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# Pirimiphos-methyl in Drinking-water:
# Use for Vector Control in Drinking-water Sources and Containers

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

**Pirimiphos-methyl in Drinking-water: Use for Vector Control in Drinking-water Sources and Containers**
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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 on selected chemicals in 1998 and on microbial aspects in 2002. The third edition of the GDWQ was published in 2004, the first addendum to the third edition was published in 2005, and the second addendum to the third edition was published in 2008.

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 (USA) 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 also 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 Meeting 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 Pirimiphos-methyl in Drinking-water: Use for Vector Control in Drinking-water Sources and Containers, Background document for development of WHO *Guidelines for Drinking-water Quality*, was prepared by Mr J.K. Fawell, United Kingdom, to whom special thanks are due.

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

Dr J. Cotruvo, Joseph Cotruvo & Associates, USA (*Materials and chemicals*)
Mr J.K. Fawell, United Kingdom (*Naturally occurring and industrial contaminants*)
Ms M. Giddings, Health Canada (*Disinfectants and disinfection by-products*)
Mr P. Jackson, WRc-NSF, United Kingdom (*Chemicals – practical aspects*)
Professor Y. Magara, Hokkaido University, Japan (*Analytical achievability*)
Dr A.V. Festo Ngowi, Tropical Pesticides Research Institute, United Republic of Tanzania (*Pesticides*)
Dr E. Ohanian, Environmental Protection Agency, USA (*Disinfectants and disinfection by-products*)

The draft text was discussed at the Working Group Meeting for the second addendum to the third edition of the GDWQ, held on 15–19 May 2006. 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 coordinators were Dr J. Bartram and Mr B. Gordon, WHO Headquarters. Ms C. Vickers provided a liaison with the Programme on Chemical Safety, WHO Headquarters. Mr R. Bos, Assessing and Managing Environmental Risks to Health, 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 |
| FAO | Food and Agriculture Organization of the United Nations |
| GDWQ | *Guidelines for Drinking-water Quality* |
| IUPAC | International Union of Pure and Applied Chemistry |
| JMPR | Joint FAO/WHO Meeting on Pesticide Residues |
| $K_{ow}$ | octanol–water partition coefficient |
| NOAEL | no-observed-adverse-effect level |
| WHO | World Health Organization |

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## *1. GENERAL DESCRIPTION*

### *1.1 Identity*

| | |
|---|---|
| CAS No.: | 29232-93-7 |
| Molecular formula: | $C_{11}H_{20}N_30_3PS$ |

The IUPAC name for pirimiphos-methyl is *O*,2-diethylamino-6-methylpirimidin-4-yl *O*,*O*-dimethyl phosphorothioate.

### *1.2 Physicochemical properties (WHO/FAO, 1996)*

| *Property* | *Value* |
|---|---|
| Melting point | 15–18 °C |
| Density | 1.157 |
| Water solubility | 5.0 mg/l at 30 °C |
| Log octanol–water partition coefficient (log $K_{ow}$) | 4.35 |
| Vapour pressure | $1.47 \times 10^{-5}$ kPa at 30 °C |

### *1.3 Major uses and sources in drinking-water*

Pirimiphos-methyl is an organophosphorus compound that is an effective stomach and contact insecticide and acaricide against a wide range of insect pests, acting by inhibition of acetylcholinesterase. It is used in a wide range of pesticidal applications (e.g. in pre-harvest cleanup of fruits and vegetables, for post-harvest spraying to wheat, barley and oat grains during storage, for treatment of structural surfaces in empty grain storage facilities), including for control of mosquitoes and flies for public health purposes (WHO, 2006a). WHO is considering pirimiphos-methyl for use as a mosquito larvicide in drinking-water in containers, particularly to control dengue fever. The manufacturer recommends the direct addition of 1 mg/litre to water.

### *1.4 Environmental fate*

Pirimiphos-methyl is fairly rapidly degraded in the environment, with a dissipation half-life measured in days. The mechanisms are volatilization and photodegradation initially, with biodegradation and chemical hydrolysis considered to be more important after about 24 h (HSDB, undated).

## *2. HUMAN EXPOSURE*

Exposure of the public through food is expected to be low in many circumstances, although high residues have been encountered in specific vegetables such as carrots on which there has been repeated use of insecticides and insufficient time allowed for breakdown before harvest. There is also a potential for exposure (above the ADI) through whole grain products, although the degradation rate depends on the moisture content of the grain during storage (EFSA, 2005). Although pirimiphos-methyl is not normally seen in drinking-water, there is potential for direct exposure through drinking-water if the pesticide is applied directly to drinking-water storage containers for use in vector control.

## *3. TOXICOLOGICAL SUMMARY*[1]

Following oral administration of pirimiphos-methyl to male rats, 80.7% and 7.3% of the administered dose were excreted via urine and faeces, respectively, within 24 h. In the dog, 48 h after dosing with either 18.4 or 16.7 mg/kg of body weight, urinary excretion was 64.4% or 82.5% and faecal excretion 17.3% or 13.3%, respectively.

Metabolic data indicated that the P–O–C bond of pirimiphos-methyl was readily cleaved and that *N*-de-ethylation and/or conjugation were further steps in the metabolism of the pyrimidine leaving group. Although the oxygen analogue of pirimiphos-methyl was not detected as a urinary metabolite, the fact that cholinesterase inhibition occurred in vivo suggests that the oxygen analogue was also formed and that its formation may be an intermediate step leading to the identified urinary products.

In rats and dogs, 2-ethylamino-4-hydroxy-6-methylpyrimidine was the major metabolite (30% of the administered dose).

The oral toxicity of pirimiphos-methyl is low. WHO has classified the compound as slightly hazardous (WHO, 1992).

The only biochemical effect consistently observed with pirimiphos-methyl in acute, short-term or long-term studies was cholinesterase inhibition.

In a series of short-term rat studies at dose levels of 0, 8, 80 or 360 mg/kg diet for 3 months, 0, 10, 250, 500 or 1000 mg/kg for 28 days, 200 mg/kg of body weight 5 times weekly for 14 days and 0, 5, 8, 10 or 50 mg/kg for 28 days (young rats), the overall NOAEL was 10 mg/kg (equivalent to 0.5 mg/kg of body weight per day), with effects on erythrocyte cholinesterase and brain acetylcholinesterase at 80 mg/kg. At high dose levels (200 mg/kg of body weight, 5 times weekly for 2 weeks), erythrocyte morphology was affected. The NOAEL in young rats was also 10 mg/kg, with brain (but not erythrocyte) acetylcholinesterase depressed at 50 mg/kg after 28 days.

In two dog studies (13 weeks at dose levels of 0, 2, 10 or 25 mg/kg of body weight per day via capsule and 0, 0.5, 2 or 10 mg/kg of body weight per day for 2 years by capsules), the NOAEL was 2 mg/kg of body weight per day, based on brain acetylcholinesterase inhibition.

In an 80-week study in mice at dietary concentrations of 0, 5, 250 or 500 mg/kg, a NOAEL based on blood cholinesterase depression was 5 mg/kg (equivalent to 0.5 mg/kg of body weight per day) (blood cholinesterase was not measured at 250 mg/kg, only at 5 and 500 mg/kg). Pirimiphos-methyl was not carcinogenic in mice.

In a 2-year study in rats at dietary concentrations of 0, 10, 50 or 300 mg/kg, tumour incidence was comparable to controls. The NOAEL was 10 mg/kg (equivalent to 0.5 mg/kg of body weight per day), with brain acetylcholinesterase inhibition occurring at higher levels. Pirimiphos-methyl was not carcinogenic in rats.

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[1] After FAO/WHO (1993).

In a four-generation reproduction study in rats at nominal dietary concentrations of 0, 20 or 200 mg/kg, dose-related reduction of pregnancy rates and reduced mating performance at 200 mg/kg were noted. Dietary analyses indicated that the 20 mg/kg diet contained only 9 mg of pirimiphos-methyl per kilogram. No NOAEL was demonstrated in this study.

A repeat study at dietary concentrations of 0, 5, 10 or 100 mg/kg for three generations (one litter per generation) did not show any adverse effects on reproductive parameters at any dose level. The NOAEL was 100 mg/kg (equivalent to 5 mg/kg of body weight per day) for reproductive effects.

In two rat teratology studies, one at dietary concentrations of 0, 10 or 200 mg/kg and the second at dose levels of 0, 1.5, 15 or 150 mg/kg of body weight per day, dosing extending over or beyond the period of embryogenesis did not demonstrate any evidence of teratogenicity. Fetotoxicity was observed at 200 mg/kg (equivalent to 10 mg/kg of body weight per day) and 150 mg/kg of body weight per day. NOAELs for maternal toxicity (15 mg/kg of body weight per day), embryotoxicity (15 mg/kg of body weight per day) and teratogenicity (≤150 mg/kg of body weight per day) were identified.

A rabbit teratogenicity study at doses of 0, 1 or 16 mg/kg of body weight per day administered from days 1 to 28 of gestation did not show any evidence of teratogenic effects. The NOAEL for fetotoxicity and teratogenicity was 16 mg/kg of body weight per day.

Four studies in hens indicated that pirimiphos-methyl does not cause delayed neurotoxicity.

After considering the available in vitro and in vivo genotoxicity data, JMPR concluded that pirimiphos-methyl was not genotoxic.

In two experimental studies with human volunteers of 28 and 56 days, the highest dose tested in both studies (0.25 mg/kg of body weight per day) failed to induce erythrocyte cholinesterase inhibition in either study.

In determining the ADI, the first multigeneration study in rats was discarded because the dietary concentrations were uncertain, and the adverse effects noted (decreased pregnancy rate and mating performance) were atypical of those normally seen in reproduction studies with organophosphorus esters (decreased pup weight gain and pup mortality during early lactation). A clear NOAEL of 100 mg/kg (equivalent to 5 mg/kg of body weight per day, the highest dose tested) was demonstrated in the repeat study.

Studies with mice, rats and dogs showed NOAELs of 0.5 mg/kg of body weight per day or above. In human studies, no cholinesterase inhibition was seen at 0.25 mg/kg of body weight per day (the highest dose tested). On this basis, JMPR revised the ADI to 0–0.03 mg/kg of body weight by applying a 10-fold safety factor to the NOAEL in the human studies.

In 2006, an acute reference dose of 0.2 mg/kg of body weight was set on the basis of applying a safety factor of 100 to the NOAEL in an acute neurotoxicity study in rats with supporting data from a 28-day human study (FAO/WHO, 2006). This reference dose is calculated in relation to exposure from a single meal or for a period of 24 h and would therefore be equivalent to exposure over a period of a day from drinking-water.

## *4. PRACTICAL ASPECTS*

### *4.1 Analytical methods and analytical achievability*

Pirimiphos-methyl can be analysed by capillary gas chromatography with flame photometric detector, electron capture detector (62.9 pg in water) or mass spectrometry (Abdel-Halim et al., 2006).

### *4.2 Use for vector control in drinking-water sources*

Pirimiphos-methyl is being considered for use as a larvicide for the control of disease-carrying mosquitoes that breed in drinking-water containers. The manufacturer recommends the direct addition of 1 mg/l to water.

Formulations of pesticides used for vector control in drinking-water should strictly follow the label recommendations and should only be those approved for such a use by national authorities, taking into consideration the ingredients and formulants used in making the final product (WHO, 2006b).

## *5. CONCLUSIONS*

It is not considered appropriate to set a formal guideline value for pirimiphos-methyl used as a vector control agent in drinking-water. The ADI determined for pirimiphos-methyl by JMPR in 1992 (FAO/WHO, 1993) was 0–0.03 mg/kg of body weight. Young animals do not appear to be significantly more sensitive than adults. At the recommended dose for drinking-water of 1 mg/l, a 60-kg adult drinking 2 litres of water would have an intake of 0.033 mg/kg of body weight, compared with the ADI of 0–0.03 mg/kg of body weight. The intake for a 10-kg child drinking 1 litre of water would be 0.1 mg/kg of body weight; for a 5-kg bottle-fed infant drinking 0.75 litre, it would be 0.15 mg/kg of body weight.

There is uncertainty regarding the level that would cause effects in humans, since the NOAEL on which the ADI is based was the highest dose tested, and so the ADI may be more conservative than is at first apparent. These intake figures are all below the acute reference dose of 0.2 mg/kg of body weight (FAO/WHO, 2006) and would not result in an acute exposure risk from the initial application of pirimiphos-methyl to drinking-water containers at the recommended dose. In addition, the low solubility and the high log $K_{ow}$ of pirimiphos-methyl indicate that it is very unlikely to remain in solution at the maximum recommended applied dose, so that the actual levels of exposure are expected to be lower than those calculated. Exposure from food is generally considered to be low, but occasional high exposures can be experienced.

National authorities should note that this document refers only to the active ingredient and does not consider the additives in different formulations.

## *6. RECOMMENDATIONS*

Based on the above calculations, pirimiphos-methyl is not recommended for direct application to drinking-water unless no other effective and safe treatments are available. If pirimiphos-methyl is applied directly to drinking-water, consideration should be given to using alternative sources of water for bottle-fed infants and small children for a period after its application, where this is practical. However, exceeding the ADI will not necessarily result in adverse effects.

In setting local guidelines or standards, health authorities should take into consideration the potential for higher rates of water consumption in the area or region under consideration and, in the case of pirimiphos-methyl, whether exposure from food will also be significant.

The diseases spread by vectors are significant causes of morbidity and mortality. It is therefore important to achieve an appropriate balance between the intake of the pesticide from drinking-water and the control of disease-carrying insects. Better than establishing guideline values are the formulation and implementation of a comprehensive management plan for household water storage and peridomestic waste management that does not rely exclusively on larviciding by insecticides, but also includes other environmental management measures and social behavioural changes.

## *7. REFERENCES*

Abdel-Halim KY et al. (2006) Organophosphorus pollutants (OPP) in aquatic environment at Damietta Governorate, Egypt: implications for monitoring and biomarker responses. *Chemosphere*, 63:1491–1498.

EFSA (2005) *Conclusion regarding the peer review of the pesticide risk assessment of the active substance pirimiphos-methyl.* European Food Standards Agency, pp. 1–53 (EFSA Scientific Report 44, finalised 10 August 2005; http://www.efsa.europa.eu/etc/medialib/efsa/science/praper/conclusions/1116.Par.0001.File.dat/praper_concl_sr44_pirimiphos-methyl_en1.pdf).

FAO/WHO (1993) Pirimiphos-methyl. In: *Pesticide residues in food: 1992 evaluations. Part II — Toxicology.* Geneva, World Health Organization, Joint FAO/WHO Meeting on Pesticide Residues (WHO/PCS/93.34; http://whqlibdoc.who.int/hq/1993/WHO_PCS_93.34.pdf).

FAO/WHO (2006) Pirimiphos-methyl. In: *Pesticide residues in food 2006.* Rome, Food and Agriculture Organization of the United Nations, Joint FAO/WHO Meeting on Pesticide Residues, pp. 178–179 (FAO Plant Production and Protection Paper 187; http://www.fao.org/ag/AGP/AGPP/Pesticid/JMPR/DOWNLOAD/2006_rep/report2006jmpr.pdf).

HSDB (undated) *Pirimiphos methyl: environmental fate and exposure.* Bethesda, MD, United States Department of Health and Human Services, National Institutes of Health, National Library of Medicine, Hazardous Substances Data Bank (http://www.toxnet.nlm.nih.gov/).

WHO (1992) *The WHO recommended classification of pesticides by hazard and guidelines to classification 1992–1993*. Geneva, World Health Organization, International Programme on Chemical Safety (WHO/PCS/92.14).

WHO (2006a) *Pesticides and their application for the control of vectors and pests of public health importance*, 6th ed. Geneva, World Health Organization, Department of Control of Neglected Tropical Diseases, Pesticides Evaluation Scheme (WHO/CDS/NTD/WHOPES/GCDPP/2006.1; http://whqlibdoc.who.int/hq/2006/WHO_CDS_NTD_WHOPES_GCDPP_2006.1_eng.pdf).
WHO (2006b) *Pirimiphos-methyl: O-2-diethylamino-6-methylpyrimidin-4-yl-O,O-dimethyl phosphorothioate*. Geneva, World Health Organization (WHO Specifications and Evaluations for Public Health Pesticides; http://www.who.int/whopes/quality/en/Pirimiphos_methyl_eval_may_06.pdf).

WHO/FAO (1996) *Pirimiphos-methyl.* Geneva, World Health Organization and Food and Agriculture Organization of the United Nations (WHO/FAO Datasheets on Pesticides No. 49; VBC/DS/82.49; http://www.inchem.org/documents/pds/pds/pest49_e.htm).