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Pyriproxyfen 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:

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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
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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

CAS	Chemical Abstracts Service
FAO	Food and Agriculture Organization of the United Nations
IPCS	International Programme on Chemical Safety
JMPR	Joint FAO/WHO Meeting on Pesticide Residues
LC_{50}	median lethal concentration
LD_{50}	median lethal dose
NOAEL	no-observed-adverse-effect level
USA	United States of America
WHO	World Health Organization

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1. GENERAL DESCRIPTION

1.1 Identity

CAS No.:	95737-68-1
Molecular formula:	$C_{20}H_{19}NO_3$

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

1.2 Physicochemical properties (IPCS, 1995)

Property	*Value*
Melting point	45–47 °C
Vapour pressure	0.0003 Pa at 20 °C
Solubility in water	0.367 mg/litre at 25 °C
Log octanol–water partition coefficient	5.37

1.3 Major uses

Pyriproxyfen is a broad-spectrum insect growth regulator with insecticidal activity against public health insect pests: houseflies, mosquitos and cockroaches. 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).

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 of 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. PYPAC was the main residue in the water phase after 12 days and accounted for 34% of the dose on day 21 (FAO/WHO, 1999).

Pyriproxyfen was the main residue throughout 1-year studies of anaerobic lake water–sediment systems, and most of the residue was in the sediment. PYPAC accounted for 16% of the dose after 1 year; because of its water solubility, it was mainly in the aqueous phase. Pyriproxyfen appeared to be degraded slowly for the first 6 months and subsequently more quickly (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. ANALYTICAL METHODS

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 µg/litre (Walters, 2001).

3. ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE

As pyriproxyfen is a new pesticide, few environmental data have yet been collected.

3.1 Water

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

3.2 Food

Pyriproxyfen is used on citrus fruit in Israel, South Africa, Spain and Italy. Pyriproxyfen 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).

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

After oral administration to rats, [^{14}C]pyriproxyfen is slowly (time to peak concentration in plasma, 8 h) and incompletely (≤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

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

g after 72 h; fat <0.1µg equivalent per g). 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.

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

The acute oral toxicity of pyriproxyfen is low, with LD_{50} values above 5000 mg/kg of body weight in mice, rats and dogs. The acute dermal toxicity is also low, with LD_{50} values greater than 2000 mg/kg of body weight in mice and rats. After exposure by inhalation, LC_{50} values above 1.3 mg/litre 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 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. The NOAEL was 120 mg/kg, equal 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, equal 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/m^3. The NOAEL was 480 mg/m^3.

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. The JMPR Meeting concluded that pyriproxyfen does not pose a carcinogenic risk to humans.

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

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

The reproductive toxicity of pyriproxyfen in rats has been investigated in a two-generation study of reproductive toxicity, 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, equal 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 F_0 generation and a reduction in the number of implantations and in the mean number of live fetuses in the F_1 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, equal 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 F_1 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 transversalium 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 F_1 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 F_1 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.

6. GUIDELINE VALUE

JMPR (FAO/WHO, 2000) established an ADI of 0.1 mg/kg of body weight on the basis of the NOAEL of 10 mg/kg of body weight per day, based on increased relative liver weight and increased total plasma cholesterol concentration in males in 1-year studies of toxicity in dogs and a safety factor of 100.

A guideline value of 0.3 mg/litre can be calculated from the ADI of 0.1 mg/kg of body weight, assuming a 60-kg adult consuming 2 litres of drinking-water per day and allocating 10% of the ADI to drinking-water.

7. REFERENCES

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