.2 (0.79–65.82)]	Country, sex, age	0 controls exposed for tannery workers; matching was not retained in the analysis Strengths: population based study with good participation rates; cases histologically confirmed; the questionnaire asked specifically about work in pelt departments Limitations: certainty of assignment of exposure to 2,4,6-TCP unclear; low power

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
Pearce et al. (1986b) New Zealand 1977–1981 Case–control	Cases: 83; Cancer registry Controls: 396; 168 cancer patients from cancer registry 228 general population controls Exposure assessment method: questionnaire; job-title based	NHL	Employment in pelt department in meat works:			Age, respondent type (proxy/ direct), sex	Strengths: population-based study; good response rates Limitations: limited exposure assessment
			Other cancer controls	4	2.3 (0.6–9.5)		
			General population controls	4	4.1 (0.9–18.6)		
			Pooled controls	4	2.7 (0.9–8.5)		
Pearce et al. (1988) New Zealand 1977–1981 Case–control	Cases: 183; NHL; cancer registry, histologically confirmed, and diagnosed under the age of 70 yr Controls: 338; patients reported to the national cancer registry with other types of cancers, randomly selected, within 2 yr of age to the case and population controls randomly selected from the 1982 New Zealand electoral roll Exposure assessment method: questionnaire; work in pelt departments in meat works or in tanneries where 2,4,6-TCP was used	NHL: ICD-9, 200 and 202	Pelt department workers	10	[1.9 (0.9–4)]	Respondent type (proxy/direct), age, sex, decade of birth	Strengths: population based study with good participation rates Limitations: level of exposure not known; low power
			Tannery workers	2	[0.5 (0.1–2.8)]		

2,4,6-TCP, 2,4,6-trichlorophenol; CI, confidence intervals; ICD, International Classification of Disease; NHL, non-Hodgkin lymphoma; PCP, pentachlorophenol; STS, soft tissue sarcoma; 2,4,6-TCP, 2,4,6-trichlorophenol; yr, year(s)

by three industrial hygienists (blinded to the disease status of the workers) to reconstruct exposure to 21 chemicals or mixtures. Kauppinen and colleagues reported a prevalence of exposure to 2,4,6-TCP of 6% within the pooled cohort, with a mean duration of employment of 4.8 years (Kauppinen et al., 1994).

Kogevinas and colleagues conducted nested case–control studies of soft tissue sarcoma and NHL among the pooled cohort of workers within the register (Kogevinas et al., 1995). Analyses were conducted using conditional logistic regression with a 5-year exposure lag. Only one exposed case of soft tissue sarcoma, (odds ratio, OR, 5.0; 95% confidence interval, CI, 0.31–79.94) and two exposed cases of NHL (OR, 0.80; 95% CI, 0.08–8.04) were identified. [Overall, this study had a strong design and exposure assessment; however, because of the low prevalence of exposure, it was underpowered for studying the association between 2,4,6-TCP and NHL or soft tissue sarcoma.]

2.2 Case–control studies

Smith and colleagues conducted a case–control study of men with soft tissue sarcoma (International Classification of Disease, ICD-9, 171) diagnosed in New Zealand between 1976 and 1980 (Smith et al., 1984). Cases were reported by public hospitals, which contributed 95% of population coverage in New Zealand to the national cancer registry, in 1976–1980. Cases were reviewed histologically by a pathologist. Controls were randomly selected from the same registry. A telephone interview was conducted with questions on activities with the potential for exposure to chlorophenoxy herbicides and chlorophenols. The questionnaire asked specifically about pelt departments in view of their use of 2,4,6-TCP for treating sheepskins. Proxy interviews were conducted with 57% of cases and 64% of controls. Four cases and one control reported working in pelt departments of meat works (OR, 4.7; [95% CI, 0.3–86]), while three cases and no controls reported working in areas of tanneries where exposure to 2,4,6-TCP may also have occurred. When these two groups were combined (six exposed cases in total), the odds ratio was 7.2 ([95% CI, 0.8–66]). Further interviews provided conflicting information on dates when 2,4,6-TCP was used, casting doubt on the exposure of four of the six cases. For example, the tannery where the exposed cases worked was closed, but a similar tannery owned by the same company in New Zealand reported that 2,4,6-TCP was used only after 1962, whereas pentachlorophenol was used only before 1962. [This study had several limitations. Other cancer patients (cancer sites not stated) were used as controls. Most of the interviews were conducted with proxies. There was low power to detect an excess risk. Although the fact that follow-up interviews were conducted was a strength, no results were presented in which cases for whom exposure to 2,4,6-TCP was doubtful were excluded.]

A similarly designed case–control study of NHL in New Zealand also provided relevant results for this evaluation (Pearce et al., 1986b, 1988). Initially, only men with NHL (ICD-9, 202 only), excluding lymphosarcoma and reticulosarcoma (ICD-9, 200), were recruited from a national cancer registry (Pearce et al., 1986b). Two matched controls per case were randomly selected from the registry. An additional control group comprised 300 men randomly selected from the 1982 electoral roll for New Zealand. During a telephone interview, participants were asked about activities with a potential for exposure to phenoxy herbicides and chlorophenols. Odds ratios were adjusted for decade of birth and whether the subject or a relative was interviewed. Odds ratios for work in pelt departments in meat works where 2,4,6-TCP was used were 2.3 [95% CI, 0.6–9.5] when using other cancer controls, and 4.1 [95% CI, 0.9–18.6] when using general population controls. The results when both sets of controls were pooled were similar

(OR, 2.7, [95% CI, 0.9–8.5]). When potentially exposed participants were further interviewed it was discovered that two out of four cases and four out of ten controls had performed tasks during which they were unlikely to have been exposed, but a revised analysis was only reported for all chlorophenols combined. No excess was observed among tannery workers when either cancer or population controls were used.

This case–control study was later expanded to include lymphosarcoma and reticulosarcoma (ICD-9, 200) and subsequently reported results for all NHL combined (ICD-9, 200, 202) (Pearce et al., 1988). A target sample of 121 cases of lymphosarcoma and reticulosarcoma was identified (100 participated, 83%) and an expanded set of 338 cancer controls (81% participation) and the population controls were not used in the further analyses. The odds ratio for work in pelt departments in meat works was 2.2 ([95% CI, 0.8–6.3]; based on 6 cases) for lymphosarcoma and reticulosarcoma. The odds ratio for NHL was 1.9 ([95% CI, 0.8–4.6]; based on 10 cases). [In this analysis, the cases and controls with questionable exposure appeared to have been removed.] The results for pelt department workers were similar to those for all meat-works employment, and the highest risk was observed among men who had worked at meat works and in fencing. No excess risk was observed for tannery workers (OR, 0.5; [95% CI, 0.1–2.8]; based on 2 exposed cases). [This study had limited precision and levels of exposure were not known. There was also the potential for exposure to pentachlorophenol and other potentially carcinogenic exposures related to fencing for participants who had worked in both jobs.]

2.3 Exposure assessment in epidemiological studies

Few epidemiological studies had evaluated exposure to 2,4,6-TCP. Several epidemiological studies relying on job classification were conducted in New Zealand (Smith et al., 1984; Pearce et al., 1986a, b, 1988). These studies used retrospective telephone interviews with patients or next of kin to determine whether each individual had worked in particular jobs for which the investigators had determined that exposure to phenoxy herbicides or chlorophenols was likely. Initial questions used a pre-specified list of occupations, and people who reported having worked in those occupations were asked subsidiary questions regarding the specific nature of the work and the potential for exposure to specific chemicals. Exposure was treated as a dichotomous variable (yes/no for each particular job) in the epidemiological analyses. Pelt departments of meat works were identified a priori as an occupation of interest due to the known use of 2,4,6-TCP in treating sheep pelts; however, Pearce et al. (1986b) reported that 6 of the 14 study participants initially reporting having worked in a pelt department had actually worked in a fellmongery removing wool before sheep skins were treated, and were thus unlikely to have been exposed to 2,4,6-TCP. Meat works employees were likely to have been exposed to other chemicals as well as 2,4,6-TCP (Pearce et al., 1986b).

Only one epidemiological study evaluating the magnitude of exposure to 2,4,6-TCP was identified (Kogevinas et al., 1995). For this study, three industrial hygienists (blinded to health status of the workers) reviewed general work processes and conditions for cancer cases and controls sampled from IARC's international register of more than 21 000 workers exposed to phenoxy herbicides, chlorophenols, and contaminants, from 11 countries in Europe, North America, and Oceania. By 1990, 19 cohorts were enrolled, including sprayers of

phenoxy herbicides and workers from companies manufacturing or formulating phenoxy acids or chlorophenols (Saracci et al., 1990). On the basis of company questionnaires regarding chemical production and use characteristics as well as the general literature, unit-less job-specific exposure intensities specific to this study were assigned for a variety of phenoxy herbicides, dioxins, and chlorophenols, including 2,4,6-TCP, based on the product of a subscore for each job task (ranging from 1 to 10, and assumed to be constant over time and equivalent across plants) and modifying factors (including for emissions of agents, average daily contact time of the workers with the contaminants, and the use of personal protective equipment) (Kauppinen et al., 1994). [Although the authors noted that dermal exposure might be important for many of these compounds, the extent to which specific exposure routes were considered in scoring was unclear.] Exposure intensities were then multiplied by job duration and summed across all jobs in each individual's work history to calculate a cumulative exposure score for each worker. [Although this method may be adequate for detecting strong contrasts in 2,4,6-TCP exposure between cases and controls, the exposure assignments probably suffer from substantial non-differential measurement error due to an apparent lack of direct measurements of 2,4,6-TCP in the workplace, resulting in attenuation of epidemiological effect estimates towards null association.]

3. Cancer in Experimental Animals

See Table 3.1.

3.1 Mouse

In a study by the United States National Cancer Institute (NCI), groups of 50 male B6C3F_1 mice (age, 6 weeks) were fed diets containing 2,4,6-TCP (purity, 96–97%; with 17 minor contaminants [not further specified]) at a concentration of 5000 or 10 000 ppm for 105 weeks. Groups of 50 female B6C3F_1 mice (age, 6 weeks) were fed diets containing 2,4,6-TCP at 10 000 (lower dose) or 20 000 (higher dose) ppm for 38 weeks, at which time the doses were reduced to 2500 (lower dose) and 5000 (higher dose) ppm because of markedly reduced body-weight gain in the treated animals. After this change in doses, the study continued for a further 67 weeks. Time-weighted average doses for females were 5214 (lower dose) and 10 428 (higher dose) ppm. The control groups comprised 20 untreated male mice and 20 untreated female mice. There was no dose-related trend in mortality in males or females. Survival of males was 16/20 for controls, 44/50 at the lower dose, and 45/50 at the higher dose. Survival of females was 17/20 for controls, 44/50 at the lower dose, and 40/50 at the higher dose. At the end of the study, body weights of treated groups of males and females were lower than those of controls. The incidence of hepatocellular adenoma was significantly increased in treated males, and in females at the higher dose. There was a significant positive trend in the incidence of hepatocellular carcinoma in females. The incidence of hepatocellular adenoma or carcinoma (combined) was significantly increased in males (in both treated groups, with a significant positive trend) and in females (at the higher dose, with a significant positive trend) (NTP, 1979). [The Working Group noted that the number of concurrent controls was small, and that the PCDD content of the diet was not determined.]

Stoner et al. (1986) evaluated tumours of the lung in the A/J mouse after administration of 2,4,6-TCP (reagent grade) in tricaprylin by gavage or by intraperitoneal injection three times per week for 8 weeks. Groups of 16 male and 16 female A/J mice (age, 6–8 weeks), were given total doses of 2,4,6-TCP of 0 (control) or 1200 mg/kg bw by gavage, or 0 (control) 240, 600, or 1200 mg/kg bw by intraperitoneal injection.

Table 3.1 Studies of carcinogenicity with 2,4,6-trichlorophenol in experimental animals

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) 6 wk 105 wk NTP (1979)	Oral 2,4,6-TCP, 96–97% Diet 0, 5000, 10 000 ppm Ad libitum 20, 50, 50 16, 44, 45	*Liver* Hepatocellular adenoma: 3/20, 22/49*, 32/47** Hepatocellular carcinoma: 1/20, 10/49, 7/47 Hepatocellular adenoma or carcinoma (combined): 4/20, 32/49*, 39/47**	 NR (trend), *[$P < 0.05$] **[$P < 0.0001$] NS $P < 0.001$ (trend); *$P = 0.001$; **$P < 0.001$	17 (unspecified) minor impurities; PCDD content was not determined Limitations: small number of controls
Full carcinogenicity Mouse, B6C3F$_1$ (F) 6 wk 105 wk NTP (1979)	Oral 2,4,6-TCP, 96–97% Diet 0, 5214, 10 428 ppm (TWA) Ad libitum 20, 50, 50 17, 44, 40	*Liver* Hepatocellular adenoma: 1/20, 12/50, 17/48* Hepatocellular carcinoma: 0/20, 0/50, 7/48 Hepatocellular adenoma or carcinoma (combined): 1/20, 12/50, 24/48*	 NR (trend), *[$P < 0.02$] $P = 0.005$ (trend) $P < 0.001$ (trend); *$P < 0.001$	Dietary levels: 38 wk at 10 000 or 20 000 ppm, then 67 wk at 2500 or 5000 ppm, resulting in TWA of 5214 and 10 428 ppm, respectively 17 (unspecified) minor impurities; PCDD content was not determined Limitations: small number of controls
Full carcinogenicity Rat, F344 (M) 6 wk 106–107 wk NTP (1979)	Oral 2,4,6-TCP, 96–97% Diet 0, 5000, 10 000ppm Ad libitum 20, 50, 50 18, 35, 34	*Haematopoietic system* Malignant lymphoma: 1/20, 2/50, 0/50 Monocytic leukaemia: 3/20 (15%), 23/50 (46%)*, 28/50 (56%)** Monocytic leukaemia or malignant lymphoma (combined): 4/20, 25/50*, 29/50**	 NS $P = 0.003$ (trend); *$P = 0.013$; **$P = 0.002$ $P = 0.006$ (trend); *$P = 0.019$; **$P = 0.004$	Limitations: small number of controls 17 (unspecified) minor impurities; PCDD content was not determined Historical control incidence at laboratory, leukaemia: 11/255 (4%)

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 (F) 6 wk 106–107 wk NTP (1979)	Oral 2,4,6-TCP, 96–97% Diet 0, 5000, 10 000 ppm Ad libitum 20, 50, 50 14, 39, 39	*Haematopoietic system* Malignant lymphoma: 0/20, 0/50, 2/50 Monocytic leukaemia: 3/20, 11/50, 10/50 Monocytic leukaemia or malignant lymphoma (combined): 3/20 (15%), 11/50 (22%), 13/50 (26%)	 NS NS NS	17 (unspecified) minor impurities; PCDD content was not determined Historical control incidence at laboratory, leukaemia or malignant lymphoma (combined): 42/420 (10%) Limitations: small number of controls

F, female; M, male; NR, not reported; NS, not significant; PCDD, polychlorinated dibenzo-*para*-dioxin; ppm, parts per million; 2,4,6-TCP, 2,4,6-trichlorophenol; TWA, time-weighted average; wk, week(s)

There was no increase in the incidence or multiplicity of tumours of the lung in treated mice when compared with vehicle controls (Stoner et al., 1986). [The Working Group noted the short duration of the experiment.]

One study in mice was judged inadequate for the evaluation by the Working Group 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 (NCI, 1968; Innes et al., 1969).

3.2 Rat

In a study by the NCI, groups of 50 male and 50 female Fischer 344 rats (age, 6 weeks) were given diets containing 2,4,6-TCP (purity, 96–97%; 17 minor contaminants [not further specified]) at a concentration of 5000 or 10 000 ppm for 106–107 weeks. Groups of 20 males and 20 females served as controls. There was no dose-related trend in mortality in males or females. Survival of males was 18/20 for the controls, 35/50 at the lower dose, and 34/50 at the higher dose, and survival of females was 14/20, 39/50, and 39/50, respectively. Throughout the study, body weights of treated groups of males and females were lower than those of controls. The incidence of monocytic leukaemia was significantly increased in both groups of treated males (controls, 3/20; lower dose, 23/50; and higher dose, 28/50) with a significant positive trend. The incidence of this neoplasm in historical controls at the laboratory was 11/255 (4%). Other adverse effects observed at 2 years in exposed males and females included leukocytosis of the peripheral blood and bone marrow hyperplasia. There was no significant increase in the incidence of tumours in treated females (NTP, 1979). [The Working Group noted the small number of concurrent controls, and that the PCDD content was not determined (although the neoplasms observed had not previously been associated with exposure to dioxin).]

4. Mechanistic and Other Relevant Data

4.1 Absorption, distribution, metabolism, and excretion

4.1.1 Introduction

[The Working Group noted that absorption, distribution, metabolism, and excretion have been much less studied for 2,4,6-TCP than for pentachlorophenol.]

4.1.2 Absorption

No data on the absorption of 2,4,6-TCP in humans or experimental systems were available to the Working Group. On the basis of analogy to other chlorophenols, 2,4,6-TCP is likely to be rapidly absorbed.

4.1.3 Distribution

(a) Humans

No data were available to the Working Group.

(b) Experimental systems

In male Wistar rats, peak concentrations were observed in all tissues 30 minutes after a single intraperitoneal dose of 2,4,6-TCP (25 mg/kg bw). The highest concentration (approximately 65 mg/kg) was found in the kidneys, followed by blood, liver, fat, muscle, and brain. After 10 hours, only trace amounts of 2,4,6-TCP remained in the blood and tissues (Pekari et al., 1986).

4.1.4 Metabolism and modulation of metabolic enzymes

(a) Metabolism

See Fig. 4.1.

(i) Humans

No data were available to the Working Group. Lindane (γ-hexachlorocyclohexane) is metabolized in part to 2,4,6-TCP by human liver microsomes (Fitzloff et al., 1982).

(ii) Experimental systems

In male Wistar or Sprague-Dawley rats dosed daily for 15 days with radiolabelled 2,4,6-TCP (25 µg) by gavage, unconjugated urinary 2,4,6-TCP and isomers represented 63% of the total administered dose. Conjugates eliminated in the urine (80% of which were conjugates with glucuronic acid) accounted for 28% of the total administered dose, and an additional 6% of the total administered dose was eliminated in the faeces (Bahig et al., 1981). Male Wistar rat liver microsomes can metabolize 2,4,6-TCP into 2,6-dichloro-1,4-hydroquinone, the 2,6-dichloro-1,4-semiquinone free radical, and two isomers of hydroxy-pentachlorodiphenyl ether (Juhl et al., 1989). Horseradish peroxidase can catalyse hydrogen peroxide (H_2O_2)-dependent oxidative 4-dechlorination of 2,4,6-TCP, leading to the formation of 2,6-dichloro-1,4-benzoquinone (Ferrari et al., 1999). [The Working Group considered that the formation in vivo of 2,6-dichloro-1,4-benzoquinone was likely, by analogy to pentachlorophenol.]

Lindane (γ-hexachlorocyclohexane) is metabolized in part to 2,4,6-TCP by male Wistar rats in vivo (Baliková et al., 1989), and by rat liver microsomes (Fitzloff et al., 1982). 2,4,6-TCP is also produced by the conversion of the α-isomer of hexachlorocyclohexane (purity, 95%) in male Wistar rats (Macholz et al., 1982), and by the conversion of prochloraz in male Sprague-Dawley rats (Laignelet et al., 1992).

(b) Modulation of metabolic enzymes

(i) Humans

2,4,6-TCP inhibited acetylcholinesterase activity in the human erythrocyte membrane in vitro (Matsumura et al., 1997). It also decreased the expression of mRNA of several enzymes involved in steroidogenesis in the human adrenocortical carcinoma cell line H295R in vitro (Ma et al., 2011; see Section 4.2.4).

(ii) Experimental systems

In male adult Sprague-Dawley rats given 2,4,6-TCP (purity, unspecified; oral doses of up to 400 mg/kg for 14 days), no significant effects were observed on *O*-ethyl *O*-*para*-nitrophenyl phenylphosphonothioate (EPN) detoxification (which involves mixed-function oxidases and arylesterase) or on uridine 5′-diphospho (UDP)-glucuronyltransferase (Carlson, 1978). In vitro, with microsomal fractions from the same rats, 2,4,6-TCP inhibited EPN detoxification and methylation of *para*-nitroanisole, but not UDP-glucuronyltransferase (Carlson, 1978).

4.1.5 Excretion

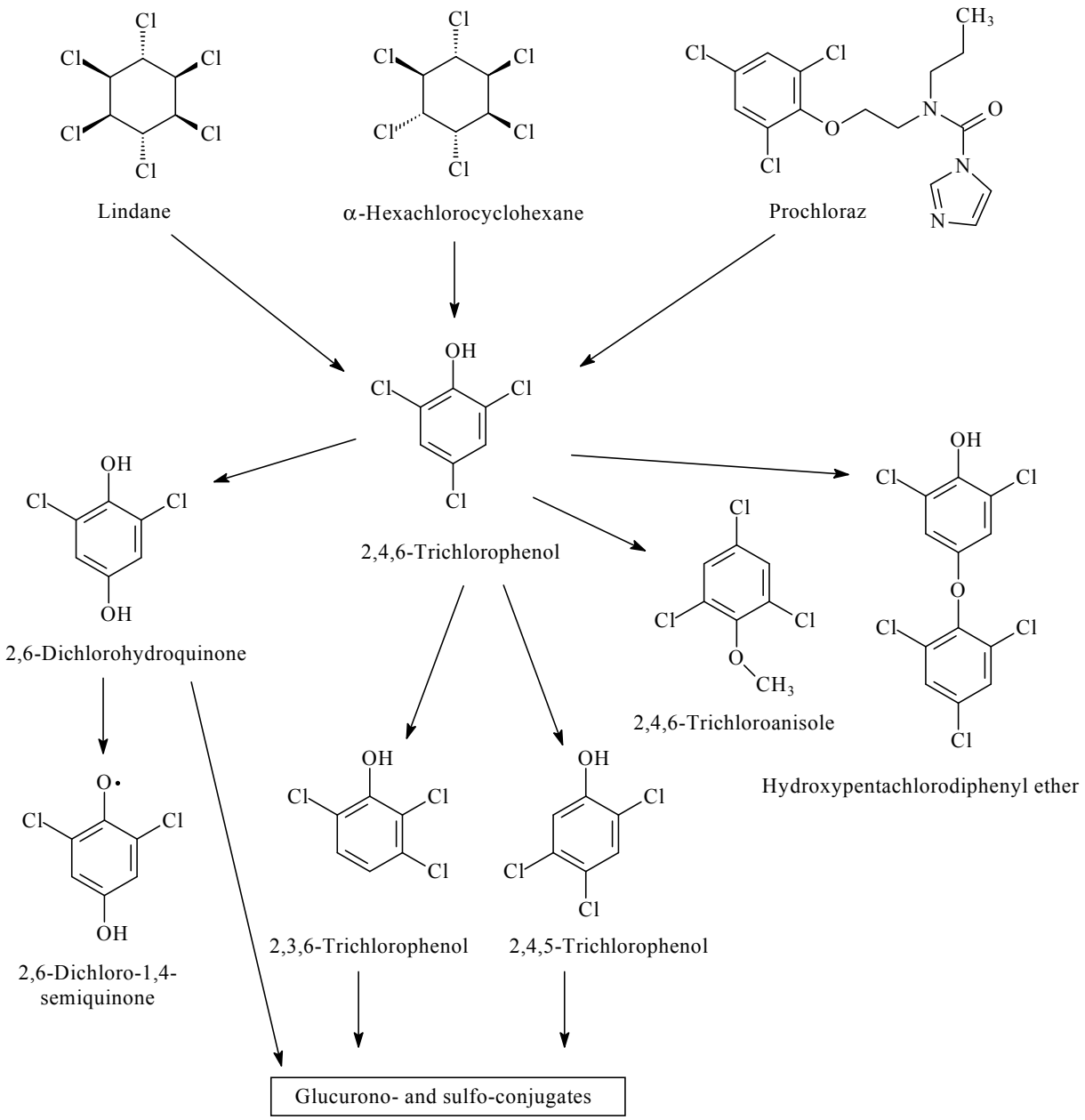
(a) Humans

2,4,6-TCP was detected in the urine of children in a study of parent-reported attention deficit hyperactivity disorder (Xu et al., 2011).

(b) Experimental systems

Half-lives for trichlorophenols range from hours to days, compounds with higher chlorine content having longer half-lives (IARC, 1986). In male Wistar or Sprague-Dawley rats dosed daily for 15 days with 25 µg of radiolabelled 2,4,6-TCP by gavage, the excretion of radiolabel in the urine and faeces reached a plateau after 2 days and decreased sharply to a few percent of the administered dose within 3 days after exposure. About 6% of the administered dose was excreted in the faeces, and the rest in the urine (Bahig

Fig. 4.1 Metabolism of 2,4,6-trichlorophenol



Compiled by the Working Group

et al., 1981). In male Wistar rats given a single intraperitoneal dose of 2,4,6-TCP at 25 mg/kg bw, 90% of the administered dose was excreted between 4 and 6 hours. The half-life of 2,4,6-TCP in all the tissues studied ranged from 1.4 to 1.8 hours. The half-life of conjugated 2,4,6-TCP in the blood was also 1.4 hours (Pekari et al., 1986).

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 2,4,6-TCP is genotoxic; induces oxidative stress; alters cell proliferation, cell death, or nutrient supply; or modulates receptor-mediated effects. For the other key characteristics of carcinogens, insufficient data were available for evaluation.

4.2.1 Genetic and related effects

(a) Humans

See Table 4.1.

No data from exposed humans were available to the Working Group.

In the human promyelocytic leukaemia cell line HL-60, 2,4,6-TCP (50 µg/mL) increased DNA damage in the comet assay (Ozaki et al., 2004).

(b) Experimental systems

No data from mammalian experimental systems in vivo were available to the Working Group.

The assay for forward mutation in L5178Y *Tk*$^{+/-}$ mouse lymphoma cells gave positive results with 2,4,6-TCP (80 µg/mL) (McGregor et al., 1988). Although 2,4,6-TCP (100 µg/mL) failed to induce mutation at the *Hprt* locus or chromosomal aberrations in Chinese hamster fibroblast V79 cells in the absence of metabolic activation (Jansson & Jansson, 1986, 1992), 2,4,6-TCP (30 µg/mL or higher) induced statistically significant, dose-related increases in the frequency of hyperdiploidy and micronucleus formation (Jansson & Jansson, 1992). Armstrong et al. (1993) also observed hyperdiploidy in V79 cells.

2,4,6-TCP did not induce structural chromosomal aberrations or sister-chromatid exchanges in Chinese hamster ovary (CHO) cells (Galloway et al., 1987). However, when the protocol was adjusted to extend the recovery period after treatment before harvest, chromosomal aberrations in CHO and V79 cells were induced by 2,4,6-TCP (600 µg/mL) both in the presence (S9) and absence of metabolic activation in CHO cells (Armstrong et al., 1993).

An elevated frequency of point mutations in the *Tp53* gene in the liver genome was seen in zebrafish exposed to 2,4,6-TCP (5 µg/L) for 10 days (Yin et al., 2009).

2,4,6-TCP induced forward mutation, but not gene conversion, in *Saccharomyces cerevisiae* (Fahrig et al., 1978). 2,4,6-TCP did not induce reverse mutations in *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537 (Haworth et al., 1983). 2,4,6-TCP (50 µg/disc) caused DNA damage, as detected by the recombinant (*rec*) assay in *Bacillus subtilis* (Ozaki et al., 2004). DNA strand breaks were detected using the Microscreen prophage-induction assay in *Escherichia coli* exposed to 2,4,6-TCP (DeMarini et al., 1990).

DNA strand breaks were induced after microsomal activation of 2,4,6-TCP (1 mM) and incubation with bacteriophage PM2 DNA plasmid (Juhl et al., 1989). 2,4,6-TCP (10 µM) formed deoxyguanosine adducts after bioactivation by a representative peroxidase system (Dai et al., 2005).

Table 4.1 Genetic and related effects of 2,4,6-trichlorophenol

End-point	Species, tissue, cell line	Results[a]		Concentration (LEC/HIC)	Comments	Reference
		Without metabolic activation	With metabolic activation			
DNA strand breaks	Human leukaemia, HL-60	+	NT	50 µg/mL	Purity, > 97%	Ozaki et al. (2004)
Tk mutation	Mouse lymphoma, L5178Y cells	+	NT	80 µg/mL	Purity, NR	McGregor et al. (1988)
Hprt mutation	Chinese hamster fibroblasts, V79	–	NT	100 µg/mL	Purity, > 99.5% Cell survival, 53%	Jansson & Jansson (1986)
Hprt mutation	Chinese hamster fibroblasts, V79	–	NT	180 µg/mL	Purity, 99.7% Cell survival, 14%	Jansson & Jansson (1992)
Chromosomal aberrations	Chinese hamster fibroblasts, V79	–	NT	60 µg/mL	Purity, 99.7%	Jansson & Jansson (1992)
Aneuploidy, micronucleus formation	Chinese hamster fibroblasts, V79	+	NT	30 µg/mL	Purity, 99.7%	Jansson & Jansson (1992)
Chromosomal aberrations	Chinese hamster ovary, CHO-W-B1	–	–	500 µg/mL	Purity, NR	Galloway et al. (1987)
Sister-chromatid exchanges	Chinese hamster ovary, CHO-W-B1	–	–	500 µg/mL	Purity, NR	Galloway et al. (1987)
Chromosomal aberrations	Chinese hamster ovary, CHO-WBL	+	+	600 µg/mL	Purity, > 99.7%	Armstrong et al. (1993)
Chromosomal aberrations	Chinese hamster fibroblasts, V79	+	NT	600 µg/mL	Purity, > 99.7%	Armstrong et al. (1993)
Aneuploidy	Chinese hamster fibroblasts, V79	+	NT	50 µg/mL		Armstrong et al. (1993)
Tumour suppressor gene (*Tp53*) mutation	Zebrafish liver in vivo	+	NA	5 µg/L, 10 d	Purity, > 98%	Yin et al. (2009)
Forward mutation	*Saccharomyces cerevisiae* MP-1	+	NT	400 mg/L	Purity, 99%	Fahrig et al. (1978)
Gene conversion	*Saccharomyces cerevisiae* MP-1	–	NT	400 mg/L	Purity, 99%	Fahrig et al. (1978)
Reverse mutation	*Salmonella typhimurium* TA98, TA100, TA1535, TA1537	–	–	666 µg/plate	Purity, "practical" grade	Haworth et al. (1983)
Differential toxicity	*Bacillus subtilis* M45 (*recA*$^-$)	+	NT	3 µg/plate	Purity, > 97%	Ozaki et al. (2004)
Differential toxicity	*Bacillus subtilis* H17 (*recA*$^+$)	+	NT	6 µg/plate	Purity, > 97%	Ozaki et al. (2004)
Prophage λ induction	*Escherichia coli* WP2s	+	+	32 µM [6.3 µg/mL]	Purity, "practical grade" Toxicity + S9 at 255 µM [50.3 µg/mL]	DeMarini et al. (1990)

Table 4.1 (continued)

End-point	Species, tissue, cell line	Results[a]		Concentration (LEC/HIC)	Comments	Reference
		Without metabolic activation	With metabolic activation			
DNA strand breaks	Bacteriophage PM2 DNA	NT	+	1 mM [200 µg/mL]	More strand breaks observed with S9 from induced rats than from non-induced rats	Juhl et al. (1989)
DNA adducts, C8-dG O-adducts, LC/MS	2′-Deoxyguanosine	–	+	10 µM [2 µg/mL]	Horseradish peroxidase/H_2O_2 system	Dai et al. (2005)

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

C8-dG O-adducts, C8-deoxyguanosine O-adduct; DMSO, dimethyl sulfoxide; HIC, highest ineffective concentration; *Hprt*, hypoxanthine guanine phosphoribosyl transferase gene; LC-MS, liquid chromatography-mass spectrometry; LEC, lowest effective concentration; NA, not applicable; NR, not reported; NT, not tested; *Tk*, thymidine kinase gene

4.2.2 Oxidative stress

No studies in exposed humans, in human cells, or in rodents in vivo were available to the Working Group.

2,4,6-TCP (1.0 mM) induced oxidative stress in mouse embryonic fibroblasts, as shown by an upregulation of nuclear-E2-related factor 2 (*Nrf2*) and haem oxygenase 1 (*Hmox-1*) mRNA expression, the nuclear translocation of Nrf2 protein, and an upregulation of reactive oxygen species evaluated with dichlorodihydrofluorescein diacetate (DCFH) by flow cytometry (Zhang et al., 2014). [The Working Group noted the recognized limitations of DCFH as a marker of oxidative stress (Bonini et al., 2006; Kalyanaraman et al., 2012).]

In studies in non-mammalian systems, electron paramagnetic resonance demonstrated free-radical generation and oxidative stress in goldfish (*Carassius auratus*) liver after intraperitoneal injection with 2,4,6-TCP at a concentration of 5 mg/kg (Ji et al., 2007; Li et al., 2007). 2,4,6-TCP (10 µM) increased malondialdehyde content and the activities of peroxidase and superoxide dismutase in one plant species, *Arabidopsis* (Li et al., 2015).

The peroxidation of 2,4,6-TCP yielded 2,6-dichloro-1,4-benzoquinone (Ferrari et al., 1999), and a 2,4,6-trichlorophenoxyl radical intermediate was demonstrated by electron spin resonance analysis (Sturgeon et al., 2011; Sumithran et al., 2012).

4.2.3 Cell proliferation, cell death, and nutrient supply

No data from exposed humans or human cells in vitro were available to the Working Group.

In long-term studies, 2,4,6-TCP (0.5% in the diet) significant increased the incidence of leukocytosis in the peripheral blood of male rats, and of hyperplasia of the bone marrow in male and female rats (NTP, 1979). In male and female mice fed diets containing 2,4,6-TCP (0.5% in the diet), focal and nodular areas of hepatocyte hyperplasia were present (NTP, 1979; Huff, 2012).

2,4,6-TCP promoted differentiation of mouse primary lineage-depleted bone marrow cells into granulocytes (at 300 µM), macrophages (at 100 µM), and erythrocytes (at 10 µM) (Henschler et al., 2001).

Liao et al. demonstrated that in monkey kidney Vero cells, 2,4,6-TCP (0.25 µg/mL) induced cell membrane damage, as shown by flow cytometry analysis and propidium iodide staining (Liao et al., 2010a, b, 2011). 2,4,6-TCP (1.0 mM) induced apoptosis in mouse embryonic fibroblasts, as demonstrated by annexin V–fluorescein isothiocyanate/propidium iodide staining and flow cytometry analysis (Zhang et al., 2014).

4.2.4 Receptor-mediated effects

No data from exposed humans were available to the Working Group.

Unlike a parent compound of 2,4,6-TCP, prochloraz (an imidazole fungicide), 2,4,6-TCP (50 µM) did not inhibit the response induced by R1881 (an androgen-receptor agonist) in an androgen-receptor reporter-gene assay (Vinggaard et al., 2002). As noted in Section 4.1, 2,4,6-TCP decreased the expression of mRNA of several enzymes involved in steroidogenesis in H295R cells (Ma et al., 2011).

4.3 Data relevant to comparisons across agents and end-points

For the results of high-throughput screening assays carried out by the Toxicity Testing in the 21st Century (Tox21) and Toxicity Forecaster (ToxCast) programmes of the government of the USA, see Section 4.3 of the *Monograph* on pentachlorophenol in the present volume.

In a microarray study in the female rare minnow, 2,4,6-TCP (at 10 μg/L) altered levels of mRNA encoding proteins related to endocrine and metabolic pathways (Fang et al., 2014).

4.4 Cancer susceptibility data

No data were available to the Working Group.

4.5 Other adverse effects

No data from exposed humans were available to the Working Group.

5. Summary of Data Reported

5.1 Exposure data

2,4,6-Trichlorophenol (2,4,6-TCP) has been used primarily in various pesticide formulations and as a wood preservative. It has also been used as a fungicide, glue preservative, insecticide, bactericide, defoliant, and herbicide, as well as an anti-mildew agent for textiles, leather, and pelts. 2,4,6-TCP is used as an intermediate for the synthesis of several chemicals, including pentachlorophenol and 2,3,4,6-tetrachlorophenol, and their sodium salts. Commercial production of technical-grade 2,4,6-TCP in the USA was first reported in 1950, with production reduced in the mid-1970s because of the high cost of removing toxic impurities such as polychlorinated dibenzo-*para*-dioxins. Although most uses of 2,4,6-TCP were subsequently cancelled in the USA, it continues to be used in the synthesis of some fungicides. There were several registered manufacturers in North America, Europe, and Asia, but production levels were not available. Data on the environmental persistence of 2,4,6-TCP were sparse.

Occupational exposure to 2,4,6-TCP has been measured in two studies of sawmill workers and in several studies of hazardous-waste incinerator workers. The highest observed occupational exposures occurred in sawmill workers who were moving wood products that had been dipped in a chlorophenol solution (mean, 5.04 μmol/L [995 μg/L]), but this was based on only seven workers.

The general population may be exposed to 2,4,6-TCP from proximity to chlorophenol-treated wood products, from air emissions from waste incinerators, and from food and water contaminated with chlorophenols. Median urinary concentrations of 2,4,6-TCP in the general population were generally < 2 μg/g creatinine.

5.2 Human carcinogenicity data

Few studies of cancer in humans have been conducted that provide results relevant to evaluation of the carcinogenicity of 2,4,6-TCP. Two population-based case–control studies conducted in New Zealand provided results for men exposed occupationally, either in meat works or tanneries. One found an increased risk of soft tissue sarcoma, while the other found an increased risk of non-Hodgkin lymphoma, neither of which was statistically significant. Both studies were based on small numbers of exposed cases, and the role for other potentially confounding factors could not be ruled out. A large, international pooled cohort of workers exposed to phenoxy herbicides, chlorophenols, and dioxins included a small proportion of workers exposed to 2,4,6-TCP, among whom there was one case of soft tissue sarcoma and two cases of non-Hodgkin lymphoma. In light of the small number of studies available for each cancer site, and the very small numbers of cases exposed to 2,4,6-TCP in each study, the Working Group concluded that there were insufficient data to draw a conclusion regarding the carcinogenicity of 2,4,6-TCP.

5.3 Animal carcinogenicity data

There was one study of carcinogenicity in male and female mice fed diets containing 2,4,6-TCP. 2,4,6-TCP increased the incidence of hepatocellular adenoma, and of hepatocellular adenoma or carcinoma (combined) (with a significant positive trend) in males and females. There was also a significant positive trend in the incidence of hepatocellular carcinoma in females.

There was one study of carcinogenicity in male and female rats fed diets containing 2,4,6-TCP. 2,4,6-TCP increased the incidence of monocytic leukaemia (with a significant positive trend) in males. No significant increase in tumour incidence was reported in females.

One study in A/J mice treated by gavage and one study in A/J mice treated by intraperitoneal administration gave negative results.

5.4 Mechanistic and other relevant data

Data on the absorption, distribution, metabolism, and excretion of 2,4,6-TCP were sparse. On the basis of analogy to other chlorophenols, 2,4,6-TCP is likely to be rapidly absorbed, widely distributed in the body by blood circulation, and predominantly metabolized to conjugates that are excreted in the urine. Excretion after a single intraperitoneal administration in rats was rapid, with 90% of the administered dose excreted within 6 hours.

Regarding the key characteristics of carcinogens, adequate data were available to evaluate whether 2,4,6-TCP is genotoxic and induces oxidative stress.

There is *moderate* evidence that 2,4,6-TCP is genotoxic. One study in human cells in vitro and several studies in bacteria reported DNA strand breaks after administration of 2,4,6-TCP. Several studies in Chinese hamster cells in vitro observed effects on chromosomes, such as chromosomal aberrations, micronucleus formation, and hyperdiploidy, but not sister-chromatid exchanges. Mutations were observed in yeast, the mouse lymphoma assay, and zebrafish, but not in bacteria or Chinese hamster fibroblasts.

There is *moderate* evidence that 2,4,6-TCP induces oxidative stress. No studies in vivo were available; however, all available studies in vitro in mouse embryonic fibroblasts, fish, and plants reported increased generation of free radicals (including reactive oxygen species) and/or increased antioxidant activities. Additionally, a phenoxyl radical intermediate had been identified.

In the Toxicity Forecaster (ToxCast) and Toxicity Testing in the 21st Century (Tox21) high-throughput testing programmes of the government of the USA, 2,4,6-TCP was largely inactive, except for in a few assays related to oxidative stress.

There were no data on cancer susceptibility and few data on other adverse effects.

6. Evaluation

6.1 Cancer in humans

There is *inadequate evidence* in humans for the carcinogenicity of 2,4,6-trichlorophenol.

6.2 Cancer in experimental animals

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

6.3 Overall evaluation

2,4,6-Trichlorophenol is *possibly carcinogenic to humans* (*Group 2B*).

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