

Chlorotoluron 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

CAS no.: 15545-48-9

Molecular formula: C₁₀H₁₃ClN₂O

The IUPAC name for chlorotoluron is 3-(3-chloro-*p*-tolyl)-1,1-dimethylurea.

Physicochemical properties (1)

<i>Property</i>	<i>Value</i>
Physical state	Colourless crystals
Melting point	147–148 °C
Vapour pressure	0.017×10^{-3} Pa at 20 °C
Density	1.4 g/cm ³ at 20 °C
Water solubility	70 mg/litre at 20 °C
Log octanol–water partition coefficient	2.29

Organoleptic properties

No odour was detected at a concentration of 9.0 mg/litre (99.3% purity, dissolved in still, bottled water, equilibrated to 40 °C, eight assessors) (Water Research Centre, unpublished data, 1990).

Major uses

Chlorotoluron is a pre- or early post-emergence herbicide widely used to control annual grasses and broad-leaved weeds in winter cereals (1).

Environmental fate

Chlorotoluron is slowly degraded in water and is quite persistent. Chemical hydrolysis is not a significant degradation mechanism. However, it is degraded by photolysis in water and under laboratory conditions; the half-lives at pH 5, 7, and 9 at 22 °C were over 200 days. In another study, half-lives of approximately 120 and 80 days were reported for river and pond water (containing 1% sediment), respectively. Degradation proceeded via *N*-demethylation, yielding 3-(3-chloro-*p*-tolyl)-1-methylurea as the major metabolite and some minor polar metabolites (Ciba-Geigy, unpublished data, 1989).

In laboratory studies, the rate of degradation of chlorotoluron in soil is slow and follows first-order kinetics. The estimated half-life in loamy sand and organic and peat soil is several months (2). Rates of degradation were nearly tripled by raising the temperature from 25 °C to 35 °C. Under field conditions, chlorotoluron appears to degrade at a higher rate. When applied in the spring on bare soil, it disappeared from the 0–5-cm soil layer with a half-life of 30–40 days; dissipation was slower in autumn (Ciba-Geigy, unpublished data, 1989).

ANALYTICAL METHODS

Chlorotoluron may be determined by separation with reverse-phase high-performance liquid chromatography followed by ultraviolet and electrochemical detection (3). Detection limits of 0.1 µg/litre have been reported (4). Gas chromatography/mass spectroscopy can also be used for the determination stage.

ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE

Air

Because of its low vapour pressure, chlorotoluron is unlikely to be a major contaminant in air.

Water

Chlorotoluron is slightly mobile in soil and likely to reach surface waters following agricultural application. It has occasionally been detected in waters in the United Kingdom at concentrations ranging from 0.4 to 0.6 µg/litre (5). In Germany, levels up to 1.2 µg/litre have been detected in drainage water from fields soon after normal treatment (Ciba-Geigy, unpublished data, 1989). In another German study, chlorotoluron was frequently detected in raw waters; concentrations of 0.2 and 0.3 µg/litre were reported for surface water and groundwater, respectively (6).

Food

It is generally considered that there is only limited exposure to chlorotoluron from food. In one study, residues of 0.04–0.08 and 0.06–0.35 mg/kg were detected in grain and straw samples, respectively (Ciba-Geigy, unpublished data, 1989). However, the majority of samples contained no measurable residues.

Estimated total exposure and relative contribution of drinking-water

Based on exposure from food and water, the estimated daily intake was 4.2 µg/person in a German study (Ciba-Geigy, unpublished data, 1989).

KINETICS AND METABOLISM IN LABORATORY ANIMALS AND HUMANS

Chlorotoluron is readily and rapidly absorbed when given orally. No evidence of its accumulation in any particular organ or tissue has been reported. In the rat, it is metabolized mainly via *N*-demethylation and stepwise oxidation of the ring methyl group to hydroxymethyl and carboxymethyl derivatives. At doses above 50 mg/kg, the phenylmethyl group is transformed to a methylthiomethyl group. Chlorotoluron is rapidly excreted in the urine in the form of metabolites, a negligible amount being excreted in expired air (Ciba-Geigy, unpublished data, 1989).

EFFECTS ON LABORATORY ANIMALS AND *IN VITRO* TEST SYSTEMS

Acute exposure

Chlorotoluron is of low acute oral toxicity in various species; oral LD₅₀s range from 2700 to more than 10 000 mg/kg of body weight. The rat dermal LD₅₀ was more than 2000 mg/kg of body weight. It caused no eye or skin irritation in the rabbit or skin sensitization in the guinea-pig (7; Ciba-Geigy, unpublished data, 1989).

Short-term exposure

Short-term feeding studies in animals suggest that chlorotoluron is of low toxicity. Rats were fed chlorotoluron in the diet at doses of 0, 800, 3200, or 12 800 mg/kg for 3 months. At the highest dose, there was a slight decrease in body weight in both males and females and an increased incidence of splenic haemosiderosis and Kupffer's cell activity in the liver. There were slight reversible increases in haemoglobin concentration, erythrocyte counts, and haematocrit values in females at 12 800 mg/kg and transient increases in serum alkaline

phosphatase activity at 3200 and 12 800 mg/kg. The NOAEL was 800 mg/kg, equal to 52 mg/kg of body weight per day (Ciba-Geigy, unpublished data, 1989).

In a 3-month study, dogs were fed diets containing 0, 600, 2400, or 9200 mg of chlorotoluron per kg. Animals in the highest dose group died after 10 weeks from severe cachexia, resulting from starvation. At the two highest doses, there were decreases in food intake and body weights, but the only histopathological changes that could be related to treatment were increased incidence of splenic and hepatic haemosiderosis (Ciba-Geigy, unpublished data, 1989).

Long-term exposure

Mice were fed chlorotoluron in the diet at levels of 0, 100, 500, or 2500 mg/kg for 2 years. At 2500 mg/kg, there was a statistically significant reduction in body weight, a slight increase in white blood cell count, increased plasma urea levels, an increase in the activity of alkaline phosphatase in females, and a statistically significant reduction in the mean relative kidney weights in both sexes. There was a slightly increased concentration of albumin in males at 500 and 2500 mg/kg. The NOAEL for this study was 100 mg/kg, equivalent to 11.3 mg/kg of body weight per day (Ciba-Geigy, unpublished data, 1989).

In a 2-year study, rats were fed chlorotoluron in the diet at dose levels of 0, 100, 500, or 2500 mg/kg. Marked depression in body weight gain was observed at 2500 mg/kg, accompanied by a slight reduction in feed consumption. At the same dose level, slight increases in the incidence of spleen haemosiderosis in females and in aminotransferase activity in males were observed. The NOAEL for this study was 100 mg/kg, equivalent to a daily intake of 5 mg/kg of body weight (Ciba-Geigy, unpublished data, 1989).

Reproductive toxicity, embryotoxicity, and teratogenicity

Chlorotoluron was not teratogenic in rats at doses of up to 1000 mg/kg of body weight per day when administered by gavage on days 6–15 of gestation (Ciba-Geigy, unpublished data, 1989). A mild retardation in the ossification rate of the hindlimb was seen in the 1000 and 500 mg/kg groups; this was considered to be related to maternal toxicity.

In a two-generation study, chlorotoluron was administered orally to rats at dietary doses of 0, 300, 1000, or 3000 mg/kg. At 3000 mg/kg, there was a significant reduction in body weight and food consumption of both parents and offspring, a significantly reduced mean number of implantation sites per dam, and depressed locomotor activity in some pups. The NOAEL in this study was 300 mg/kg (Ciba-Geigy, unpublished data, 1989).

No changes were observed in the testes and spermatozoa of male rats given chlorotoluron intragastrically at doses of 0.2 or 2.0 mg/kg of body weight per day, 5 days per week for 10 weeks, although the offspring had lower body weights and body lengths. When the doses were administered in the feed, no effects were observed in the fetuses, indicating that the toxicity is affected by the method of administration (8).

Mutagenicity and related end-points

Chlorotoluron and its metabolites have shown no evidence of mutagenicity in a number of bacterial or *in vitro* and *in vivo* mammalian test systems (Ciba-Geigy, unpublished data, 1989).

Carcinogenicity

No carcinogenic effects were reported in rats exposed to doses of 0, 100, 500, or 2500 mg/kg in the diet for 2 years. However, in a 2-year dietary study, an increased incidence of

adenomas and carcinomas of the kidney was reported in male mice at 2500 mg/kg. The incidence of hepatocellular carcinomas was also increased in male mice receiving 2500 mg/kg and slightly increased at 500 mg/kg. When the incidences of hepatocellular carcinomas and adenomas were combined, the total number of tumours remained within the historical control ranges. No carcinogenic effects were reported at 100 mg/kg of diet (Ciba-Geigy, unpublished data, 1989). These studies suggest that chlorotoluron has a carcinogenic potential that is both species- and sex-specific.

EFFECTS ON HUMANS

No cases of human poisonings have been reported following chlorotoluron exposure.

GUIDELINE VALUE

Chlorotoluron is of low toxicity in acute, short-term, and long-term exposures in animals, but has been shown to cause an increase in adenomas and carcinomas of the kidney in male mice given high doses for 2 years. Chlorotoluron and its metabolites have shown no evidence of genotoxicity. In view of this, the guideline value can be calculated using a TDI approach.

The NOAEL in a 2-year feeding study in mice was 11.3 mg/kg of body weight per day (Ciba-Geigy, unpublished data, 1989). A TDI of 11.3 µg/kg of body weight can be calculated by applying an uncertainty factor of 1000 (100 for inter- and intraspecies variation and 10 for evidence of carcinogenicity). An allocation of 10% of the TDI to drinking-water results in the guideline value of 30 µg/litre (rounded figure).

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