Isoproturon 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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GENERAL DESCRIPTION

Identity

CAS no.: 34123-59-6
Molecular formula: C₁₂H₁₈N₂O
The IUPAC name for isoproturon is 3-(4-isopropylphenyl)-1,1-dimethylurea or 3-<em>p</em>-cumenyl-1,1-dimethylurea.

Physicochemical properties (1)

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical state</td>
<td>Colourless crystals</td>
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<tr>
<td>Melting point</td>
<td>155–156 °C</td>
</tr>
<tr>
<td>Vapour pressure</td>
<td>0.003 × 10⁻³ Pa at 20 °C</td>
</tr>
<tr>
<td>Water solubility</td>
<td>72 mg/litre at 20 °C</td>
</tr>
</tbody>
</table>

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'-diisopropylaizoxybenzene. 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 LD₅₀ varies considerably according to the vehicle used (11). Oral LD₅₀s 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 isoproturon 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 isoproturon 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**

Isoproturon 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 isoproturon 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**

Isoproturon 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 isoproturon 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, isoproturon 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 isoproturon 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 isoproturon and another group with NDEA only. In isoproturon-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**

Isoproturon 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