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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 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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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
DNA	deoxyribonucleic acid
FAO	Food and Agriculture Organization of the United Nations
IARC	International Agency for Research on Cancer
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

Permethrin is a contact insecticide effective against a broad range of pests in agriculture, forestry and public health.

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. ANALYTICAL METHODS

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).

3. ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE

3.1 Water

Surface waters may become contaminated by permethrin applied directly to water for mosquito control purposes, in discharges from production plants and from agricultural sources. Concentrations as high as 0.8 mg/litre have been recorded in surface water. Levels in drinking-water have not been reported, but it is generally considered that permethrin is readily removed by conventional treatment methods and that neither *cis*- nor *trans*-permethrin reacts with chlorine under normal disinfection conditions (Fielding & Haley, 1989). 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).

3.2 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).

4. 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.

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

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 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.

5. EFFECTS ON EXPERIMENTAL ANIMALS AND IN VITRO TEST SYSTEMS[2]

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

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

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 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.

6. CONCLUSIONS

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

An ADI of 0.05 mg/kg of body weight was established 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 a safety factor of 100.

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, because permethrin occurs at concentrations well below those at which toxic effects are observed, it is not considered necessary to derive a health-based guideline value.

7. REFERENCES

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