

Bentazone in Drinking-water

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 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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Prof. Y. Magara, Hokkaido University, Japan (*Analytical achievability*)
Mr P. Jackson, WRc-NSF, United Kingdom (*Treatment achievability*)

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:

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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

ADI	acceptable daily intake
CAS	Chemical Abstracts Service
DT ₅₀	degradation half-time
EPA	Environmental Protection Agency (USA)
FAO	Food and Agriculture Organization of the United Nations
IPCS	International Programme on Chemical Safety
IUPAC	International Union of Pure and Applied Chemistry
JMPR	Joint FAO/WHO Meeting on Pesticide Residues
KIWA	Netherlands Waterworks Testing and Research Institute
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.:	25057-89-0
Molecular formula:	C ₁₀ H ₁₂ N ₂ O ₃ S

The IUPAC name for bentazone is 3-isopropyl-(1H)-2,1,3-benzothiadiazin-4(3H)-one 2,2-dioxide. Technical bentazone is 92–96% pure. Its main impurities are *N*-isopropylsulfamoyl anthranilic acid (reactant; 2.4%), sodium chloride (raw material; 1.0%) and anthranilic acid (reactant; 0.6%). Some 50 other compounds have been found as impurities at very low concentrations (FAO/WHO, 1991).

1.2 Physicochemical properties

<i>Property</i>	<i>Value</i>
Melting point	137–139 °C
Density	1.5 g/cm ³ at 20 °C
Water solubility	500 mg/litre at 20 °C
Log octanol–water partition coefficient	Low
Vapour pressure	0.46 × 10 ⁻³ Pa at 20 °C

1.3 Major uses

Bentazone is a contact herbicide used in winter and spring cereals, maize, peas, rice and soy beans. It is absorbed by the leaves and has a short herbicidal effect (Worthing, 1991).

1.4 Environmental fate

The degradation rate of bentazone is significantly faster in the field than in laboratory studies. However, use of the estimated average field degradation half-time (DT₅₀) of 12 days in simple models rather than the laboratory DT₅₀ of 45 days, while reducing the observed potential leaching from “substantial” to “marginal,” still leaves cause for concern regarding leaching.

Under many field conditions, degradation of bentazone will be complete in the upper soil layers. This is particularly true for dry conditions and will still hold for conditions of non-extreme rainfall. However, compounds with this high water solubility and these low soil adsorption characteristics are liable to leach under conditions of extreme rainfall (such as storms shortly after application). Bentazone will be expected to pass both through the soil profile and via cracks to the underlying aquifer. Once outside the zone of biological action, there is no abiotic mechanism for its degradation. Some contamination of the groundwater would be expected to occur under these circumstances. This potential has been confirmed by some reports of bentazone in groundwater (IPCS, 1997).

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2. ANALYTICAL METHODS

Bentazone may be determined by extraction with dichloromethane followed by gas chromatography with electron capture detection. The detection limit in tap water and river water is about 0.05 µg/litre (FAO/WHO, 1991).

3. ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE

3.1 Air

Bentazone is unlikely to occur in air owing to its low vapour pressure.

3.2 Water

Bentazone can be detected in groundwaters in cultivated areas where it is used. Surface waters can be polluted by effluents from production plants, drainage waters and actual use in the water (rice fields). Concentrations range from <0.1 to 6 µg/litre in groundwater and from <0.1 to 2 µg/litre in surface water (KIWA, 1990).

3.3 Food

The low octanol–water partition coefficient of bentazone precludes its bioaccumulation in food. It may be present in crayfish farmed in rice fields where it is sprayed (US EPA, 1987).

4. KINETICS AND METABOLISM IN LABORATORY ANIMALS AND HUMANS¹

After oral administration to rats, [phenyl-U-¹⁴C]bentazone was extensively absorbed and rapidly excreted in the urine. In rats given a single dose, 83–94% appeared in the urine by 24 h and 90–97% by 120 h after dosing, with less than 0.7% in the residual carcass. Biliary excretion of the compound amounted to less than 2% of the dose. Bentazone undergoes very limited biotransformation in rats. Bentazone was the major compound identified in urine, representing 81–91% of the dose in males and 77–89% in females. 6-Hydroxybentazone was present in amounts up to 6.3% of the dose, and isomeric 8-hydroxybentazone was present in trace amounts (0–0.23% of the dose). There were no major differences among the groups. Glucuronide or sulfate conjugation was either negligible or non-existent; 6- and 8-hydroxybentazone are also metabolites of bentazone in plants.

¹ This section has been taken from FAO/WHO (1999).

5. EFFECTS ON EXPERIMENTAL ANIMALS AND IN VITRO TEST SYSTEMS²

Bentazone is more acutely toxic to rats than are its two hydroxylated metabolites when given by the oral route. The acute oral LD₅₀ of technical-grade bentazone was estimated to be 1800 mg/kg of body weight in males and 1500 mg/kg of body weight in females. The acute oral LD₅₀ value for 6- and 8-hydroxybentazone was 5000 mg/kg of body weight. WHO (1996) has classified bentazone as slightly hazardous.

The two studies described below indicate that 8-hydroxybentazone does not have the anticoagulant and diuretic effects of bentazone at the doses tested and has less systemic toxicity than the parent compound under the test conditions. No data were available on the short-term toxicity of 6-hydroxybentazone.

Rats received technical-grade bentazone in the diet at concentrations of 0, 400, 1200 or 3600 mg/kg for 13 weeks. The body weights of females were decreased and were statistically significantly different from those of controls at 3600 mg/kg from week 10 onward. Examination of haematological parameters indicated statistically significant increases in prothrombin time and partial thromboplastin time in males at 3600 mg/kg in comparison with controls. Bentazone had a diuretic effect in animals of both sexes, reaching statistical significance at 3600 mg/kg. The NOAEL for systemic toxicity was 1200 mg/kg (equal to 78 mg/kg of body weight per day) on the basis of statistically significant decreased body weights in females throughout the latter part of the treatment, increased prothrombin time and partial thromboplastin time in males, increased output of urine with decreased specific gravity in animals of both sexes, and some degree of kidney hypertrophy in both males and females at 3600 mg/kg, equal to 240 mg/kg of body weight per day.

Rats received 8-hydroxybentazone in the diet at concentrations of 0, 400, 1200 or 3600 mg/kg for 3 months. No compound-related effects were observed on body weights, clinical signs, food consumption, haematological, clinical chemical or urinary parameters, clotting time, organ weights or gross or histopathological appearance. The NOAEL was 3600 mg/kg (equal to 260 mg/kg of body weight per day), the highest dose tested.

The following two studies of developmental toxicity indicate that bentazone has effects at doses below a maternally toxic dose, whereas 8-hydroxybentazone had no developmental or maternal toxicity at any of the doses tested.

Pregnant rats received technical-grade bentazone by gavage at 0, 40, 100 or 250 mg/kg of body weight per day on days 6–15 of gestation. The NOAEL for maternal toxicity was 250 mg/kg of body weight per day, the highest dose tested. The NOAEL for developmental toxicity was 100 mg/kg of body weight per day on the basis of significantly decreased mean fetal weights and delays in tissue ossification, which reached statistical significance on a litter basis at the highest dose.

² This section has been taken from FAO/WHO (1999).

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No developmental toxicity was observed in pregnant rats that received 8-hydroxybentazone by gavage at 0, 40, 100 or 250 mg/kg of body weight per day on days 6–15 of gestation. The NOAEL for developmental toxicity was 250 mg/kg of body weight per day, the highest dose tested.

Bentazone, 6-hydroxybentazone and 8-hydroxybentazone did not induce reverse mutation in bacteria, and 8-hydroxybentazone did not induce gene mutation in mammalian cells or micronucleus formation in mice *in vivo*. The JMPR Meeting concluded that neither bentazone nor its metabolites are genotoxic.

6. CONCLUSIONS

8-Hydroxybentazone is less toxic than the parent compound. On the basis of the structural similarities between the 6- and 8-hydroxy isomers, the JMPR Meeting concluded that the 6-hydroxy isomer is also less toxic than the parent. Therefore, JMPR maintained the ADI of 0.1 mg/kg of body weight for bentazone established in 1991; this ADI was derived by applying a 100-fold safety factor to a NOAEL of 200 mg/kg (equal to 9 mg/kg of body weight per day in males and 11 mg/kg of body weight per day in females), based upon changes in urine volume and colour, partial thromboplastin time in males and clinical chemical parameters obtained in a 2-year toxicity/carcinogenicity study in rats (FAO/WHO, 1992). The ADI was supported by NOAELs in mice (100 mg/kg, equal to 12 mg/kg of body weight per day) and dogs (400 mg/kg, equivalent to 10 mg/kg of body weight per day). A 3-month study in dogs, even though it indicated a lower NOAEL, was not used, since the number of animals (three per sex per dose) was low.

Bentazone does not seem to accumulate in the environment, and exposure from food is unlikely to be high. A health-based value of 300 µg/litre can therefore be calculated on the basis of an ADI of 0.1 mg/kg of body weight established by JMPR and a 10% allocation of the ADI to drinking-water. However, because bentazone usually occurs at concentrations in drinking-water well below those at which toxic effects are observed, it is not considered necessary to derive a guideline value for bentazone in drinking-water.

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