

Chlorophenols in Drinking-water

Background document for development of
WHO Guidelines for Drinking-water Quality

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Preface

One of the primary goals of WHO and its member states is that “all people, whatever their stage of development and their social and economic conditions, have the right to have access to an adequate supply of safe drinking water.” A major WHO function to achieve such goals is the responsibility “to propose regulations, and to make recommendations with respect to international health matters”

The first WHO document dealing specifically with public drinking-water quality was published in 1958 as *International Standards for Drinking-Water*. It was subsequently revised in 1963 and in 1971 under the same title. In 1984–1985, the first edition of the WHO Guidelines for drinking-water quality (GDWQ) was published in three volumes: Volume 1, Recommendations; Volume 2, Health criteria and other supporting information; and Volume 3, Surveillance and control of community supplies. Second editions of these volumes were published in 1993, 1996 and 1997, respectively. Addenda to Volumes 1 and 2 of the second edition were published in 1998, addressing selected chemicals. An addendum on microbiological aspects reviewing selected microorganisms was published in 2002.

The GDWQ are subject to a rolling revision process. Through this process, microbial, chemical and radiological aspects of drinking-water are subject to periodic review, and documentation related to aspects of protection and control of public drinking-water quality is accordingly prepared/updated.

Since the first edition of the GDWQ, WHO has published information on health criteria and other supporting information to the GDWQ, describing the approaches used in deriving guideline values and presenting critical reviews and evaluations of the effects on human health of the substances or contaminants examined in drinking-water.

For each chemical contaminant or substance considered, a lead institution prepared a health criteria document evaluating the risks for human health from exposure to the particular chemical in drinking-water. Institutions from Canada, Denmark, Finland, France, Germany, Italy, Japan, Netherlands, Norway, Poland, Sweden, United Kingdom and United States of America prepared the requested health criteria documents.

Under the responsibility of the coordinators for a group of chemicals considered in the guidelines, the draft health criteria documents were submitted to a number of scientific institutions and selected experts for peer review. Comments were taken into consideration by the coordinators and authors before the documents were submitted for final evaluation by the experts meetings. A “final task force” meeting reviewed the health risk assessments and public and peer review comments and, where appropriate, decided upon guideline values. During preparation of the third edition of the GDWQ, it was decided to include a public review via the world wide web in the process of development of the health criteria documents.

During the preparation of health criteria documents and at experts meetings, careful consideration was given to information available in previous risk assessments carried out by the International Programme on Chemical Safety, in its Environmental Health

Criteria monographs and Concise International Chemical Assessment Documents, the International Agency for Research on Cancer, the joint FAO/WHO Meetings on Pesticide Residues, and the joint FAO/WHO Expert Committee on Food Additives (which evaluates contaminants such as lead, cadmium, nitrate and nitrite in addition to food additives).

Further up-to-date information on the GDWQ and the process of their development is available on the WHO internet site and in the current edition of the GDWQ.

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GENERAL DESCRIPTION

Identity

<i>Compound</i>	<i>CAS no.</i>	<i>Molecular formula</i>
2-Chlorophenol	95-57-8	$\text{ClC}_6\text{H}_4\text{OH}$
2,4-Dichlorophenol	120-83-2	$\text{Cl}_2\text{C}_6\text{H}_3\text{OH}$
2,4,6-Trichlorophenol	88-06-2	$\text{Cl}_3\text{C}_6\text{H}_2\text{OH}$

A total of 19 possible chlorinated phenols exist, but only 2-chlorophenol (2-CP), 2,4-dichlorophenol (2,4-DCP), and 2,4,6-trichlorophenol (2,4,6-TCP) will be evaluated here, as these are the most likely to occur in drinking-water as possible by-products of disinfection.

Physicochemical properties (1–3)

<i>Property</i>	<i>2-CP</i>	<i>2,4-DCP</i>	<i>2,4,6-TCP</i>
Boiling point (°C)	175–176	210–211	246
Melting point (°C)	8.7	43–44	68
Density (g/cm ³)	1.24	1.38	1.49
Vapour pressure (kPa)	0.133 (12.1 °C)	0.133 (53 °C)	0.133 (76 °C)
Water solubility (mg/litre)	28 000	4500	900
Log octanol–water partition coefficient	2.15	3.06	–

Note: Conversion factors in air: 2-CP, 1 ppm = 5.26 mg/m³; 2,4-DCP, 1 ppm = 6.67 mg/m³; 2,4,6-TCP, 1 ppm = 8.08 mg/m³.

Organoleptic properties

Chlorophenols generally have very low organoleptic thresholds. The taste thresholds in water for 2-CP, 2,4-DCP, and 2,4,6-TCP are 0.1, 0.3, and 2 µg/litre, respectively. Odour thresholds are 10, 40, and 300 µg/litre, respectively (2).

Major uses

2-CP is used as a precursor in the production of higher chlorophenols and dyestuffs, and as a preservative. 2,4-DCP is used as a mothproofing agent, germicide and antiseptic, and in the production of the pesticide 2,4-D. 2,4,6-TCP is used in the production of 2,3,4,6-tetrachlorophenol and pentachlorophenol, and as a germicide, glue and wood preservative, and antimildew agent (4,5).

ANALYTICAL METHODS

EPA methods 604 (6,7), 525 (8), and 8270 (9) are used for the determination of chlorophenols. The most sensitive technique involves the formation of the pentafluorobenzyl ether derivatives (an option in method 604); the method has a detection limit of 0.5–5 µg/litre. Chlorophenols can also be determined by gas chromatography with an electron-capture detector. The detection limits are 1–10 µg/litre for monochlorophenols, 0.5 µg/litre for dichlorophenols, and 0.01 µg/litre for trichlorophenols (1).

ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE

Water

Chlorophenols are present in drinking-water as a result of the chlorination of phenols during disinfection, as by-products of the reaction of hypochlorite with phenolic acids, as biocides, or as degradation products of phenoxy herbicides. Data from 40 Canadian treatment plants indicate that chlorophenol levels in drinking-water are generally quite low but vary considerably from one location to another (10). Chlorination increased the concentrations of 2-CP (maximum 65 ng/litre), 2,4-DCP (72 ng/litre), and 2,4,6-TCP (719 ng/litre). Drinking-water from the Ruhr area of Germany contained 2,4-DCP at 3B6 ng/litre and 2,4,6-TCP at 1 ng/litre (1). Several chlorophenols were present in Finnish tapwater at levels roughly one order of magnitude higher than those found in Germany (11).

KINETICS AND METABOLISM IN LABORATORY ANIMALS AND HUMANS

Chlorophenols are well absorbed after oral administration (12), and they readily penetrate the skin (13). Chlorophenols do not appear to accumulate in body tissues in rats but are rapidly metabolized and eliminated from the body (14–16). The major metabolite is the glucuronide conjugate of the parent chlorophenol. Less abundant metabolites include sulfate conjugates and possibly chloromethoxyphenol isomers of the parent compounds (12,14,16,17). Chlorophenols are readily excreted as glucuronide conjugates in urine and, to a lesser extent, faeces (12,16,18).

EFFECTS ON LABORATORY ANIMALS AND *IN VITRO* TEST SYSTEMS

2-Chlorophenol

2-Chlorophenol

Acute exposure

The oral LD₅₀ for 2-CP in mice was reported to be 670 mg/kg of body weight (19).

Long-term exposure

Immunological (e.g. humoral and cell-mediated immunity, macrophage function) and haematological (e.g. red and white blood cell count, haematocrit, haemoglobin) effects were assessed in groups of 12–20 weanling female Sprague-Dawley rats exposed to 0, 5, 50, or 500 mg of 2-CP per litre in drinking-water (0, 0.5, 5, or 50 mg/kg of body weight per day) in a reproductive study. Females were exposed from 3 weeks of age until breeding at 90 days, and throughout gestation to parturition. No treatment-related differences were found. A NOAEL of 50 mg/kg of body weight per day can be identified (15,20).

Reproductive toxicity, embryotoxicity, and teratogenicity

Groups of 12–20 weanling female Sprague-Dawley rats were exposed to 0, 5, 50, or 500 mg of 2-CP per litre in drinking-water (0, 0.5, 5, or 50 mg/kg of body weight per day) for 10 weeks, then bred. Treatment was continued during breeding, gestation, and weaning. Parameters evaluated included percentage conception, litter size, birth weight, number of stillbirths, weanling weight, and haematology in weanling rats. A treatment-related increase in conception rate, an increase in the number of stillbirths, and a decrease in the size of the litters were observed at the highest dose (15,21).

Carcinogenicity

In a 24-month experiment, female Sprague-Dawley rats (12–22 per dose) were given 2-CP in drinking-water at 0, 5, 50, or 500 mg/litre (0, 0.5, 5, or 50 mg/kg of body weight per day) for 10 weeks, then bred. Ethylurea and nitrite, precursors of the transplacental carcinogen nitrosoethylurea (NEU), were administered to females on days 14–21 of pregnancy. The effects on tumour incidence and latency were most evident in male progeny that received 2-CP with NEU, both pre- and postnatally. The lowest level of 2-CP appeared to exert the greatest effect. The authors suggested that 2-CP is a co-carcinogen (21).

2,4-Dichlorophenol

Acute exposure

The acute oral LD₅₀s for 2,4-DCP in rats ranged from 580 to 4000 mg/kg of body weight (22,23). Acute oral LD₅₀s were 1276 and 1352 mg/kg of body weight for male and female CD-1 mice, respectively (24).

Short-term exposure

CD-1 mice (20 per sex per dose) were exposed to 2,4-DCP in drinking-water for 90 days at concentrations of 0.2, 0.6, or 2.0 g/litre (mean daily doses of 50, 143, and 491 mg/kg of body weight for females and 40, 114, and 383 mg/kg of body weight for males). There were no significant differences in body weight gain and no differences in terminal organ weights or organ weight ratios. Haematological differences, namely an increase in leukocytes (high dose) and in polymorphonuclear leukocytes (low dose), were observed only in males. Changes in clinical chemistry parameters, namely a decrease in creatinine (low dose), an increase in BUN/creatinine ratios (mid-dose), and an increase in alkaline phosphatase (high dose), were significant in females. These changes were not consistently dose-related, and a LOAEL cannot be established (24).

ICR mice of both sexes were fed 2,4-DCP in the diet at 0, 0.05%, 0.1%, or 0.2% (0, 45, 100, or 230 mg/kg of body weight per day) for 6 months. Hyperplasia of hepatic cells was reported in one of seven animals receiving 0.2%. There were no other significant differences in histopathology, organ or body weight gains, red or white blood cell counts, or alanine aminotransferase and aspartate aminotransferase activities at any dose. The authors identified a NOAEL of 100 mg/kg of body weight per day (23).

Pre- and postnatal treatment of rats with 300 mg of 2,4-DCP per litre of drinking-water for 147 days significantly increased liver and spleen weights and enhanced humoral immune responsiveness. Cell-mediated immunity was depressed at 30 and 300 mg/litre. No histopathological changes were reported. Based on these findings, a NOAEL of 3 mg/litre (0.3 mg/kg of body weight per day) and a LOAEL of 30 mg/litre (3 mg/kg of body weight per day) can be identified (25).

Long-term exposure

Investigations of the effects of long-term exposure to 2,4-D have been designed primarily to test its carcinogenic properties and are described below.

Reproductive toxicity, embryotoxicity, and teratogenicity

Administration of 2,4-DCP (0, 50, 150, or 500 mg/kg of body weight per day) in drinking-water to male CD-1 mice for 90 days had no effect on sperm motility or ability to penetrate ova (26). Exposure of female rats to 0, 3, 30, or 300 mg of 2,4-DCP per litre in drinking-water from 3 weeks of age throughout parturition and lactation had no significant effect on

conception, litter size and weight, number of stillborn pups, or survival of weanlings continued on treatment for 5 weeks (25).

Mutagenicity and related end-points

2,4-DCP did not show mutagenic potential in *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537 with and without metabolic activation (27). In eukaryotic test assays, 2,4-DCP was not mutagenic in primary hepatocyte cultures, as shown by the absence of unscheduled DNA synthesis (28).

Carcinogenicity

F344 rats and B6C3F₁ mice were given 2,4-DCP in feed for 2 years at dietary concentrations of 0, 5000, or 10 000 mg/kg (mice and male rats) and 0, 2500, or 5000 mg/kg (female rats) (male rats: 0, 210, or 440 mg/kg of body weight per day; female rats: 0, 210, or 250 mg/kg of body weight per day; male mice, 0, 800, or 1300 mg/kg of body weight per day; female mice, 0, 430, or 820 mg/kg of body weight per day). There was no evidence of carcinogenicity in either species. The maximum tolerated dose was probably reached, judging from the lower body weight in the treated animals, especially at the high dose. Survival was not affected in either species (29).

2,4,6-Trichlorophenol

Acute exposure

The oral LD₅₀ for 2,4,6-TCP has been reported as 820 mg/kg of body weight in rats (30). Short-term exposure

2,4,6-TCP was mixed with corn oil and administered daily by gavage to Sprague-Dawley rats (10 per sex per dose) for 90 consecutive days at 0, 80, 240, or 720 mg/kg of body weight per day. At 240 mg/kg of body weight per day, liver weight increased in males and adrenal gland weight increased in females. At the highest dose, treatment-related effects included salivation, increased weights of the kidneys, liver, adrenal glands, and testes, and an increase in serum albumin, total protein, and serum alanine aminotransferase, as well as a decrease in urinary pH. No gross or histopathological changes were seen. In this study, a LOAEL of 240 mg/kg of body weight per day and a NOAEL of 80 mg/kg of body weight per day were identified (Bercz JP et al., unpublished data, 1989).

Long-term exposure

Female Sprague-Dawley rats (12–14 per dose) were exposed to 2,4,6-TCP in drinking-water at 0, 3, 30, or 300 mg/litre from 3 weeks of age and throughout breeding, gestation, parturition, and lactation. Ten pups from each dose group were weaned at 3 weeks and continued on treatment for 12–15 weeks. A dose-related increase in the liver weight of the pups reached statistical significance at 30 and 300 mg/litre. At 300 mg/litre, the spleen weight of the pups also increased significantly. No treatment-related changes in cell-mediated immunity, humoral immunity, or macrophage function were seen in the treated groups. In this study, a LOAEL of 30 mg/litre (3 mg/kg of body weight per day) and a NOAEL of 3 mg/litre (0.3 mg/kg of body weight per day) were identified (21).

F344 rats (50 per sex per dose) were given 2,4,6-TCP in their feed at 0, 5000, or 10 000 mg/kg (0, 250, or 500 mg/kg of body weight per day) for 106–107 weeks. Mean body weights of both dosed groups were lower than those of corresponding controls and were dose-related throughout the study. Other clinical signs were common to both the dosed and the control groups. There was no significant dose-related trend in mortality. In a similar experiment in

B6C3F₁ mice, dose-related decreases in mean body weights were seen in male and female mice. Other clinical signs were common to both dosed and control groups. There was no statistically significant dose-related trend in mortality in either sex (30).

Reproductive toxicity, embryotoxicity, and teratogenicity

Sprague-Dawley rats were exposed to 2,4,6-TCP at 0, 30, or 300 mg/litre in drinking-water from 3 weeks of age to parturition. There were no statistically significant treatment-related effects on percentage conception, litter size, percentage stillborn, birth weight, and percentage survival to weaning (21).

Male Long-Evans hooded rats were given 2,4,6-TCP at 0 or 1000 mg/kg of body weight in corn oil by gavage, 5 days per week for 11 weeks (average 0 or 714 mg/kg of body weight per day), then bred with untreated females. No treatment-related effects were seen in copulatory behaviour, semen characteristics, organ weights, fertility, or fetal outcome. Female rats were given 0, 100, 500, or 1000 mg/kg of body weight by gavage, 5 days per week for 2 weeks prior to and during mating and up to day 21 of gestation. No treatment-related effects were reported in litter size or pup survival at the dose levels tested (31).

Mutagenicity and related end-points

Mutagenic activity was not detected in *S. typhimurium* strains TA98, TA100, TA1535, and TA1537 with and without metabolic activation (27). 2,4,6-TCP showed weak but significant mutagenic activity in the MP-1 strain of *Saccharomyces cerevisiae* (32). There was no effect on mitotic crossing-over or mitotic gene conversion. Pregnant mice injected with 2,4,6-TCP displayed a slightly increased frequency of spotted coat in the offspring, indicative of weak mutagenic activity (32).

Carcinogenicity

Administration of 2,4,6-TCP to mice at 100 mg/kg of body weight for 72 weeks led to increases in the incidences of hepatomas and reticulum-cell sarcomas. However, the incidences were not statistically significant if males and females are considered separately or if matched controls are considered (33).

F344 rats and B6C3F₁ mice were administered 2,4,6-TCP (96–97% pure) in the feed for over 2 years. Rats and male mice received doses of 0, 5000, or 10 000 mg/kg of body weight and female mice received time-weighted average doses of 0, 5214, or 10 428 mg/kg of body weight. A statistically significant dose-related increase in the incidence of lymphomas or leukaemias was observed in male rats (3/20, 23/50, and 29/50 for control, low-, and high-dose groups, respectively). In addition, the combined incidence of hepatocellular carcinomas and adenomas was significantly increased as compared with controls in both male and female mice (30). The 2,4,6-TCP may have been contaminated with 1,3,6,8-tetrachlorodibenzo-p-dioxin (1,3,6,8-TCDD), which might also be capable of inducing liver tumours in mice but is not expected to induce leukaemias in male rats, as the 2,3,7,8-TCDD isomer does not appear to do so (34).

GUIDELINE VALUES

2-Chlorophenol

Because of the limited database on the toxicity of 2-CP, no health-based guideline value has been derived.

2,4-Dichlorophenol

Because the database for the toxicity of 2,4-DCP is limited, no health-based guideline value has been derived.

2,4,6-Trichlorophenol

2,4,6-TCP has been reported to induce lymphomas and leukemias in male rats and hepatic tumours in male and female mice. IARC has concluded that 2,4,6-TCP is possibly carcinogenic to humans (Group 2B) (35). The compound has not been shown to be mutagenic in the Ames test but has shown weak mutagenic activity in other in vitro and in vivo assays.

A guideline value can be derived for 2,4,6-TCP by applying the linearized multistage model to leukaemias in male rats observed in a 2-year feeding study (33). The hepatic tumours found in this study were not used for risk estimation, because of the possible role of contaminants in their induction. The concentrations of 2,4,6-TCP in drinking-water (and hence the guideline values) associated with 10^{-4} , 10^{-5} , and 10^{-6} excess lifetime cancer risks are 2000, 200, and 20 µg/litre, respectively.

The lowest reported taste threshold for 2,4,6-TCP is 2 µg/litre. If water containing this chlorophenol is free from taste, it is unlikely to present an undue risk to health.

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