

# Isoproturon in Drinking-water

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

**© World Health Organization 2003**

All rights reserved. Publications of the World Health Organization can be obtained from Marketing and Dissemination, World Health Organization, 20 Avenue Appia, 1211 Geneva 27, Switzerland (tel: +41 22 791 2476; fax: +41 22 791 4857; email: [bookorders@who.int](mailto:bookorders@who.int)). Requests for permission to reproduce or translate WHO publications – whether for sale or for noncommercial distribution – should be addressed to Publications, at the above address (fax: +41 22 791 4806; email: [permissions@who.int](mailto:permissions@who.int)).

The designations employed and the presentation of the material in this publication do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries.

The mention of specific companies or of certain manufacturers' products does not imply that they are endorsed or recommended by the World Health Organization in preference to others of a similar nature that are not mentioned. Errors and omissions excepted, the names of proprietary products are distinguished by initial capital letters.

The World Health Organization does not warrant that the information contained in this publication is complete and correct and shall not be liable for any damages incurred as a result of its use.

## 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.

## Acknowledgements

The work of the following coordinators was crucial in the development of this background document for development of WHO *Guidelines for drinking-water quality*:

J.K. Fawell, Water Research Centre, United Kingdom  
(inorganic constituents)  
U. Lund, Water Quality Institute, Denmark  
(organic constituents and pesticides)  
B. Mintz, Environmental Protection Agency, USA  
(disinfectants and disinfectant by-products)

The WHO coordinators were as follows:

*Headquarters:*

H. Galal-Gorchev, International Programme on Chemical Safety  
R. Helmer, Division of Environmental Health

*Regional Office for Europe:*

X. Bonnefoy, Environment and Health  
O. Espinoza, Environment and Health

Ms Marla Sheffer of Ottawa, Canada, was responsible for the scientific editing of the document.

The efforts of all who helped in the preparation and finalization of this document, including those who drafted and peer reviewed drafts, are gratefully acknowledged.

The convening of the experts meetings was made possible by the financial support afforded to WHO by the Danish International Development Agency (DANIDA), Norwegian Agency for Development Cooperation (NORAD), the United Kingdom Overseas Development Administration (ODA) and the Water Services Association in the United Kingdom, the Swedish International Development Authority (SIDA), and the following sponsoring countries: Belgium, Canada, France, Italy, Japan, Netherlands, United Kingdom of Great Britain and Northern Ireland and United States of America.

## GENERAL DESCRIPTION

### *Identity*

CAS no.: 34123-59-6

Molecular formula: C<sub>12</sub>H<sub>18</sub>N<sub>2</sub>O

The IUPAC name for isoproturon is 3-(4-isopropylphenyl)-1,1-dimethylurea or 3-*p*-cumenyl-1,1-dimethylurea.

### *Physicochemical properties (1)*

<i>Property</i>	<i>Value</i>
Physical state	Colourless crystals
Melting point	155–156 °C
Vapour pressure	0.003 × 10 <sup>-3</sup> Pa at 20 °C
Water solubility	72 mg/litre at 20 °C

### *Organoleptic properties*

No odour was detected at a concentration of 8.0 mg/litre (99% purity, dissolved in still, bottled water, equilibrated to 40 °C, eight assessors) (Water Research Centre, unpublished data, 1990).

### *Major uses*

Isoproturon is a selective, systemic herbicide used in the control of annual grasses and broad-leaved weeds in cereals (1,2).

### *Environmental fate*

Isoproturon is mobile in soil and has been detected in both surface water and groundwater. In water, it is quite persistent and hydrolyses slowly; the half-life is about 30 days (3). In soil, isoproturon undergoes enzymatic and microbial demethylation at the urea nitrogen and hydrolysis of the phenylurea to form 4-(2-hydroxyisopropyl)aniline. It also undergoes some photochemical degradation; photometabolites identified include 3-(4-isopropylphenyl)-1-methylurea, 3-(4-isopropylphenyl)urea, 4,4'-diisopropylazobenzene, and 4,4'-diisopropylazoxybenzene. Under field conditions, its half-life is about 40 days in temperate climates and 15 days in tropical climates (4).

## ANALYTICAL METHODS

Isoproturon may be determined by separation by reverse-phase high-performance liquid chromatography followed by ultraviolet or electrochemical detection. High levels of phenoxyacidic herbicides may interfere with the determination (5). Detection limits between 10 and 100 ng/litre have been reported (6,7).

## ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE

### *Air*

Because of isoproturon's low vapour pressure and short half-life in soil, it is unlikely that there is significant human exposure from air.

## ***Water***

Raw waters may become contaminated with isoproturon from production plant discharges and diffuse agricultural sources. In Germany, concentrations of between 0.1 and 0.125 µg/litre have been recorded in surface water (8). In groundwater, it has been detected at concentrations of between 0.05 and 0.1 µg/litre (8,9). Levels above 0.1 µg/litre have occasionally been detected in drinking-water (3).

## ***Food***

It is generally considered that diet is not a major source of exposure to isoproturon for the general population. No measurable residues of isoproturon or any metabolites containing the isopropylaniline moiety were detected in grain samples, where the detection limit ranged from 0.1 to 0.01 mg/kg (10).

## ***Estimated total exposure and relative contribution of drinking-water***

The data on environmental levels of isoproturon are limited. However, results suggest that exposure of the general population to this compound is not significant.

## **KINETICS AND METABOLISM IN LABORATORY ANIMALS AND HUMANS**

Isoproturon is readily and rapidly absorbed when given orally. Distribution is rapid, and no accumulation of isoproturon in any particular organ or tissue has been reported (11). It is rapidly metabolized by the rat, the major routes being *N*-demethylation and oxidation of the *N*-methyl groups and isopropyl moiety followed by conjugation reactions. The *N*-hydroxymethyl derivative of substituted urea has not been detected, although this compound may be formed at a low concentration as a short-term intermediate. In the rat, isoproturon metabolites are rapidly excreted in the urine (10,11).

## **EFFECTS ON LABORATORY ANIMALS AND *IN VITRO* TEST SYSTEMS**

### ***Acute exposure***

Isoproturon is of low acute oral toxicity in mammals, although the LD<sub>50</sub> varies considerably according to the vehicle used (11). Oral LD<sub>50</sub>s range from 1826 to 3600 mg/kg of body weight for a number of species (11,12). It does not cause skin and eye irritation or sensitization after repeated dermal exposure (11).

### ***Short-term exposure***

In a 90-day dietary study in rats, animals receiving 400 mg/kg and higher showed a dose-dependent and reversible increase in liver weight, proliferation of the smooth endoplasmic reticulum in hepatocytes, and induction of several hepatic enzymes. Reversible haemolytic anaemia was also observed at 2000 mg/kg.

The NOAEL was 80 mg/kg, equal to a daily dose of 7 mg/kg of body weight (11).

In a 90-day study, beagle dogs fed isoproturon at dose levels of 0, 50, 100, or 500 (which was increased to 800) mg/kg of diet showed a dose-dependent increase in liver weight. Toxic haemolytic anaemia and Heinz body formation were seen at the highest dose. Haematological abnormalities were also present in the 100 mg/kg group. The NOAEL for this study was 50 mg/kg, equivalent to a daily intake of 3.2 mg/kg of body weight (11).

Liver damage was not observed in a 30-day dietary study in mice, suggesting that isoprotruron metabolism may be different in this species. The NOAEL was 2000 mg/kg, equal to a daily intake of 307 and 378 mg/kg of body weight in male and female mice, respectively (11).

### ***Long-term exposure***

Rats (80 per sex per dose, species not specified) were given isoprotruron in the daily diet at concentrations of 0, 80, 400, or 2000 mg/kg for 104 or 115 weeks. At the highest dose, serum enzyme activities and cholesterol values were increased, indicative of hepatic enzyme induction. At the two highest doses, there was a marginal reduction of all red blood cell parameters, liver weights were increased, and acidophilic foci (areas of hepatocellular change) were noted on histopathological examination. The NOAEL was 80 mg/kg, equal to a daily intake of 3.1 and 3.8 mg/kg of body weight in males and females, respectively (11).

### ***Reproductive toxicity, embryotoxicity, and teratogenicity***

Isoprotruron was not teratogenic in rats or rabbits administered doses up to 25 or 100 mg/kg of body weight per day by gavage, respectively. In a two-generation study, rats were fed isoprotruron at concentrations of 0, 80, 400, or 2000 mg/kg of diet per day. Marked indications of toxicity to the parents and pups were observed at the highest dose. Litter sizes and numbers of implantations were reduced as a result of maternal toxicity. A slight inhibition of body weight gain was also found in the group receiving 400 mg/kg of diet. No effects on reproduction, fertility, or sexual maturation were reported, and a NOAEL of 80 mg/kg of diet was identified (11).

### ***Mutagenicity and related end-points***

Isoprotruron has been tested in a number of *in vitro* and *in vivo* short-term assays for mutagenicity. The majority of the evidence, particularly in recent years, indicates that it is not mutagenic in bacterial, eukaryotic, or *in vitro* and *in vivo* mammalian test systems (11).

### ***Carcinogenicity***

In a 2-year study in CD-1 mice, no evidence was found to show that isoprotruron was carcinogenic (11). In addition, no evidence of hepatic enzyme induction or increased liver weights was seen. In a 2-year dietary study in Sprague-Dawley rats, isoprotruron caused an increase in hepatocellular tumours, but only at doses that also caused liver toxicity. No liver toxicity was apparent at 80 mg/kg of diet, nor was there an increase in the incidence of tumours. From these studies, it appears that isoprotruron may be a tumour promoter (11).

This was confirmed in a promoter study in male rats in which animals were pretreated with nitrosodiethylamine (NDEA) for 14 days followed by a treatment-free week. One group of animals was subsequently treated for 31 weeks with isoprotruron and another group with NDEA only. In isoprotruron-treated animals, there was a marked increase in the incidence of preneoplastic and neoplastic lesions in the liver as compared with the NDEA-treated group (11).

## **EFFECTS ON HUMANS**

Isoprotruron has been in commercial use for a relatively short period, and so far no cases of human poisoning have been reported. Data on human health effects are limited to studies involving occupational exposures. One 3-year study was carried out on a group of workers employed in various parts of the manufacturing process. Urine and blood analysis failed to show any pathological abnormalities in the peripheral blood count or any indication of haemolytic anaemia (11).

## GUIDELINE VALUE

The NOAELS in a 90-day study in dogs and a 2-year feeding study in rats were approximately 3 mg/kg of body weight per day (11). A TDI of 3 µg/kg of body weight can be calculated by applying an uncertainty factor of 1000 (100 for inter- and intraspecies variation and 10 because there is evidence of non-genotoxic carcinogenicity in rats). With an allocation of 10% of the TDI to drinking-water, a guideline value of 9 µg/litre was calculated.

## REFERENCES

1. Royal Society of Chemistry. *The agrochemicals handbook*, 3rd ed. Cambridge, 1991.
2. Worthing CR, ed. *The pesticide manual*, 9th ed. Farnham, British Crop Protection Council, 1991.
3. Department of the Environment. *Pesticides in water supplies*. London, 1989 (DoE Reference: WS/45/1/1).
4. Kulshrestha G, Muckerjee SK. The photochemical decomposition of the herbicide isoproturon. *Pesticide science*, 1986, 17:289-494.
5. Department of the Environment. The determination of carbamates, thiocarbamates, related compounds and ureas in waters 1987. In: *Methods for the examination of waters and associated materials*. London, Her Majesty's Stationery Office, 1987.
6. Crathorne B, James CP, Stratford JA. *HPLC method for the analysis of chlortoluron, isoproturon, and linuron in water*. Medmenham, Water Research Centre, 1987 (Water Research Centre Report PRU 1498-M UK).
7. Schussler W. Automatic measurement of some common herbicides by LC using simultaneous UV detection and electrochemical detection in series. *Chromatographia*, 1989, 27(9/10):431-435.
8. Reupert R, Ploeger E. Determination of N-herbicides in groundwater, drinking-water and surface water: analytical method and results. *Vom Wasser*, 1989, 72:211-233.
9. Johnen BG, Iwan J. Results and implications from monitoring German raw water for residues of a wide range of pesticides. *Brighton Crop Protection Conference, Pesticide Discussion*, 1988, 1:319-328.
10. *Re-evaluation of the toxicological properties of isoproturon and its safety in use* (unpublished report A 27779, submitted to WHO by Ciba-Geigy, Hoechst, Rhône-Poulenc).
11. *Isoproturon—Summary and evaluation of the toxicological data for isoproturon—active ingredient technical*. 1989 (unpublished report A 40025, submitted to WHO by Hoechst).
12. Mihailov G, Borisov I, Nikiforov I. [Clinico-experimental research on acute isoproturon poisoning in sheep.] *Veterinarno-medicinski nauki*, 1987, 24(2):30-35 (in Bulgarian).