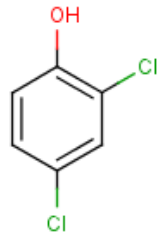
POLYCHLOROPHENOLS AND THEIR SALTS

Chlorophenols are chlorinated aromatic ring structures consisting of the benzene ring, –OH group and atom(s) of chlorine. Jointly with the 19 possible isomers, chloroderivatives of methyl- and ethyl-phenols are also considered as chlorophenols (Ivanciuc et al., 2006).

Among the 19 possible congeners of chlorophenols, 2-chlorophenol (2-CP), 2,4-dichlorophenol (2,4-DCP), 2,4,6- trichlorophenol (2,4,6-TCP) and pentachlorophenol (PCP) are listed in the Priority Pollutant List of the US Environmental Protection Agency (ATSDR, 2007).

Chemical structure



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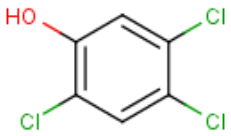
CAS No. 120-83-2
$C_6H_4Cl_2O$



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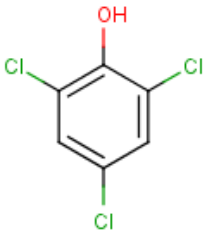
$C_6H_3Cl_3O$



2,4,6-Trichlorophenol
CAS No. 88-06-2
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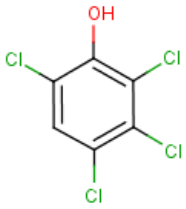
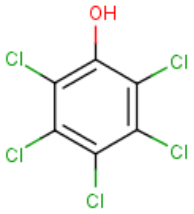


2,3,4,6-Tetrachlorophenol
CAS No 58-90-2
$C_6H_2Cl_4O$



Pentachlorophenol
CAS No 87-86-5
C_6HCl_5O

Properties

Table 1: Physical and chemical properties of chlorophenol compounds (source: Oloaniran & Igbinosa, 2011)

Compound	Melting point (°C)	Density (g cc^{-1})	Log K_{ow}	Log K_{oc}	Solubility in water (g L^{-1})	Vapor pressure (mm Hg)	Henry's law constant (atm m^3 mol^{-1})	Boiling point (°C)	pKa
2-Chlorophenol	9.3	1.2634	2.17	1.25–3.7	28.5	0.99	6.8×10^{-6}	174.9	8.49
4-Chlorophenol	43.2–43.7	1.2238	2.4	1.2–2.7	27.1	0.23	9.2×10^{-7}	220	8.85
2,4-Dichlorophenol	45	1.383	3.2	2.42–3.98	4.5	0.14	4.3×10^{-6}	210	7.68
2,4,5-Trichlorophenol	67	1.678	3.72	2.55–3.98	0.948	0.05	5.1×10^{-6}	235	7.43
2,4,6-Trichlorophenol	69	1.4901	3.69	1.94–3.34	0.8	0.03	5.7×10^{-6}	246	7.42
2,3,4,5-Tetrachlorophenol	116–117	1.67	4.8	2.9–4.14	0.166	0.0059	1.3×10^{-6}	Sublimes	6.96
2,3,4,6-Tetrachlorophenol	70	1.83	4.45	3.2–4.21	0.183	0.0059	3.6×10^{-6}	64	5.38
2,3,5,6-Tetrachlorophenol	115	1.84	4.9	3.88–4.90	0.1	0.0059	2.2×10^{-6}	288	5.48
Pentachlorophenol	190	1.987	5.01	1.2	0.014	0.0002	na	310	4.74

Octanol–water partition coefficient (K_{ow}); organic-carbon partitioning coefficient (K_{oc}); dissociation constant (pKa); not available (na).

Contamination source

Chlorophenols are found in wastewater, sludge products, surface waters, and groundwater (Olaniran & Igbinosa, 2011). Other sources of contamination are accidental spills, hazardous waste disposal sites, storage tanks, or municipal landfills. They are also used as bactericides, insecticides, herbicides, fungicides, wood preservatives and as intermediates in the production of dyes and pharmaceuticals (ATSDR, 2007; Olaniran & Igbinosa, 2011). Other sources of chlorophenols in the environment are processes of biodegradation of pesticides and herbicides. The herbicides 2,4-dichlorophenoxyacetic acids (2,4-D) and 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) often used on food crop can be broken down to 2,4-dichlorophenols and 2,4,5-trichlorophenols (ATSDR, 2007).

Chlorophenolic compounds and chlorophenols are formed during de combustion of organic matters and the incineration of municipal waste (Olaniran & Igbinosa, 2011).
The 2-CP, 2,4-DCP and 2,4,6-TCP are widely chosen as precursors for the manufacturing of other chlorophenol products and 2,4-DCP, 2,4,6-TCP and PCP are used as pesticides, herbicides, fungicides, molluscides, acaricides, bactericides, and mould inhibitors. Besides, 2-CP, 4-CP, 2,4-DCP and 2,4,6-TCP are the most significant chlorinated phenols formed as by-products of water chlorination (ATSDR, 1999; Czaplicka, 2004).
2,4,5-trichlorophenol has been used as a fungicide and a bactericide. 2,4,6-trichlorophenol has been used as a pesticide. 2,3,4,6-tetrachlorophenol has been used as a fungicide. Chlorophenols have also been formulated and used as salts in some applications (IARC, 1999).

- Pentachlorophenol (PCP)

Pentachlorophenol (PCP) is a man-made chemical that was first produced more than 80 years ago. It has a variety of applications in agriculture, industry, and domestic fields. Pentachlorophenol and its salt, sodium pentachlorophenate, were used primarily as wood preservatives on telephone poles, pilings and fence posts. They protect construction lumber, and also poles and posts, from fungal rots and decay. They also preventstaining. PCP has also been used as an herbicide, defoliant, fungicide, pre-harvest dessicant, bactericide, insecticide, and molluscicide and to control termites.
In Europe, pentachlorophenol and its derivatives, sodium pentachlorophenate and pentachlorophenyl laurate were used to control sap stain in green lumber. It was also used in Europe on millwork to prevent the growth of mould and fungi, and as a preservative for waterproof materials (i.e., tarpaulins) that are used in outdoor applications. In the United States, it was used almost entirely for treatment of utility poles (Agency for Toxic Substances and Disease Registry, 1994).
PCP has also been used for various pest controls and in anti-fouling agents, but was banned in textile products worldwide (Rylander et al., 2012). In the 1970s and 1980s, large quantities of PCP were produced in the United States, however, by the end of the 1980s, the U.S Environmental Protection Agency restricted the use of PCP to wood preservatives only (Fisher, 1991). Currently, it is not possible to purchase PCP treated wood for the general public in the U.S (Ruder and Yiin, 2011) but 11 million pounds were still produced in 2002 (U.S. EPA, 2008). The use of PCP in Europe decreased considerably during the 1990s (Zheng et al., 2011). In 2003, China produced approximately 3000 tons of PCP (Zheng et al., 2012). Sixty percent of the produced PCP quantities are used as a pesticide for controlling the vector-borne disease schistosomiasis. The remaining 40% are mainly used as wood preservatives.

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

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

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

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

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

Chlorophenolic compounds are recalcitrant to biodegradation and are therefore persistent in the environment. Because of their lipophilicity they can be transported through the cell membrane and

bio-accumulate in aquatic organisms (Pedroza et al., 2007).

In addition to environmental contamination of food, another potential source for chlorophenol contamination of food is migration from packaging materials. Shang-Zhi and Stanley (1983) reported levels of 0.1-0.68 ppm 2,4,6-TCP and 0.14-0.55 ppm 2,3,4,6-TeCP in cardboard food containers. Analysis for other chlorophenols was not completed. Shang-Zhi and Stanley (1983) indicated that the source of chlorophenol contamination was polyvinyl acetate and starch adhesives used in carton manufacture (ATSDR, 1999).

Bioaccumulation and bioconcentation

The bioaccumulation potential of 2-CP, 4-CP, 2,4-DCP, 2,4,5-TCP, 2,4,6-TCP, and 2,3,4,6-TeCP was reviewed by Loehr and Krishnamoorthy (1988). Based on bioconcentration values and log octanol/water partition coefficients, they concluded that all chlorophenols studied had the potential for accumulation in aquatic organisms. Logs of bioconcentration factors ranged from 0.81-2.33 for 2-CP, 1.79-3.28 for 2,4,5-TCP, and 1.952.3 for 2,3,4,6-TeCP (ATSDR, 1999).

Research on biomagnification of chemical residues within the aquatic food chain indicates that the potential for residue accumulation by fish through food chains is relatively insignificant (<10%) for most compounds when compared to the tissue residues resulting from the bioconcentration process (i.e., direct uptake from water) (Barrows et al. 1980). These data suggest that only those chemicals that are relatively persistent in fish tissues appear to have any potential for significant transfer through food chains (Barrows et al. 1980). A very short tissue half-life of <l day was measured after bluegill sunfish exposure to 2-CP was terminated (Veith et al., 1980). Therefore, due to their relatively low bioconcentration factors (<1,000) and short biological half-lives (<7 days), monochlorophenols will probably not biomagnify within aquatic food chains (Barrows et al., 1980). Data regarding the biomagnification of the higher chlorophenols were not located (ATSDR, 1999).

Studies on the uptake of 2,4-DCP from solution and soil by oats and soybeans is reported by ATSDR (1999). The compound was taken up by the plants, with the concentrations decreasing as the plants matured. At maturity, 2,4-DCP in oat seeds was below detection (<0.001 µg/g) and in soybeans was 0.003 µg/g. Data regarding the uptake of other chlorophenols by plants were not located.

It is not known whether 2,3,4,6-TeCP biomagnifies up the terrestrial food chain. Based on physical properties (i.e., greatest log octanol water partition coefficient), the tetrachlorophenols, rather than lower chlorinated phenols, would have the greatest potential to biomagnify (ATSDR, 1999).

Analytical method

Spectrometry technique and gas chromatography with electron capture detection permit the analysis of polychlorophenols.

Toxicity

Chlorophenolic compounds are considered harmful for human health due to their potential carcinogenic and mutagenic activity, and toxicity (ATSDR, 2007).

Carcinogenicity

Human carcinogenicity data

Mortality and/or cancer incidence has been analyzed in several cohort studies of chemical manufacturers, almost all of which have been incorporated within a multicentre international collaborative study, and also in a case–control study nested within this cohort. Two other cohort studies have focused on leather tanneries in Sweden and sawmills in Canada where chlorophenols were used. In addition, case–control studies have examined the association of chlorophenols with soft-tissue sarcoma (one study in New Zealand, four in Sweden and one in the United States), non-Hodgkin lymphoma (one study in New Zealand, one in Sweden and one in the United States), thyroid cancer (one study in Sweden), nasal and nasopharyngeal cancer (one study in Sweden), colon cancer (one study in Sweden) and liver cancer (one study in Sweden). These investigations have shown significant associations with several types of cancer, but the most consistent findings have been for soft-tissue sarcoma and non-Hodgkin lymphoma. Although the odds ratios in some case–control studies may have been inflated by recall bias, this cannot explain all of the findings. Nor are they likely to have arisen by chance. It is not possible, however, to exclude a confounding effect of polychlorinated dibenzo-*para*-dioxins which occur as contaminants in chlorophenols (Collins et al., 2006, McLean et al., 2009, Zheng et al., 2009).

Animal carcinogenicity data

2,4-Dichlorophenol was tested in one study in mice and in two studies in rats by oral administration. No increase in the incidence of tumours was found. 2,4,5-Trichlorophenol has not been adequately tested for carcinogenicity. 2,4,6-Trichlorophenol was tested in one study in mice and in one study in rats by oral administration and in one study in mice in a screening test for lung tumours. In mice, it increased the incidences of benign and malignant tumours of the liver and in rats mononuclear cell leukaemia. It did not induce lung adenomas in mice. No data on the carcinogenicity of tetrachlorophenols in experimental animals were available to the Working Group. Three different pentachlorophenol formulations were tested for carcinogenicity by oral administration in two experiments in mice and in one study in rats. In mice, a dose-related increase in the incidence of hepatocellular adenomas and carcinomas was observed in males exposed to either formulation and of hepatocellular adenomas in females exposed to one of the formulations. A dose-related increase in the incidence of adrenal phaeochromocytomas was observed in male mice exposed to either formulation, and an increase was also seen in females exposed to one of the formulations at the highest dose. A dose-related increase in the incidence of malignant vascular tumours of the liver and spleen was seen in female mice exposed to either formulation. In rats, no increase in tumours was seen following oral administration of pentachlorophenol for 24 months. However, in rats in the same study receiving a higher concentration for 12 months and held for an additional year, an increased incidence of mesotheliomas of the tunica vaginalis was observed (IARC, 1999).

There is *limited evidence* in humans for the carcinogenicity of combined exposures to polychlorophenols or to their sodium salts. There is *evidence suggesting lack of carcinogenicity* of 2,4-dichlorophenol in experimental animals. There is *inadequate evidence* in experimental animals for the carcinogenicity of 2,4,5-trichlorophenol. There is *limited evidence* in experimental animals for the carcinogenicity of 2,4,6- trichlorophenol. There is *sufficient evidence* in experimental animals for the carcinogenicity of pentachlorophenol. Combined exposures to polychlorophenols or to their sodium salts are *possibly carcinogenic to humans (Group 2B) (IARC, 1999)*.

Kinetics

Chlorophenols are absorbed fairly rapidly, distributed mainly to the kidney and liver and excreted principally via urine; low chlorine-substituted compounds are conjugated with sulfate and glucuronide to a greater extent than the more highly chlorine-substituted compounds. Chlorinated *para*-hydroquinone formation is a minor metabolic pathway but not for 2,3,5,6-tetrachlorophenol and pentachlorophenol. In rats, the liver is the main target organ. Otherwise, few remarkable effects have been observed. 2,4,6-trichlorophenol may exhibit weak aneugenic and clastogenic activity. According to IARC, information on other chlorophenols is inadequate to allow assessment of their genotoxicity. Pentachlorophenol, after metabolic activation, may exhibit weak clastogenic activity by enhancing oxidative DNA damage (IARC, 1999).
PCP is efficiently absorbed through the skin, the lungs, and the gastrointestinal tract. For the general population, the uptake of PCP by the oral route is the most important.

Acute toxicity

The main risks in acute poisoning are: hyperpyrexia, tachycardia, and a rise in the metabolic rate leading to death by cardiac arrest.
Symptoms of acute systemic poisoning are: headache, profuse sweating, depression, nausea, weakness, and sometimes fever; tachycardia, tachypnea, pain in the chest, thirst. Abdominal colic is frequent. Mental distress can occur, progressing to coma and occasionally convulsions; irritation of the skin, mucous membranes, and respiratory tract (including painful irritation of the nose and intense sneezing when pentachlorophenol is inhaled); contact dermatitis and chloracne (International Programme on Chemical Safety Poisons Information Monograph 405 Chemical, 1989).

Chronic toxicity

In chronic exposure, the main risks are: skin, blood, neurological and respiratory disorders, porphyria, non-specific symptoms, and the possibility of cancer.
Chronic exposure can cause: porphyria cutanea tarda, weight loss, increased basal metabolic rate, functional changes of the liver and kidneys. Insomnia and vertigo have also been reported.

Target organs are: skin, respiratory system, central nervous system (CNS), liver and kidneys, but especially metabolism at the cellular level.

Establishment of Health Based Reference Values

Non cancer effect

The predominant noncancer effect of subchronic and chronic oral exposure to PCP is hepatic toxicity. The US EPA established a LOAEL of 1.5 mg/kg-day based on hepatotoxicity in dogs (Mecler, 1996) characterized by dose-related increases in incidence and severity of pigmentation, cytoplasmic vacuolation, chronic inflammation, and severely discolored livers accompanied by increased relative liver weight and serum enzymes, and increased absolute liver weight (statistically significant in females) (US EPA, 2010).

The derivation of the reference dosis (RfD) for liver effects from the 1-year toxicity study in beagle dogs (Mecler, 1996) is calculated from the LOAEL by application of a composite uncertainty factor (UF). The composite UF of 300 consists of individual UFs of 10 for intra-species variation, 10 for inter-species variation, and 3 for the use of a LOAEL instead of a NOAEL. The US EPA (2010) established a RfD of 0.005 mg/kg/day (=1.5 mg/kg-day ÷ 300).

RIVM suggest a TDI of 3.10^{-3} mg/kg/day for chronic exposure to 2,4,6-trichlorophenol by oral route (Baars et al., 2001). This value was established for 2,4 dichlorophenol and than applied to all other chlorophenols (mono, di, tri and tetra) (INERIS, 2005).

Cancer effect

US EPA (2010) selected the most sensitive cancer risk estimate, the slope factor of 4 × 10-1 (mg/kg-day)-1 derived for technical-grade PCP, which is the higher cancer potency of the two formulations, to represent the cancer risk estimate for PCP.

Levels of exposure associated with carcinogenic effects of chlorophenols has been reported by Demers et al. (2006) and Cooper and Jones (2008). Since cancer effects could occur at lower exposure levels, a system developed by US EPA estimated excess risks, ranging from a risk of 1 in 10 000 to 1 in 10 000 000. An oral Minimal Risk Level (MRL) of 0.003 mg/kg/day would be applicable to TCPs for intermediate exposure duration according to the updated toxicological profiles of chlorophenols of the Agency for Toxic Substances and Disease Registry of the US Department of Health and Human Services (ATSDR, 2007).

Occurrence in food

Chlorophenols have been measured in chlorinated drinking water at parts per trillion (ppt) concentrations (ATSDR, 1999).

4-CP, 2,4DCP, and 2,4,6-TCP were not detected (detection limit 0.02 mg/kg) in fish from 13 Lake Michigan tributaries or in fish from northern Alberta, Canada, (detection limit 0.01 µg/g) (ATSDR, 1999). Fish in the Fraser River estuary downstream from a lumber mill were found to contain chlorophenols including 2,4,5-TCP, 2,4,6-TCP, 2,3,5,6-TeCP, 2,3,4,6-TeCP, and 2,3,4,5-TeCP. Among the chlorophenols discussed in this profile, 2,3,4,6-TeCP was the most predominant compound, and the highest concentrations (49 ng/g) were found in sculpin, which had concentrations of about 400 times the concentration found in water in the estuary. Trichlorophenol (combined 2,4,5 and 2,4,6 isomers) concentrations of 29-629 ppb (wet weight) were measured in fish livers collected from the Pacific Ocean 6 km northwest of the discharge zone for the Los Angeles County waste water treatment plant. Concentrations in edible tissues were not measured (ATSDR, 1999).

PCP could be found in drinking water, fish, meat, berries, vegetables and grains (Rylander et al., 2012).

Dietary exposure assessment

PCP has been detected in the serum, urine, adipose tissues, and even the seminal fluid of the general population. Concentration in blood of 6300 ng/l (n=20 samples) have been reported by Dirtu et al. (2010) in Belgium in 2000. Koppen et al. (2002) reported median concentration of 713.37 ng/g fat in a pooled sample of serum from 200 women (50-65 years) living in Flanders (Belgium). Rylander et al. (2012) reported median concentration of 711 ng/l ww in blood of postmenopausal women from general Norwegian population (sampled in 2004).

Although food monitoring data are lacking, exposure to 2,4-DCP through the ingestion of food is expected to be relatively minor. Estimates of total chlorophenol intake reviewed by WHO (1989) ranged from 2.2 µg/person/day assuming contaminated water and fish were the main sources of exposure, to about 10-40 µg/person/day assuming indoor rooms were treated with a chlorophenol preservative.

Risk characterization

Nougadère et al. (2011) have calculated a EDI (mean % of TDI) for pentachlorophenol between 0

and 0.5% for the French children and between 0 and 0.3% for the French adult on basis of a TDI of 0.03 mg/kg bw/day from EPA (1993).

Legislation

The World Health Organization has established an international drinking-water guideline for 2,4,6-trichlorophenol of 200 µg/l and a provisional international drinking water guideline for pentachlorophenol of 9 µg/l. No international guideline for 2,4- dichlorophenol, 2,4,5- trichlorophenol or 2,3,4,6-tetrachlorophenol in drinking-water has been established (WHO, 1993).

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