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Permethrin 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 on selected chemicals in 1998 and on microbial aspects in 2002. The third edition of the GDWQ was published in 2004, and the first addendum to the third edition was published in 2005.

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 and 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 of potential health concern in drinking-water. In the first and second editions, these constituted Volume 2 of the GDWQ. Since publication of the third edition, they comprise a series of free-standing monographs, including this one.

For each chemical contaminant or substance considered, a lead institution prepared a background 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 documents for the third edition and addenda.

Under the oversight of a group of coordinators, each of whom was responsible for a group of chemicals considered in the GDWQ, 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. The draft documents were released to the public domain for comment and submitted for final evaluation by expert meetings.

During the preparation of background documents and at expert 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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The work of the following working group coordinators was crucial in the development of this document and others contributing to the first addendum to the third edition:

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The draft text was discussed at the Working Group Meeting for the first addendum to the third edition of the GDWQ, held on 17–21 May 2004. The final version of the document takes into consideration comments from both peer reviewers and the public. The input of those who provided comments and of participants in the meeting is gratefully acknowledged.

The WHO coordinator was Dr J. Bartram, Coordinator, Water, Sanitation and Health Programme, WHO Headquarters. Ms C. Vickers provided a liaison with the International Programme on Chemical Safety, WHO Headquarters. Mr Robert Bos, Water, Sanitation and Health Programme, WHO Headquarters, provided input on pesticides added to drinking-water for public health purposes.

Ms Penny Ward provided invaluable administrative support at the Working Group Meeting and throughout the review and publication process. 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
DNA	deoxyribonucleic acid
FAO	Food and Agriculture Organization of the United Nations
GDWQ	*Guidelines for Drinking-water Quality*
JMPR	Joint FAO/WHO Meeting on Pesticide Residues
LD_{50}	median lethal dose
NOAEC	no-observed-adverse-effect concentration
NOAEL	no-observed-adverse-effect level
WHO	World Health Organization

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1. GENERAL DESCRIPTION

1.1 Identity

CAS No.:	52645-53-1
Molecular formula:	$C_{21}H_{20}Cl_2O_3$

Permethrin is the common name for 3-phenoxybenzyl (1RS)-*cis*, *trans*-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylate. It is a mixture of four stereoisomers of the (1R, *trans*), (1R, *cis*), (1S, *trans*) and (1S, *cis*) configurations. In most technical products, the *cis*:*trans* ratio is about 2:3, and the 1R:1S ratio is 1:1 (racemic). The composition ratio of the above isomers is about 3:2:3:2 (IPCS, 1990). Of the four isomers, the (1R, *cis*) and the (1R, *trans*) isomers are the two esters primarily responsible for insecticidal activity. The term permethrin is used here to refer to material with a *cis*:*trans* ratio of 2:3, unless otherwise stated.

1.2 Physicochemical properties (IPCS, 1990)

Property	*Value*
Physical state	Crystal or viscous liquid
Melting point	34–39 °C
Boiling point	220 °C
Water solubility	0.2 mg/litre at 30 °C
Log octanol–water partition coefficient	6.5

1.3 Organoleptic properties

An organoleptic threshold in water of 0.2 mg/litre was reported in one study (Musamuhamedov, 1988).

1.4 Major uses and sources in drinking-water

Permethrin is a contact insecticide used against a broad range of pests in agriculture, forestry and public health. Surface waters may become contaminated by permethrin applied directly to water for mosquito control purposes, in discharges from production plants and from agricultural sources.

1.5 Environmental fate

Permethrin is photodegraded both in water and on soil surfaces. Ester cleavage and *cis–trans* interconversion are the major reactions. At equilibrium, the *trans* isomer constitutes 65–70% of the mixture. The major products of the ester cleavage of permethrin include 3-phenoxybenzaldehyde, 3-phenoxybenzoic acid, 3-phenoxybenzyl-3,3-dimethylacrylate and benzyl alcohols, as well as the corresponding acids (IPCS, 1990).

In soil, permethrin is rapidly degraded by hydrolysis and microbial action under aerobic conditions. Similar degradation processes seem to occur under anaerobic conditions, but at slower rates. In laboratory studies, the soil half-life was approximately 28 days. The *trans* isomer was more rapidly degraded than the *cis* isomer, and ester cleavage was the major initial degradative reaction. In plants, permethrin degrades with a half-life of approximately 10 days (IPCS, 1990).

2. ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE

2.1 Water

Concentrations as high as 0.8 mg/litre have been recorded in surface water. Levels in drinking-water have not been reported. When permethrin is used to control aquatic invertebrates in water mains, concentrations of about 10 µg/litre will be present in the water for short periods (Fawell, 1987).

2.2 Food

Exposure of the general population to permethrin is mainly via the diet. Residue levels in crops grown according to good agricultural practice are generally low. The resulting exposure is expected to be low, but precise data from total diet studies are lacking (IPCS, 1990).

3. KINETICS AND METABOLISM IN LABORATORY ANIMALS AND HUMANS[1]

The metabolism of [^{14}C]permethrin was studied in rats, lactating goats and cattle and laying hens. Permethrin was rapidly absorbed, distributed and excreted in these species after oral administration. The metabolism of the pyrethroid was extensive, yielding a vast number of polar degradates. Ester cleavage, hydroxylation, oxidation and ultimately conjugation are the critical biological mechanisms of the metabolism of permethrin in the species studied. The metabolites that were common to all species were 4'-hydroxypermethrin, dichlorovinyl acid and phenoxybenzyl alcohol. Dichlorovinyl acid and phenoxybenzoic acid have been identified in human urine after dermal application of permethrin.

In rats, 96% of an administered dose was recovered in urine and faeces within 12 days, while the total radiolabelled residues in tissues accounted for 0.3–0.8% of the dose. Recovery in urine and faeces within 24 h accounted for about 40% and 25% of the dose of *cis* isomer and 65% and 10% of the dose of *trans* isomer, respectively. Repeated exposure resulted in temporary accumulation in fat tissue, but the chemical dissipated rapidly once exposure ceased.

In lactating goats and cows dosed orally with permethrin, recovery in urine and faeces accounted for at least 65% of the dose, and the total radiolabelled residues in liver and

[1] This section is taken from FAO/WHO (2000).

milk samples represented 0.2–0.5%. Permethrin was extensively metabolized and readily eliminated after oral administration to laying hens, ≥90% of the administered dose being excreted, while the total radiolabel in egg and liver samples accounted for 0.1–0.2% of the dose.

4. EFFECTS ON EXPERIMENTAL ANIMALS AND IN VITRO *TEST SYSTEMS*[1]

The toxicity of permethrin is influenced by many factors, including the *cis*:*trans* isomer ratio, the carrier or vehicle and the strain of animal used. The *cis* isomer is considerably more toxic than the *trans* isomer. The oral LD_{50} values in rats ranged from 6000 mg/kg of body weight for the 20:80 *cis*:*trans* isomeric mixture to 220 mg/kg of body weight for the 80:20 *cis*:*trans* isomeric mixture. Undiluted technical-grade permethrin (25:75 to 40:60 *cis*:*trans* isomeric mixtures) has low acute toxicity after oral, dermal and inhalation exposure. It was mildly irritating to the eyes and slightly irritating to skin. It was not a skin sensitizer when tested by the Magnusson and Kligman method.

WHO (1999) has classified permethrin as "moderately hazardous."

Studies in which rats, mice, rabbits, guinea-pigs and dogs received repeated administrations by the inhalation, oral and dermal routes showed that the main effects of technical-grade permethrin are on clinical signs, especially tremor and hyperexcitability, body weight and liver weight. In these short-term studies, the NOAEL or NOAEC values were 250 mg/m^3 in a 13-week study in rats exposed by inhalation; 5 mg/kg of body weight per day in a 52-week study in which dogs received the compound in gelatin capsules orally; and 1000 mg/kg of body weight per day in a 21-day study in rabbits treated dermally.

In two long-term studies in rats in different laboratories with different strains, permethrin was not carcinogenic, but the evidence for carcinogenicity in mice was conflicting. In two studies conducted on the same strain in the same laboratory, permethrin increased the incidences of lung and liver tumours in one study but not in the other. The spontaneous background incidence of both these tumour types is known to be extremely variable. A third study, conducted on a different mouse strain, gave negative results. Thus, the weight of evidence supports the conclusion that permethrin has very weak oncogenic potential, and the probability that it has oncogenic potential in humans is remote. The NOAEL for long-term toxicity in rats was 100 mg/kg, equivalent to 5 mg/kg of body weight per day, on the basis of clinical signs and changes in body and organ weights and blood chemistry at 500 mg/kg. The NOAEL for long-term toxicity in mice was 500 mg/kg, equivalent to 75 mg/kg of body weight per day, on the basis of changes in organ weights at 2000 mg/kg.

No genotoxic activity was observed in an adequate battery of tests for DNA damage and mutagenicity *in vitro*, but there was evidence that permethrin can induce

[2] This section is taken from FAO/WHO (2000).

chromosomal aberrations in mammalian cells *in vitro.* No tests have been carried out in mammals for DNA damage, mutagenicity or clastogenicity *in vivo.* A test for dominant lethal effects in male mice showed no activity.

In a multigeneration study of reproductive toxicity in rats, the NOAEL for systemic and reproductive toxicity was 180 mg/kg of body weight per day. In a second multigeneration study in rats, a NOAEL could not be identified for systemic toxicity, as effects were seen at 500 mg/kg, equivalent to 33 mg/kg of body weight per day, the lowest dose tested; the NOAEL for reproductive toxicity in the same study was 2500 mg/kg, equivalent to 170 mg/kg of body weight per day, the highest dose tested.

In a study of developmental toxicity in rabbits, the NOAEL for maternal effects was 600 mg/kg of body weight per day and that for developmental toxicity was 1200 mg/kg of body weight per day. In three studies of developmental toxicity in rats, the NOAEL for maternal toxicity was 83 mg/kg of body weight per day and the NOAEL for developmental toxicity was 225 mg/kg of body weight per day, the highest dose tested. In a study of developmental toxicity in mice, no NOAEL was identified for maternal toxicity, whereas the NOAEL for developmental effects was 400 mg/kg of body weight per day, the only dose tested. The JMPR Meeting concluded that technical-grade permethrin is not a reproductive or developmental toxin.

The results of acute and 90-day studies of neurotoxicity in rats and of an acute study of delayed neurotoxicity in hens showed that technical-grade permethrin does not induce neuropathological changes. The NOAEL for neurotoxicity in a study in rats given a single dose was 150 mg/kg of body weight, on the basis of clinical signs of neurotoxicity and significant changes in measurements in a functional observational battery of tests at 300 mg/kg of body weight. The NOAEL for neurotoxicity in a 13-week study in rats was 15 mg/kg of body weight per day, on the basis of clinical signs of neurotoxicity and significant changes in measurements in the functional observational battery of tests at 90 mg/kg of body weight per day.

5. PRACTICAL ASPECTS

5.1 Analytical methods and analytical achievability

Permethrin may be determined by gas–liquid chromatography with an electron capture or flame ionization detector. The minimum detectable concentration is about 0.05 µg/litre (IPCS, 1990).

5.2 Treatment and control methods and technical achievability

Permethrin removal from raw water is not normally an issue. Permethrin adsorbs to a wide range of materials, and it is generally considered that permethrin is readily removed by conventional treatment methods. Neither *cis*- nor *trans*-permethrin reacts with chlorine under normal disinfection conditions (Fielding & Haley, 1989).

6. GUIDELINE VALUE

IARC (1991) has classified permethrin in Group 3 (not classifiable as to its carcinogenicity to humans), as there are no human data and only limited data from animal studies regarding carcinogenicity. Permethrin is not genotoxic.

JMPR (FAO/WHO, 2000) established an ADI of 0.05 mg/kg of body weight for technical-grade permethrin with *cis*:*trans* ratios of 25:75 to 40:60 on the basis of the NOAEL of 100 mg/kg, equivalent to 5 mg/kg of body weight per day, in the 2-year study in rats, which was based on clinical signs and changes in body and organ weights and blood chemistry at 500 mg/kg, and the NOAEL of 5 mg/kg of body weight per day in a 1-year study in dogs, based on reduced body weight at 100 mg/kg of body weight per day, and applying an uncertainty factor of 100 (FAO/WHO, 2000).

A health-based value of 20 µg/litre (rounded value) can be derived by allocating 1% of the ADI of 0.05 mg/kg of body weight to drinking-water, because there is significant exposure to permethrin from the environment. However, concentrations of permethrin in drinking-water are usually far below levels of health concern. It is therefore not considered necessary to derive a health-based guideline value where permethrin is not added directly to water as a larvicide.

If permethrin is to be used for short periods as a larvicide for the control of mosquitos and other insects of health significance in drinking-water sources, the share of the ADI allocated to drinking-water may be increased to 20%. In such cases, the guideline value would be 300 µg/litre.

Adding permethrin directly to drinking-water for public health purposes is not recommended by WHO, as part of its policy to exclude the use of any pyrethroids for larviciding of mosquito vectors of human disease. This policy is based on concern over the possible accelerated development of vector resistance to synthetic pyrethroids, which, in their application to insecticide-treated mosquito nets, are crucial in the current global malaria strategy.

7. REFERENCES

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