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Chlorophenols

Guidelines

The maximum acceptable concentrations (MAC) and aesthetic objectives (AO) for four chlorophenols in drinking water are:

	MAC		AO	
	mg/L	**μg/L**	**mg/L**	**μg/L**
2,4-dichlorophenol	*0.9*	*900*	*≤ 0.0003*	*≤ 0.3*
2,4,6-trichlorophenol	*0.005*	*5*	*≤ 0.002*	*≤ 2*
2,3,4,6-tetrachlorophenol	*0.1*	*100*	*≤ 0.001*	*≤ 1*
pentachlorophenol	*0.06*	*60*	*≤ 0.030*	*≤ 30*

Identity, Use and Sources in the Environment

Chlorophenols are organic chemicals in which one or more hydrogen atoms of phenol (1-hydroxybenzene) are replaced by one or more atoms of chlorine. There are 19 chlorophenol congeners:

2-chlorophenol (2-CP)
3-chlorophenol (3-CP)
4-chlorophenol (4-CP)

2,3-dichlorophenol (2,3-DCP)
2,4-dichlorophenol (2,4-DCP)
2,5-dichlorophenol (2,5-DCP)
2,6-dichlorophenol (2,6-DCP)
3,4-dichlorophenol (3,4-DCP)
3,5-dichlorophenol (3,5-DCP)

2,3,4-trichlorophenol (2,3,4-TCP)
2,3,5-trichlorophenol (2,3,5-TCP)
2,3,6-trichlorophenol (2,3,6-TCP)
2,4,5-trichlorophenol (2,4,5-TCP)
2,4,6-trichlorophenol (2,4,6-TCP)
3,4,5-trichlorophenol (3,4,5-TCP)

2,3,4,5-tetrachlorophenol (2,3,4,5-TeCP)
2,3,4,6-tetrachlorophenol (2,3,4,6-TeCP)
2,3,5,6-tetrachlorophenol (2,3,5,6-TeCP)

pentachlorophenol (PCP)

All the chlorophenols are solids (melting points 33 to 191°C) except 2-CP, which is a liquid with a melting point of 9°C. Most chlorophenols and all of their sodium salts are soluble in water. Solubility is slight for a few, including PCP (solubility 9.6 mg/L at 20°C). Vapour pressures are low for the higher molecular weight compounds. The log octanol–water partition coefficient increases with the number of chlorine atoms from 2.15 for 2-CP to 5.0 for PCP.[1,2]

Chlorophenols with few chlorine atoms are used mainly as starting materials for the synthesis of higher chlorinated phenols or chlorophenol-derived products, such as the chlorophenoxyacetic acid herbicides.

Chlorophenols are no longer manufactured in Canada; however, they continue to be imported. They are widely used in pesticides; currently, there are seven chlorinated phenols incorporated into 110 pesticide products registered for use in Canada under the Pest Control Products Act.[3] Both PCP and TeCPs are used extensively as wood preservatives[4] and account for the majority of chlorophenols imported for use in Canada. In 1984, sales of chlorophenol-containing products (tonnes of active ingredient) registered under the Pest Control Products Act were as follows:[5]

PCP and its sodium salt	3400 tonnes
TeCPs and their sodium salts	490 tonnes
2,4,5-TCP and its sodium salt	< 1 tonne

Exposure

Chlorophenols may be introduced into water either during their manufacture and use or through degradation of other chemicals (e.g., phenoxyalkanoic acids). Chlorophenols may also be formed as a result of the chlorination of humic matter or of natural carboxylic acids during the chlorination of municipal drinking water.[3,4] Low solubility in water may be increased by formation of the sodium or potassium salt congeners. Pentachlorophenol is the most persistent of the chlorophenols.

Concentrations of chlorophenols in Canadian surface waters rarely exceed 2 μg/L.[3] Amounts of chlorophenols in drinking water have recently been determined at 40 potable water treatment plants across Canada.[6] Pentachlorophenol was found in more than 20% of the samples of raw water taken in the fall and winter, at concentrations up to 53 ng/L; mean concentrations were 1.9 and 2.8 ng/L, respectively. The chlorinated phenols identified most frequently in treated

water samples were 4-CP, 2,4-DCP and 2,4,6-TCP. Mean concentrations of 4-CP and 2,4-DCP were less than 10 ng/L, regardless of time of year of sampling. Mean concentrations of 2,4,6-TCP were ≤40 ng/L. In Alberta, treated water from 29 municipal drinking water supplies was sampled for five chlorophenols (2-CP, 2,4-DCP, 2,4,5-TCP, 2,4,6-TCP and PCP) for two to four years. 2,4,6-Trichlorophenol was detected in 12 of 29 supplies at concentrations ranging from a trace to 3 μg/L. Pentachlorophenol was detected in two of 29 supplies at the detection limit (1 μg/L).[7]

Low concentrations (<0.01 mg/kg) of TeCPs and PCP have been detected in Canadian foods.[3] Higher concentrations have been found, however, in products derived from animals exposed to PCP-contaminated wood and wood shavings and in some vegetables stored in PCP-treated wooden bins. There is a paucity of data concerning levels of chlorophenols in air in Canada. Air in PCP-treated homes can contain PCP at concentrations as high as 1 $\mu g/m^3$.[3]

Other sources of human exposure to chlorophenols include disinfectants, photographic solutions, fabrics and pharmaceuticals.[3] Treated wood containing PCP and TeCPs may also contribute to exposure.

Total exposure of adult Canadians to chlorophenols has been estimated to be approximately 15 μg/d;[3] the percent contribution of each route of exposure is as follows:

food	40%
water	19%
indoor and ambient air	28%
miscellaneous	13%

Analytical Methods and Treatment Technology

Chlorophenols in water may be analysed by derivatization followed by gas chromatography and mass spectrometry or electron capture detection. The practical quantitation limits (PQL) (based on the ability of laboratories to measure chlorophenols within reasonable limits of precision and accuracy) range from 0.002 to 0.008 μg/L.[6]

Available data indicate that concentrations of 2,4,6-TCP and other chlorophenols are not reduced significantly during conventional drinking water treatment processes. Although few relevant data are available, it is likely that concentrations below 1 μg/L can commonly be achieved by packed tower aeration and granular activated carbon adsorption.[8]

Health Effects

Chlorophenols are readily absorbed when administered by the oral, inhalation or dermal routes.[1,2] They accumulate mostly in the liver and kidney of experimental animals and to a lesser degree in the brain, muscle and fat.[1] They are bound to glucuronide or sulphate in the liver. 2,3,5,6-Tetrachlorophenol is metabolized to a more toxic substance, tetrachloro-p-hydroquinone. Chlorophenols are eliminated primarily in the urine in both free and bound forms, with lesser amounts in faecal matter. Four human volunteers who ingested PCP at a concentration of 0.1 mg/kg bw eliminated 74 and 12% of the administered dose as PCP and PCP-glucuronide, respectively, in their urine within eight days.[9] Another 4% was eliminated in the faeces.

The toxic effects of chlorophenols are directly proportional to the degree of chlorination.[3] Acute exposure to lesser chlorinated phenols in humans results in muscular twitching, spasms, tremors, weakness, ataxia, convulsions and collapse. Acute poisoning by PCP is characterized by general weakness, fatigue, ataxia, headache, anorexia, sweating, hyperpyrexia, nausea, vomiting, tachycardia, abdominal pain, terminal spasms and death. In man, the minimum lethal oral dose of PCP has been estimated to be 29 mg/kg bw.

Soft-tissue sarcomas, Hodgkin's disease and leukaemia have been reported in epidemiological studies of occupational groups exposed to chlorinated phenols and phenoxy acids. The World Health Organization examined data for 2,4,5-TCP, 2,4,6-TCP and PCP and concluded that, at the time of review, the data were inadequate for an evaluation of carcinogenicity.[10]

Slight changes in liver histopathology were reported in male mice following six months of exposure to 2,4-DCP at 230 mg/kg bw per day in their diet.[11] The authors concluded that the no-observed-adverse-effect level (NOAEL) was 100 mg/kg bw per day. The study was, however, limited, and the published report was incomplete: only one sex was used; the period of administration ranged from five to six months; and only seven of the 10 animals in each group were examined.

Lower chlorinated phenols were tested for carcinogenicity by Boutwell and Bosch.[12] Site-specific papillomas were observed when solutions of 2-CP or 2,4-DCP were applied to the skin of mice without the addition of any tumour initiators. When the initiator 9,10-dimethyl-1,2-benzanthracene (DMBA) was used, carcinomas were observed at the treatment site in some mice. These data are, however, inadequate for a proper assessment of the carcinogenicity of these chlorophenols.

In a National Cancer Institute bioassay, 50 male and 50 female rats were administered either 5000 or 10 000 ppm 2,4,6-TCP (96 to 97% pure) in their diet for 106 or 107 weeks.[13] Fifty male mice were administered either 5000 or 10 000 ppm for 105 weeks. Fifty female mice were initially given 10 000 or 20 000 ppm for 38 weeks, followed by 2500 or 5000 ppm for 67 weeks. 2,4,6-Trichlorophenol was carcinogenic to male rats, inducing lymphomas or leukaemias, and carcinogenic to

mice of both sexes, inducing hepatocellular carcinomas or adenomas. The test compound was 96 to 97% pure, containing up to 17 minor contaminants. Chlorinated dibenzo-p-dioxin content was not determined.

The carcinogenicity of PCP has been investigated in two chronic studies. Two hybrid strains of mice were exposed to PCP at 46.4 mg/kg bw per day, by gavage for three weeks, followed by exposure to 130 ppm in the diet for 74 weeks.[14] There were no significant increases in tumour incidence in male or female mice of either strain.

In a second chronic bioassay of PCP, male and female rats were administered PCP in the diet for 22 to 24 months, at concentrations of 0, 1, 3, 10 or 30 mg/kg bw per day.[15] Clinical examination revealed effects at the highest dose level, including decreased body weight gain in females, increased serum glutamic pyruvic transaminase activity in both males and females and increased specific gravity of urine in females. Histological examination indicated an accumulation of pigment in the liver and kidney of female rats treated with 30 and 10 mg/kg bw per day and of male rats treated with 30 mg/kg bw per day. Ingestion of 3 mg/kg bw per day or less by females and 10 mg/kg bw per day by males was not associated with significant toxicological effects. It should be noted that group size was limited to 27 rats and that there was high mortality in both control and exposed males. It was determined that the test compound was composed of 90% PCP, 10% TeCPs and small amounts of TCPs and non-phenolics.

Pentachlorophenol does not appear to be a potent mutagen. It probably does not cause point mutations and does not seem to cause chromosomal aberrations. However, PCP has been demonstrated to increase mitotic gene conversion.[2]

Chlorophenols are not considered to be teratogenic, although animal studies indicate that PCP and TeCPs can be embryotoxic.[16,17] Delayed ossification of the skull bones was observed in rat foetuses of dams fed 30 mg/kg bw per day of 2,3,4,6-TeCP (99.6% pure) in corn oil by gavage during days 6 to 15 of gestation.[16] A NOAEL of 10 mg/kg bw per day was proposed by the authors for embryotoxicity. In a similar study with PCP, delayed ossification was observed at the lowest dose level tested (5 mg/kg bw per day).[17]

Pentachlorophenol caused a reduction in mean adult body weight when administered to female rats at 30 mg/kg bw per day prior to mating, during mating and gestation and throughout lactation.[15] There was also a significant decrease in neonatal survival and growth among litters of females in this group. Ingestion of 3 mg/kg bw per day had no effect on reproduction, neonatal growth, survival or development. The test compound was 90% PCP and 10% TeCPs. Trichlorophenols and non-phenolics were present in small quantities.

Classification and Assessment

2,4-Dichlorophenol: The data available are considered to be inadequate to classify 2,4-DCP with respect to its potential carcinogenicity. It has, therefore, been included in Group VA (inadequate data for evaluation).

For compounds classified in Group VA, the maximum acceptable concentration (MAC) is derived on the basis of division of the NOAEL or lowest-observed-adverse-effect level (LOAEL) in an animal species by an uncertainty factor. For 2,4-DCP, the acceptable daily intake (ADI) is derived as follows:

$$\text{ADI} = \frac{100 \text{ mg/kg bw per day}}{1000} = 0.1 \text{ mg/kg bw per day}$$

where:

- 100 mg/kg bw per day is the NOAEL observed in the only available subchronic (six months) feeding study,[11] which suffered from methodological limitations
- 1000 is the uncertainty factor (×10 for less-than-lifetime study and limitations in study design; ×10 for intraspecies variation; and ×10 for interspecies variation).

2,4,6-Trichlorophenol: 2,4,6-Trichlorophenol is classified in Group II — probably carcinogenic to man (inadequate evidence in humans, sufficient evidence in animals); it has been shown to be carcinogenic to male rats and mice of both sexes.[13] Incorporating a surface area correction and using the robust linear extrapolation model, one can calculate that the unit lifetime risk associated with the ingestion of 1 µg/L 2,4,6-TCP in drinking water ranges from 1.8×10^{-8} (based on hepatocellular carcinomas in female mice) to 4.3×10^{-7} (based on leukaemia in male rats)*.[18] The estimated ranges of concentrations in drinking water corresponding to lifetime risks of 10^{-5}, 10^{-6} and 10^{-7} for these same tumour types based on the model described above are as follows:

Lifetime risk	Concentrations in drinking water (µg/L)
10^{-5}	23 – 555.6
10^{-6}	2.3 – 55.6
10^{-7}	0.23 – 5.6

2,3,4,6-Tetrachlorophenol: The available data are inadequate to classify 2,3,4,6-TeCP with respect to its potential carcinogenicity. It is therefore classified in Group VA (inadequate data for evaluation). The ADI is derived as follows:

$$\text{ADI} = \frac{10 \text{ mg/kg bw per day}}{1000} = 0.01 \text{ mg/kg bw per day}$$

* Average adult body weight = 70 kg; average daily intake of drinking water = 1.5 L.

where:

- 10 mg/kg bw per day is the NOAEL for embryotoxicity observed in a short-term study[16]
- 1000 is the uncertainty factor (×10 for intraspecies variation; ×10 for interspecies variation; and ×10 for use of short-term bioassay data).

Pentachlorophenol: The available epidemiological data and results of studies in experimental animals are inadequate to classify PCP with respect to its potential carcinogenicity. It is therefore included in Group VA (inadequate data for evaluation). The ADI is derived as follows:

$$\text{ADI} = \frac{3 \text{ mg/kg bw per day}}{500} = 0.006 \text{ mg/kg bw per day}$$

where:

- 3 mg/kg bw per day is the NOAEL reported in both a subchronic reproductive study and a limited chronic study[15]
- 500 is the uncertainty factor (×10 for intraspecies variation; ×10 for interspecies variation; and ×5 for limitations of the chronic study).

Aesthetic Considerations

Threshold odour values (TOV) for some chlorophenols are shown below:

Substance	TOV (μg/L)	Reference
2-CP	0.1	19
3-CP	0.1	20
4-CP	0.1	20
2,3-DCP	0.04	20
2,4-DCP	0.3	21
2,5-DCP	0.5	20
2,6-DCP	0.2	20
3,4-DCP	0.3	20
2,4,5-TCP	1.0	20
2,4,6-TCP	2.0	20
2,3,4,6,-TeCP	1.0	20
PCP	30	22

Rationale

2,4-Dichlorophenol: Because 2,4-DCP is classified in Group VA (inadequate data for evaluation), the MAC is derived from the ADI as follows:

$$\text{MAC} = \frac{0.1 \text{ mg/kg bw per day} \times 70 \text{ kg} \times 0.20}{1.5 \text{ L/d}} \cong 0.9 \text{ mg/L}$$

where:

- 0.1 mg/kg bw per day is the ADI, as derived above
- 70 kg is the average body weight of an adult
- 0.20 is the proportion of total daily intake ingested in drinking water
- 1.5 L/d is the average daily consumption of drinking water for an adult.

Based on the threshold odour value, the aesthetic objective (AO) for 2,4-DCB is ≤0.0003 mg/L.

2,4,6-Trichlorophenol: Because 2,4,6-TCP is classified in Group II (probably carcinogenic to man), the MAC is derived based on consideration of available practicable treatment technology and estimated lifetime cancer risks. Because the MAC must also be measurable by available analytical methods, the PQL is also taken into consideration in its derivation.

An MAC of 0.005 mg/L (5 μg/L) for 2,4,6-TCP was established, therefore, on the basis of the following considerations:

(1) The estimated maximum unit lifetime cancer risk associated with the ingestion of 1 μg/L 2,4,6-TCP in drinking water is 4.3×10^{-7} (based on leukaemias in male rats). Therefore, the estimated lifetime risk associated with the ingestion of drinking water containing 5 μg/L 2,4,6-TCP (i.e., 2.2×10^{-6}) is within a range that is considered to be "essentially negligible."

(2) Although it is unlikely that 2,4,6-TCP concentrations are reduced significantly during conventional drinking water treatment processes, limited data available indicate that concentrations in Canadian drinking water supplies are generally considerably less than 5 μg/L. Although few relevant data are available, it is likely that concentrations of 2,4,6-TCP below 1 μg/L can be achieved by packed tower aeration and granular activated carbon adsorption.

(3) The PQL (based on the ability of laboratories to measure 2,4,6-TCP within reasonable limits of precision and accuracy) is 0.008 μg/L.

Based on the threshold odour value, the aesthetic objective (AO) for 2,4,6-TCP is ≤0.002 mg/L.

2,3,4,6-Tetrachlorophenol: Because 2,3,4,6-TeCP is classified in Group VA (inadequate data for evaluation), the MAC is derived from the ADI as follows:

$$\text{MAC} = \frac{0.01 \text{ mg/kg bw per day} \times 70 \text{ kg} \times 0.20}{1.5 \text{ L/d}} \cong 0.100 \text{ mg/L}$$

where:

- 0.01 mg/kg bw per day is the ADI, as derived above
- 70 kg is the average body weight of an adult
- 0.20 is the proportion of total daily intake ingested in drinking water
- 1.5 L/d is the average daily consumption of drinking water for an adult.

Based on the threshold odour value, the aesthetic objective (AO) for 2,3,4,6-TeCP is ≤0.001 mg/L.

Pentachlorophenol: Because pentachlorophenol is classified in Group VA (inadequate data for evaluation), the MAC is derived from the ADI as follows:

$$\text{MAC} = \frac{0.006 \text{ mg/kg bw per day} \times 70 \text{ kg} \times 0.20}{1.5 \text{ L/d}} \cong 0.06 \text{ mg/L}$$

where:

- 0.006 mg/kg bw per day is the ADI, as derived above
- 70 kg is the average body weight of an adult
- 0.20 is the proportion of total daily intake ingested in drinking water
- 1.5 L/d is the average daily consumption of drinking water for an adult.

Based on the threshold odour value, the aesthetic objective (AO) for PCP is ≤0.030 mg/L.

Other chlorophenols: There are no data available to serve as a basis for establishing MACs for the other chlorophenols.

References

1. World Health Organization. Environmental health criteria for chlorophenols other than pentachlorophenol. Supplement. Draft, July 31 (1986).

2. World Health Organization. Environmental health criteria for pentachlorophenol. Draft, March 19 (1986).

3. Department of National Health and Welfare. Chlorophenols and their impurities: a health hazard evaluation. Draft report, Bureau of Chemical Hazards (1986).

4. Exon, J.H. A review of chlorinated phenols. Vet. Hum. Toxicol., 26(6): 508 (1984).

5. Environment Canada. Dioxin-containing chemicals: sales and imports. Commercial Chemicals Branch (1985).

6. Sithole, B.B. and Williams, D.T. Halogenated phenols in water at forty Canadian potable water treatment facilities. J. Assoc. Off. Anal. Chem., 69(5): 807 (1986).

7. Alberta Environment. Drinking water survey 1978–1985. Municipal Engineering Branch, Pollution Control Division, Edmonton (1985).

8. McDonald, R.A. Water treatment technology review—control of chemical contaminants. Contractor's report for Department of National Health and Welfare, M.R.2, McDonald and Associates, Regina (1985).

9. Braun, W.H., Blau, G.E. and Chenoweth, M.B. The metabolism/pharmacokinetics of pentachlorophenol in man, and a comparison with the rat and a monkey model. Toxicol. Appl. Pharmacol., 45(1): 278 (1978).

10. World Health Organization. Guidelines for drinking-water quality. Vol. 2. Health criteria and other supporting information. Geneva (1984).

11. Kobayashi, S., Toida, S., Kawamura, H., Chang, H.S., Fukuda, T. and Kawaguchi, K. Chronic toxicity of 2,4-dichlorophenol in mice: a simple design for the toxicity of residual metabolites of pesticides. J. Med. Soc. Toho (Japan), 19(3–4): 356 (1972).

12. Boutwell, R.K. and Bosch, D.K. The tumor-promoting action of phenol and related compounds for mouse skin. Cancer Res., 19: 413 (1959).

13. National Cancer Institute. Bioassay of 2,4,6-trichlorophenol for possible carcinogenicity. Tech. Rep. Ser. No. 155, DHEW Publ. No. (NIH) 79-1711, U.S. Department of Health, Education and Welfare (1979).

14. Innes, J.R.M., Ulland, B.M., Valerio, M.G., Petrucelli, L., Fishbein, L., Hart, E.R., Pallotta, A.J., Bates, R.R., Falk, H.L., Gart, J.J., Klein, M., Mitchell, I. and Peters, J. Bioassay of pesticides and industrial chemicals for tumorigenicity in mice: a preliminary note. J. Natl. Cancer Inst., 42(6): 1101 (1969).

15. Schwetz, B.A., Quast, J.F., Keeler, P.A., Humiston, C.G. and Kociba, R.J. Results of two-year toxicity and reproduction studies on pentachlorophenol in rats. In: Pentachlorophenol: chemistry, pharmacology and environmental toxicology. K. Rao (ed.). Plenum Press, New York, NY. pp. 301–309 (1978).

16. Schwetz, B.A., Keeler, P.A. and Gehring, P.J. Effect of purified and commercial grade tetrachlorophenol on rat embryonal and fetal development. Toxicol. Appl. Pharmacol., 28(1): 146 (1974).

17. Schwetz, B.A., Keeler, P.A. and Gehring, P.J. The effect of purified and commercial grade pentachlorophenol on rat embryonal and fetal development. Toxicol. Appl. Pharmacol., 28(1): 151 (1974).

18. Murdoch, D. Risk assessments—drinking water—revision. Memorandum to V. Armstrong, Monitoring and Criteria Division, Department of National Health and Welfare, November 17 (1986).

19. U.S. Environmental Protection Agency. Ambient water quality criteria for 2-chlorophenol. EPA-440/5-80-034, NTIS Publ. No. PB81-117459, Office of Water Regulations and Standards (1980).

20. U.S. Environmental Protection Agency. Ambient water quality criteria for chlorinated phenols. EPA-440/5-80-032, NTIS Publ. No. PB81-117434, Office of Water Regulations and Standards (1980).

21. U.S. Environmental Protection Agency. Ambient water quality criteria for 2,4-dichlorophenol. EPA-440/5-80-042, NTIS Publ. No. PB81-117533, Office of Water Regulations and Standards (1980).

22. U.S. Environmental Protection Agency. Ambient water quality criteria for pentachlorophenol. EPA-440/5-80-065, NTIS Publ. No. PB81-117764, Office of Water Regulations and Standards (1980).