

**Pyriproxyfen in Drinking-water:
Use for Vector Control in Drinking-water Sources and Containers**

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 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.

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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 second addendum to the third edition:

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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 | <i>Guidelines for Drinking-water Quality</i> |
| IUPAC | International Union of Pure and Applied Chemistry |
| JMPR | Joint FAO/WHO Meeting on Pesticide Residues |
| K_{ow} | octanol–water partition coefficient |
| LC ₅₀ | median lethal concentration |
| LD ₅₀ | median lethal dose |
| NOAEL | no-observed-adverse-effect level |
| 4'-OH-pyriproxyfen | 4-(4'-hydroxyphenoxy)phenyl-2-(2-pyridyloxy)-propyl ether |
| PYPAC | 2-(2-pyridyloxy)propionic acid |
| WHO | World Health Organization |

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1. GENERAL DESCRIPTION

1.1 Identity

CAS No.: 95737-68-1
Molecular formula: C₂₀H₁₉NO₃

The IUPAC name for pyriproxyfen is 4-phenoxyphenyl (*RS*)-2-(2-pyridyloxy)propyl ether.

1.2 Physicochemical properties (IPCS, 1995)

| <i>Property</i> | <i>Value</i> |
|--|---------------------|
| Melting point | 45–47 °C |
| Water solubility | 0.367 mg/l at 25 °C |
| Log octanol–water partition coefficient (log <i>K_{ow}</i>) | 5.37 |
| Vapour pressure | 0.0003 Pa at 20 °C |

1.3 Major uses and sources in drinking-water

Pyriproxyfen is a broad-spectrum insect growth regulator with insecticidal activity against public health insect pests: houseflies, mosquitoes and cockroaches. It is a juvenile hormone analogue that interferes with metamorphosis (growth, development and maturation) in insects and prevents them from reaching maturity and reproducing. In agriculture and horticulture, pyriproxyfen has registered uses for the control of scale, whitefly, bollworm, jassids, aphids and cutworms (FAO/WHO, 1999). Pyriproxyfen is one of several insecticides used for the control of the red imported fire ant (*Solenopsis invicta*) in California, USA (Sullivan, 2000).

WHO has assessed pyriproxyfen for use as a mosquito larvicide in drinking-water in containers, particularly to control dengue fever. The recommended dosage of pyriproxyfen in potable water in containers should not exceed 0.01 mg/l under the WHO Pesticides Evaluation Scheme (WHO, 2006a,b).

1.4 Environmental fate

Pyriproxyfen degrades rapidly in soil under aerobic conditions, with a half-life of 6.4–36 days (Sullivan, 2000). Pyriproxyfen disappeared from aerobic lake water–sediment systems with half-lives ranging from 16 and 21 days. Pyriproxyfen was the main residue in the sediment during the 1-month studies, and 4'-OH-pyriproxyfen accounted for 7.5% and 9.5% of the dose after 7 days (FAO/WHO, 1999). In a photolysis study, pyriproxyfen was exposed to sunlight in sterilized distilled water and sterilized lake water. The estimated photolytic half-lives were 17.5 and 21 days, respectively. A theoretical half-life of 16 days was calculated for 40°N latitude. The main photoproducts were PYPAC and carbon dioxide (FAO/WHO, 1999).

2. ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE

As pyriproxyfen is a relatively new pesticide, few environmental data have been collected to date. However, there is potential for direct exposure through drinking-water when pyriproxyfen is directly applied to drinking-water storage containers.

During May 2001, surface water samples were collected from five sites in Orange County, California, USA. Water samples showed no detectable concentrations of pyriproxyfen.

Pyriproxyfen is used on citrus fruit in Israel, South Africa, Spain and Italy. Residues in the 18 trials in those countries were as follows: oranges, 0.02–0.25 mg/kg; grapefruit, 0.03–0.08 mg/kg; and mandarins, 0.02–0.53 mg/kg. The maximum concentration on citrus fruit was about 1 mg/kg. Residues were not detected in the edible pulp (FAO/WHO, 1999).

These data indicate that exposure to pyriproxyfen from food and drinking-water will be very low.

3. TOXICOLOGICAL SUMMARY¹

After oral administration to rats, [¹⁴C]pyriproxyfen is slowly (time to peak concentration in plasma, 8 h) and incompletely ($\leq 50\%$ of the dose) absorbed, but is then rapidly eliminated, predominantly in the faeces (90%), with only 4–11% in the urine, after 48 h. Absorbed pyriproxyfen is excreted mainly via the bile (34–37% of the administered dose in 48 h). The metabolism of pyriproxyfen is qualitatively similar in rats, mice, lactating goats and laying hens. A large number of metabolites have been detected, the main route of biotransformation being 4'-hydroxylation. Other pathways include hydroxylation of the pyridyl ring, ether cleavage and conjugation. Mice conjugate a much greater proportion of the dose than rats. The concentration of pyriproxyfen in tissues other than fat was very low (generally <0.01 μg equivalent per gram after 72 h; fat, <0.1 μg equivalent per gram). The half-times of the radiolabel in tissues, including blood and fat, were 8–36 h. The dermal absorption of pyriproxyfen has not been studied.

The acute oral toxicity of pyriproxyfen is low, with LD₅₀ values above 5000 mg/kg of body weight in mice, rats and dogs. The acute dermal toxicity is also low, with LD₅₀ values greater than 2000 mg/kg of body weight in mice and rats. After exposure by inhalation, LC₅₀ values above 1.3 mg/l of air are found in mice and rats. WHO (2001) has classified pyriproxyfen as “unlikely to present acute hazard in normal use”. Pyriproxyfen was mildly irritating to the eye but not to the skin of rabbits. It did not sensitize the skin of Hartley guinea-pigs in a maximization test.

In short- and long-term studies of the effects of pyriproxyfen in mice, rats and dogs, the liver was the main toxicological target, with increases in liver weight and changes in plasma lipid concentrations, particularly cholesterol, at doses of 120 mg/kg of body weight per day and above in rats. There was some evidence that the compound might cause modest anaemia in mice, rats and dogs at high doses. In mice treated with

¹ After FAO/WHO (2000).

pyriproxyfen in the diet for 3 months, additional effects seen included increased mortality rates, histopathological changes in the kidney and decreased body weight. The NOAEL was 150 mg/kg of body weight per day in mice, 23 mg/kg of body weight per day (two studies) in rats and 100 mg/kg of body weight per day in dogs fed pyriproxyfen in the diet for 3 months. In long-term studies of toxicity in mice, pyriproxyfen also caused a dose-dependent increase in the occurrence of systemic amyloidosis, which was associated with increased mortality rates and is often associated with perturbation of the immune system. The NOAEL was 120 mg/kg, equivalent to 16 mg/kg of body weight per day. In rats, the only additional effect was reduced body weight gain, and the NOAEL was 600 mg/kg, equivalent to 27 mg/kg of body weight per day. In two 1-year studies in dogs, pyriproxyfen was administered in capsules. The overall NOAEL was 10 mg/kg of body weight per day on the basis of increased relative liver weight and increased total plasma cholesterol concentration in males. There was some evidence that pyriproxyfen can act as a hepatic enzyme inducer, at least in dogs. Pyriproxyfen was not toxic when administered dermally to rats for 21 days at doses of up to 1000 mg/kg of body weight per day. Inhalation of pyriproxyfen for 4 h per day for 28 days caused only minor effects in rats (initial salivation, sporadically reduced body weight gain, slightly increased serum lactate dehydrogenase activity) at 10 000 mg/m³. The NOAEL was 480 mg/m³.

Pyriproxyfen was not carcinogenic when given in the diet at doses up to 420 mg/kg of body weight per day in a study in mice or at doses up to 140 mg/kg of body weight per day in rats. Pyriproxyfen showed no evidence of carcinogenicity in a 1-year study in dogs at doses up to 1000 mg/kg of body weight per day. JMPR concluded that pyriproxyfen does not pose a carcinogenic risk to humans.

Pyriproxyfen was not genotoxic in an adequate range of tests for mutagenicity and cytogenicity in vitro and in vivo. JMPR concluded that pyriproxyfen is not genotoxic.

The reproductive toxicity of pyriproxyfen in rats has been investigated in a two-generation study, a study involving treatment of males and females before and in the early stages of gestation (segment 1) and a study of treatment during the prenatal and lactation periods (segment 3). The NOAEL for maternal toxicity was 1000 mg/kg, equivalent to 98 mg/kg of body weight per day, in the two-generation study and 100 mg/kg of body weight per day in the segment 3 study. Reproductive toxicity was observed only in the segment 3 study, in which there was an increased number of stillbirths in the F0 generation and a reduction in the number of implantations and in the mean number of live fetuses in the F1 generation at 500 mg/kg of body weight per day. The NOAEL for reproductive toxicity was 300 mg/kg of body weight per day. No reproductive toxicity was observed in the two-generation study, the NOAEL being 5000 mg/kg, equivalent to 340 mg/kg of body weight per day, the highest dose tested, or in the segment 1 study, the NOAEL being 1000 mg/kg of body weight per day, the highest dose tested.

The developmental toxicity of pyriproxyfen has been studied in rats and rabbits. In rats, a NOAEL for maternal toxicity was not identified, as decreased body weight gain was observed at 100 mg/kg of body weight per day, the lowest dose tested. Pyriproxyfen caused little developmental toxicity and was not teratogenic. In a segment 3 study, the F1 offspring were subjected to a series of developmental tests for possible neurotoxicity, including physical indices, tests of behaviour, motor and

sensory function and learning ability. Although there were some effects on growth at doses of ≥ 300 mg/kg of body weight per day, there was no developmental neurotoxicity at 500 mg/kg of body weight per day, the highest dose tested. Visceral anomalies (dilatation of the renal pelvis) were found at doses of ≥ 300 mg/kg of body weight per day. The NOAEL for developmental toxicity was 100 mg/kg of body weight per day, on the basis of retarded physical development and visceral anomalies at higher doses. In a more conventional study of developmental toxicity in rats, no evidence of growth retardation or of developmental neurotoxicity was found at doses up to and including 1000 mg/kg of body weight per day, the highest dose tested. There was an increased frequency of skeletal variations (opening of the foramen transversarium of the seventh cervical vertebra) in fetuses at 300 mg/kg of body weight per day. The frequency of visceral anomalies was significantly increased in F1 offspring some weeks after birth. The NOAEL for developmental toxicity was 300 mg/kg of body weight per day, on the basis of an increased frequency of skeletal variations with visceral anomalies in F1 offspring at 1000 mg/kg of body weight per day. In a study of developmental toxicity in rabbits, signs of maternal toxicity (abortion and premature delivery) were evident at doses of ≥ 300 mg/kg of body weight per day (NOAEL = 100 mg/kg of body weight per day). No developmental toxicity was observed, the NOAEL being 1000 mg/kg of body weight per day, the highest dose tested.

The ADI of 0–0.1 mg/kg of body weight was derived by applying an uncertainty factor of 100 to two 1-year studies in dogs in which the overall NOAEL was 10 mg/kg of body weight per day.

4. PRACTICAL ASPECTS

4.1 Analytical methods and analytical achievability

Pyriproxyfen can be analysed by extraction into dichloromethane, followed by column chromatography cleanup. The residue is then determined by gas–liquid chromatography with a nitrogen–phosphorus detector; the detection limit is about 0.02 mg/kg (FAO/WHO, 1999). Alternatively, pyriproxyfen in water can be analysed by extraction with an organic solvent followed by high-performance liquid chromatography and an ultraviolet detector. The detection limit is 0.1 $\mu\text{g/l}$ (Walters, 2001).

4.2 Use for vector control in drinking-water sources

Pyriproxyfen is used as a larvicide for control of disease-carrying mosquitoes that breed in drinking-water containers at a dosage not exceeding 0.01 mg/l.

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.

5. CONCLUSIONS

It is not considered appropriate to set a formal guideline value for pyriproxyfen used for vector control in drinking-water. The ADI determined by JMPR in 1999 was 0–0.1 mg/kg of body weight. Young animals do not appear to be significantly more sensitive than adults. The maximum dosage in drinking-water of 0.01 mg/l would be equivalent to less than 1% of the ADI allocated to drinking-water for a 60-kg adult drinking 2 litres of water per day. For a 10-kg child drinking 1 litre of water, the exposure would be 0.01 mg, compared with an exposure of 1 mg at the ADI. For a 5-kg bottle-fed infant drinking 0.75 litre per day, the exposure would be 0.0075 mg, compared with an exposure of 0.5 mg at the ADI. Exposure from food is considered to be relatively low. In addition, the low solubility and the high log K_{ow} of pyriproxyfen indicate that it is unlikely to remain in solution at the maximum recommended applied dose, and the actual levels of exposure are likely to be even lower than those calculated.

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

6. RECOMMENDATIONS

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. However, exceeding the ADI will not necessarily result in adverse effects.

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.

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