Chlorpyrifos in Drinking-water

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

The first draft of Chlorpyrifos in Drinking-water, Background document for development of WHO Guidelines for Drinking-water Quality, was prepared by Dr P. Toft, Canada, to whom special thanks are due.

The work of the following working group coordinators was crucial in the development of this document and others in the third edition:

- Mr J.K. Fawell, United Kingdom (Organic and inorganic constituents)
- Dr E. Ohanian, Environmental Protection Agency, USA (Disinfectants and disinfection by-products)
- Ms M. Giddings, Health Canada (Disinfectants and disinfection by-products)
- Dr P. Toft, Canada (Pesticides)
- Prof. Y. Magara, Hokkaido University, Japan (Analytical achievability)
- Mr P. Jackson, WRc-NSF, United Kingdom (Treatment achievability)

The contribution of peer reviewers is greatly appreciated. The draft text was posted on the world wide web for comments from the public. The revised text and the comments were discussed at the Final Task Force Meeting for the third edition of the GDWQ, held on 31 March to 4 April 2003, at which time the present version was finalized. The input of those who provided comments and of participants in the meeting is gratefully reflected in the final text.

The WHO coordinators were as follows:

- Dr J. Bartram, Coordinator, Water Sanitation and Health Programme, WHO Headquarters, and formerly WHO European Centre for Environmental Health
- Mr P. Callan, Water Sanitation and Health Programme, WHO Headquarters
- Mr H. Hashizume, Water Sanitation and Health Programme, WHO Headquarters

Ms C. Vickers provided a liaison with the International Chemical Safety Programme, WHO Headquarters.

Ms Marla Sheffer of Ottawa, Canada, was responsible for the scientific editing of the document.

Many individuals from various countries contributed to the development of the GDWQ. The efforts of all who contributed to the preparation of this document and in particular those who provided peer or public domain review comment are greatly appreciated.
Acronyms and abbreviations used in the text

ADI acceptable daily intake
CAS Chemical Abstracts Service
EPA Environmental Protection Agency (USA)
FAO Food and Agriculture Organization of the United Nations
GEMS Global Environment Monitoring System
HSDB Hazardous Substances Data Bank
IUPAC International Union of Pure and Applied Chemistry
JMPR Joint FAO/WHO Meeting on Pesticide Residues
LD₅₀ median lethal dose
NOAEL no-observed-adverse-effect level
TCP 3,5,6-trichloro-2-pyridyl phosphate
USA United States of America
WHO World Health Organization
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1. GENERAL DESCRIPTION

1.1 Identity

CAS No.: 2921-88-2
Molecular formula: C₉H₁₁Cl₃NO₃PS

The IUPAC name for chlorpyrifos is O,O-diethyl O-3,5,6-trichloro-2-pyridyl phosphorothioate. Its chemical structure is shown below:

\[
\text{Cl} \quad \text{N} \quad \text{OP(OCH₂CH₃)₂} \\
\text{Cl} \quad \text{S} \quad \text{Cl} \quad \text{Cl}
\]

1.2 Physicochemical properties (Agriculture Canada, 1982; Suntio et al., 1988)

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melting point</td>
<td>42 °C</td>
</tr>
<tr>
<td>Vapour pressure</td>
<td>(2.49 \times 10^{-3}) Pa at 25 °C</td>
</tr>
<tr>
<td>Solubility in water</td>
<td>2 mg/litre at 25 °C</td>
</tr>
<tr>
<td>Log octanol–water partition coefficient</td>
<td>4.82–5.11</td>
</tr>
</tbody>
</table>

1.3 Major uses

Chlorpyrifos is a broad-spectrum organophosphorus insecticide, used for the control of mosquitos, flies, various crop pests in soil and on foliage, household pests and aquatic larvae. It is used as a soil treatment (pre-plant and at planting), as a seed treatment and as a foliar spray, directed spray and dormant spray.

1.4 Environmental fate

Chlorpyrifos is strongly absorbed by soil and does not readily leach from it (HSDB, 1988). It persists in soil for 60–120 days and degrades there primarily through microbial action. The primary degradation product is 3,5,6-trichloro-2-pyridinol, which is further broken down to organochlorine compounds and carbon dioxide (FAO/WHO, 2000).

Owing to its non-polar nature, chlorpyrifos has a low solubility in water and great tendency to partition from aqueous into organic phases in the environment.
2. ANALYTICAL METHODS

Organophosphorus insecticides in water may be determined by extraction separately into hexane and dichloromethane, separation by gas chromatography and flame thermionic or flame photometric detection. The detection limit is 1 µg/litre (U.K. Department of the Environment, 1983).

3. ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE

3.1 Water

Chlorpyrifos was not detected in surveys of municipal and private drinking-water supplies in Canada between 1971 and 1986 (Health Canada, 1989).

US EPA (1998) has reported detecting chlorpyrifos in surface waters, with the majority of results being below 0.1 µg/litre and with a maximum reported concentration of 0.4 µg/litre. It was detected in groundwater in less than 1% of the wells tested, with the majority of measurements being below 0.01 µg/litre.

3.2 Food

Chlorpyrifos was detected in only 49 of 6391 domestic food samples in the USA, 94% of which had concentrations below 2.0 mg/kg (Hundley et al., 1988). Based on a US market basket survey, the average daily intake of chlorpyrifos was estimated to be 0.241 µg (Gartrell et al., 1986).

Estimated Theoretical Maximum Daily Intakes for the five GEMS/Food regional diets, based on existing maximum residue limits, were in the range of 6–30% of the ADI (see below) (FAO/WHO, 2000).

4. KINETICS AND METABOLISM IN LABORATORY ANIMALS AND HUMANS

After oral administration to rats, radiolabelled chlorpyrifos was rapidly and extensively absorbed (up to about 90% of the dose) and eliminated, predominantly in the urine (68–93%) and faeces (6–15% of the dose), within about 72 h of administration. The urinary metabolites included the glucuronide (about 80%) and sulfate (about 5%) conjugates of chlorpyrifos and 3,5,6-trichloro-2-pyridyl phosphate (TCP; about 12%). The tissue concentrations of residues of [14C]chlorpyrifos were very low (generally <1 mg/kg) within 72 h of dosing. The longest half-time of residues in rats was 62 h in fat, and low levels were also detected in the fat of several other species and in the milk of goats.

In humans who were poisoned with chlorpyrifos formulations, diethylphosphorus metabolites were excreted in the urine by first-order kinetics, with an average

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1 This section is taken from FAO/WHO (2000).
elimination half-time of $6.1 \pm 2.2$ h in the fast phase and of $80 \pm 26$ h in the slow phase. In volunteers, the time to maximal concentration of TCP in the blood was $0.5$ h after oral dosing and $22$ h after dermal treatment, but the elimination half-time by both routes was $27$ h, and the percentage of the administered dose recovered from the urine was $70\%$ after oral dosing and $1.3\%$ after dermal administration.

Chlorpyrifos is rapidly metabolized by mixed-function oxidases to the highly reactive chlorpyrifos oxon by oxidative desulfuration. The oxon can be deactivated by hydrolysis to diethylphosphate and 3,5,6-trichloropyridinol, while a minor reaction pathway is hydrolysis to monoethyl 3,5,6-trichloro-2-pyridinyl phosphorothioate.

5. EFFECTS ON LABORATORY ANIMALS AND IN VITRO TEST SYSTEMS

The lowest oral LD$_{50}$ value was $96$ mg/kg of body weight (range $96–475$ mg/kg of body weight) in rats and $100$ mg/kg of body weight (range $100–150$ mg/kg of body weight) in mice. Female rats were generally more sensitive to the acute effects of chlorpyrifos than males. The signs of acute intoxication with chlorpyrifos were consistent with cholinesterase inhibition. The acute dermal LD$_{50}$ of chlorpyrifos was $>2000$ mg/kg of body weight in rats and $>1200$ mg/kg of body weight in rabbits.

WHO (1999) has classified chlorpyrifos as “moderately hazardous.”

Chlorpyrifos was irritating to the eye and skin of rabbits, but it did not sensitize the skin of guinea-pigs in Magnusson-Kligman maximization or Buehler tests.

In short-term studies, the NOAEL for inhibition of erythrocyte cholinesterase activity was $0.03$ mg/kg of body weight per day in dogs and $0.1$ mg/kg of body weight per day in rats. The NOAEL for inhibition of brain cholinesterase activity was $1$ mg/kg of body weight per day in dogs and rats. The signs of toxicity were largely limited to cholinergic signs and decreased body weights and/or food consumption. The NOAEL for these effects in short-term studies was $1$ mg/kg of body weight per day in rats, and the NOAEL for clinical signs was $3$ mg/kg of body weight per day in dogs. In mice, ocular effects and histopathological alterations (including adrenal lipogenic pigmentation and ocular keratitis) were observed (NOAEL 50 mg/kg; equal to $7$ mg/kg of body weight per day). In rats, the NOAEL for increased fatty vacuolation of the adrenal zonal fasciculata and changes in haematological and clinical chemical parameters was $5$ mg/kg of body weight per day. When rats received chlorpyrifos dermally for 21 days, the NOAEL for inhibition of cholinesterase activity in erythrocytes and brain was $5$ mg/kg of body weight per day.

In long-term studies, inhibition of cholinesterase activity was again the main toxicological finding in all species. In rats, the NOAEL was $0.1$ mg/kg of body weight per day for inhibition of erythrocyte acetylcholinesterase activity and $1$ mg/kg of body weight per day for inhibition of brain acetylcholinesterase activity, but clinical signs were not seen at doses up to $10$ mg/kg of body weight per day, and the NOAEL for

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2 This section is taken from FAO/WHO (2000).
reduction in body weight was 1 mg/kg of body weight per day. In mice, erythrocyte and brain acetylcholinesterase activities were inhibited at 50 mg/kg, equal to 6.1 mg/kg of body weight per day, and the NOAEL was 5 mg/kg, equal to 0.7 mg/kg of body weight per day. Cholinergic signs and reductions in body weight were reported only at the highest dietary concentration of 250 mg/kg (equal to 32 mg/kg of body weight per day). Other treatment-related findings included effects on the liver in mice, with a NOAEL of 50 mg/kg (equal to 6.6 mg/kg of body weight per day), and increased adrenal weight in rats, with a NOAEL of 1 mg/kg of body weight per day. There was no treatment-related increase in the incidence of neoplastic lesions in any of the long-term studies. The Meeting concluded that chlorpyrifos is unlikely to pose a carcinogenic risk to humans.

Chlorpyrifos was not genotoxic in an adequate range of studies in vitro and in vivo. The Meeting concluded that chlorpyrifos is not genotoxic.

In multigeneration studies of reproductive toxicity in rats, the treatment-related effects of chlorpyrifos were limited to inhibition of cholinesterase activity, consistent with that seen in other short- and long-term studies, and fetotoxicity, characterized by reduced pup viability, body weights and survival. No significant treatment-related clinical signs were reported. The NOAEL for inhibition of maternal acetylcholinesterase activity was 0.1 mg/kg of body weight per day for erythrocytes and 1 mg/kg of body weight per day for brain. The NOAEL for developmental toxicity was 1 mg/kg of body weight per day. No effects on reproductive parameters were observed at the highest dose tested, 5 mg/kg of body weight per day.

In studies of developmental toxicity in mice, rats and rabbits, the maternal effects included inhibition of erythrocyte and/or brain acetylcholinesterase activity and cholinergic signs (lowest NOAEL, 1 mg/kg of body weight per day in rats and mice) and reductions in body weight and food consumption (lowest NOAEL, 2.5 mg/kg of body weight per day in rats). The observed fetal toxicity (lowest NOAEL, 2.5 mg/kg of body weight per day in rats) and developmental toxicity (NOAEL, 1 mg/kg of body weight per day in rats) were consistent with treatment-related maternal toxicity; there was no evidence of treatment-related malformations in any of the studies. There was no effect on cognitive function (learning, memory and habituation) in pups exposed to chlorpyrifos in utero and for a period postpartum at doses up to and including the highest dose of 5 mg/kg of body weight per day, while inhibition of cholinesterase activity, decreased brain weight and delayed development were seen at lower doses, consistent with findings in other studies.

In studies of delayed neurotoxicity, chlorpyrifos was given to chickens as either single or repeated doses. Significant inhibition of both cholinesterase and neuropathy target esterase activity was observed, and mild delayed neuropathy was seen in a number of studies; aggressive antidotal therapy was always necessary to allow at least some of the treated birds to survive. Despite the marked cholinergic toxicity of chlorpyrifos, there was no evidence that it caused delayed neurotoxicity, and there was no increase in the incidence of histopathological lesions in the nerve tissues of birds treated at doses up to 10 mg/kg of body weight per day for up to 91 days. In a number of studies
in rats given single doses of up to 100 mg/kg of body weight, repeated doses of up to 10 mg/kg of body weight per day for 4 weeks or repeated doses of up to 15 mg/kg of body weight per day for 13 weeks, there were no treatment-related neurological lesions or effects on cognition and no inhibition of neuropathy target esterase activity, although significant inhibition of erythrocyte, brain and peripheral tissue cholinesterase activity was seen at some doses. In a study that included a functional observational battery of tests, clinical signs of intoxication were observed after a single dose only when brain acetylcholinesterase activity was inhibited by more than 60% or when whole-blood cholinesterase activity was inhibited by more than 80%.

6. EFFECTS ON HUMANS

When chlorpyrifos was applied as a single dose of up to 5 mg/kg of body weight to the skin of volunteers for 12 h, erythrocyte cholinesterase activity was not significantly inhibited. Plasma cholinesterase activity was inhibited after 20 12-h dermal exposures to 5 mg/kg of body weight per day over 4 weeks or after three daily 12-h exposures to 25 mg/kg of body weight per day on consecutive days, but erythrocyte cholinesterase activity was not inhibited under any treatment regimen.

A single oral dose of up to 1 mg/kg of body weight or repeated doses of up to 0.1 mg/kg of body weight per day for 9 days did not significantly inhibit erythrocyte acetylcholinesterase activity in volunteers. No clinical signs were observed in these studies. Inhibition of erythrocyte acetylcholinesterase activity was observed in a single female volunteer (of a group of six men and six women) given a single oral dose of 2 mg/kg of body weight.

In a case of human poisoning with chlorpyrifos at an estimated dose of 300–400 mg/kg of body weight, significant inhibition of neuropathy target esterase in lymphocytes and of plasma and erythrocyte acetylcholinesterase activity was reported, with severe cholinergic signs, which required aggressive, extensive antidotal therapy and artificial ventilation. Mild distal axonopathy consistent with organophosphate-induced delayed polyneuropathy was reported some weeks after the poisoning incident.

7. GUIDELINE VALUE

The ADI of 0.01 mg/kg of body weight established by the 1982 JMPR Meeting (FAO/WHO, 1983) was based on a NOAEL of 0.1 mg/kg of body weight per day for inhibition of erythrocyte acetylcholinesterase activity in humans. The 1999 JMPR Meeting (FAO/WHO, 2000) affirmed this ADI on the basis of the NOAEL of 1 mg/kg of body weight per day for inhibition of brain acetylcholinesterase activity in studies in mice, rats and dogs, using a 100-fold safety factor, and on the basis of the NOAEL of 0.1 mg/kg of body weight per day for inhibition of erythrocyte acetylcholinesterase activity in humans, using a 10-fold safety factor.

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3 This section is taken from FAO/WHO (2000).
CHLORPYRIFOS IN DRINKING-WATER

Because chlorpyrifos is used as a mosquito larvicide in water bodies, it is felt desirable to establish a guideline value for drinking-water. Assuming a 10% allocation of the ADI of 0.01 mg/kg of body weight to drinking-water, the guideline value for chlorpyrifos is therefore 30 µg/litre.

8. REFERENCES


