

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

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

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

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

© World Health Organization 2008

All rights reserved. Publications of the World Health Organization can be obtained from WHO Press, World Health Organization, 20 Avenue Appia, 1211 Geneva 27, Switzerland (tel.: +41 22 791 3264; fax: +41 22 791 4857; e-mail: bookorders@who.int). Requests for permission to reproduce or translate WHO publications — whether for sale or for non-commercial distribution — should be addressed to WHO Press, at the above address (fax: +41 22 791 4806; e-mail: 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. Dotted lines on maps represent approximate border lines for which there may not yet be full agreement.

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.

All reasonable precautions have been taken by the World Health Organization to verify the information contained in this publication. However, the published material is being distributed without warranty of any kind, either expressed or implied. The responsibility for the interpretation and use of the material lies with the reader. In no event shall the World Health Organization be liable for damages arising from its use.

The named authors alone are responsible for the views expressed in this publication.

Printed by the WHO Document Production Services, Geneva, Switzerland

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.

Acknowledgements

The first draft of Diflubenzuron in Drinking-water: Use for Vector Control in Drinking-water Sources and Containers, Background document for development of WHO *Guidelines for Drinking-water Quality*, was prepared by Mr J.K. Fawell, United Kingdom, to whom special thanks are due.

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:

Dr J. Cotruvo, Joseph Cotruvo & Associates, USA (*Materials and chemicals*)
Mr J.K. Fawell, United Kingdom (*Naturally occurring and industrial contaminants*)
Ms M. Giddings, Health Canada (*Disinfectants and disinfection by-products*)
Mr P. Jackson, WRc-NSF, United Kingdom (*Chemicals – practical aspects*)
Professor Y. Magara, Hokkaido University, Japan (*Analytical achievability*)
Dr A.V. Festo Ngowi, Tropical Pesticides Research Institute, United Republic of Tanzania (*Pesticides*)
Dr E. Ohanian, Environmental Protection Agency, USA (*Disinfectants and disinfection by-products*)

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 |
| LD ₅₀ | median lethal dose |
| NOAEL | no-observed-adverse-effect level |
| WHO | World Health Organization |

Table of contents

| | |
|--|---|
| 1. GENERAL DESCRIPTION | 1 |
| 1.1 Identity | 1 |
| 1.2 Physicochemical properties | 1 |
| 1.3 Major uses and sources in drinking-water | 1 |
| 1.4 Environmental fate | 1 |
| 2. HUMAN EXPOSURE..... | 2 |
| 3. TOXICOLOGICAL SUMMARY | 2 |
| 4. PRACTICAL ASPECTS | 2 |
| 4.1 Analytical methods and analytical achievability | 2 |
| 4.2 Use for vector control in drinking-water sources | 3 |
| 5. CONCLUSIONS..... | 3 |
| 6. RECOMMENDATIONS..... | 4 |
| 7. REFERENCES | 4 |

This document is based on IPCS (1996), WHO/FAO (1996), and FAO/WHO (2002).

1. GENERAL DESCRIPTION

1.1 Identity

CAS No.: 35367-38-5
Molecular formula: $C_{14}H_9ClF_2N_2O_2$

The IUPAC name for diflubenzuron is 1-(4-chlorophenyl)-3-(2,6-difluorobenzoyl)-urea.

1.2 Physicochemical properties

| <i>Property</i> | <i>Value</i> |
|---|---|
| Melting point | 230–232 °C |
| Density | 1.56 |
| Water solubility (20 °C) | 0.2 mg/l |
| Log octanol–water partition coefficient (log K_{ow}) | 3.89 |
| Vapour pressure | 0.000 12 mPa; virtually non-volatile from water |

1.3 Major uses and sources in drinking-water

Diflubenzuron is a halogenated benzoylphenyl urea, an effective stomach and contact insecticide that acts by inhibiting chitin synthesis and so interfering with the formation of the cuticle. It is used in public health applications against mosquito and noxious fly larvae. WHO has assessed diflubenzuron as a mosquito larvicide suitable for application to containers of non-potable water (WHO, 2006a) and is considering it for use as a mosquito larvicide for drinking-water in containers, particularly to control dengue fever. The recommended dosage of diflubenzuron in potable water in containers should not exceed 0.25 mg/l (WHO Pesticides Evaluation Scheme, personal communication, 2006). Specific formulations for control of vectors are specified by WHO (WHO, 2006b).

1.4 Environmental fate

Diflubenzuron is a direct-acting insecticide normally applied directly to plants or water. It is rapidly adsorbed to soil and particles and is immobile in soil. It will also rapidly adsorb to sediments and the sides of vessels and pipes, but it may also partition into the surface film because of its low water solubility and high K_{ow} . In soils, over 90% is degraded by hydrolysis to 2,6-difluorobenzoic acid and 4-chlorophenylurea. In neutral and alkaline waters, diflubenzuron is rapidly hydrolysed. The parent compound and 4-chlorophenylurea may persist on sediment for more than 30 days (IPCS, 1996). Diflubenzuron is fairly unstable in water, with a half-life of approximately 0.5 day for solutions exposed to natural sunlight in the laboratory (Anton et al., 1993).

2. HUMAN EXPOSURE

It is reported that exposure of the public through either food or drinking-water is negligible (IPCS, 1996). However, there is a potential for direct exposure through drinking-water when diflubenzuron is directly applied to drinking-water storage containers.

3. TOXICOLOGICAL SUMMARY

Diflubenzuron is rapidly absorbed to a moderate extent (approximately 30%) from the gastrointestinal tract. Absorbed diflubenzuron is extensively metabolized, and >90% of the metabolites are excreted within 48 h, mostly in the urine, although some biliary excretion and enterohepatic circulation also occur.

Diflubenzuron is considered to be of very low acute toxicity, with oral LD₅₀s in mice and rats of >4500 mg/kg of body weight. The primary target for toxicity is the erythrocytes, although the mechanism of haematotoxicity is uncertain. High doses (10 000 mg/kg of body weight, 25% formulation) caused a small but significant increase in methaemoglobinaemia in mice and rats. The NOAELs for methaemoglobin and sulfhaemoglobin formation in mice, rats and dogs were 1.2, 2.0 and 2.0 mg/kg of body weight per day, respectively, after long-term exposure. Haematotoxicity showed both dose- and time-related trends, with the dose resulting in the detection of methaemoglobin decreasing with increasing duration of exposure. The NOAEL for pathological findings was the same as that for methaemoglobin formation in rats and dogs, but somewhat higher in mice. There were changes in liver spleen and bone marrow associated with haematotoxicity.

Diflubenzuron has been adequately tested for both genotoxicity and carcinogenicity, and there was no evidence that it is either genotoxic or carcinogenic.

Diflubenzuron was not fetotoxic or teratogenic and did not show significant signs of reproductive toxicity. There was evidence that young animals were not significantly more sensitive than adults to the effects of diflubenzuron.

In 2001, JMPR reconfirmed the previously established ADI of 0–0.02 mg/kg of body weight, based on the NOAEL for haematological effects of 2.0 mg/kg of body weight per day in the 2-year studies in rats and the 52-week study in dogs. However, the Committee also considered that an acute reference dose for diflubenzuron was unnecessary (FAO/WHO, 2002).

4. PRACTICAL ASPECTS

4.1 Analytical methods and analytical achievability

The concentration of diflubenzuron may be determined by high-performance liquid chromatography with ultraviolet detector (detection limit 0.05 mg/l) (Miliadis et al., 1999) or with fluorescence detector after on-line post-elution photoirradiation (detection limit 0.05 mg/l) (Martinez-Galera et al., 2001). The concentration of diflubenzuron may also be determined by gas chromatography with electron capture detection (detection limit 0.05 mg/l) (Mensah et al., 1997). It may also be determined

by liquid chromatography using negative-ion, selected-ion monitoring atmospheric pressure chemical ionization–mass spectrometry (detection limit 0.025 mg/l) (Barnes et al., 1995), using electrospray mass spectrometry (detection limit 0.002 µg/l), or using thermospray mass spectrometry (detection limit 0.002 µg/l) (Molina et al., 1995).

4.2 Use for vector control in drinking-water sources

Diflubenzuron is being considered for use as a larvicide for control of disease-carrying mosquitoes that breed in drinking-water containers. The maximum dose recommended by the WHO Pesticides Evaluation Scheme for this purpose is 0.25 mg/l. Users should carefully follow the recommendations for use.

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 diflubenzuron used as a vector control agent in drinking-water. The ADI determined by JMPR in 2001 was 0.02 mg/kg of body weight (FAO/WHO, 2002). Young animals do not appear to be significantly more sensitive than adults. Where diflubenzuron is used for vector control in potable water, this will involve considerably less than lifetime exposure. The maximum dosage in drinking-water of 0.25 mg/l would be equivalent to approximately 40% 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 0.25 mg, compared with an exposure of 0.2 mg at the ADI. For a 5-kg bottle-fed infant drinking 0.75 litre per day, the exposure would be 0.19 mg, compared with an exposure of 0.1 mg at the ADI. Exposure from food is considered to be negligible. However, the low solubility and the high log K_{ow} of diflubenzuron 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 much 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. Consideration should be given to using alternative sources of water for bottle-fed infants for a period after an application of diflubenzuron, where this is practical. 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.

7. REFERENCES

Anton FA et al. (1993) Degradational behavior of the pesticides glyphosate and diflubenzuron in water. *Bulletin of Environmental Contamination and Toxicology*, 51(6):881–888.

Barnes KA et al. (1995) Determination of the pesticide diflubenzuron in mushrooms by high-performance liquid chromatography–atmospheric pressure chemical ionization mass spectrometry. *Journal of Chromatography A*, 712:85–93.

FAO/WHO (2002) Diflubenzuron. In: *Pesticide residues in food — 2001 evaluations. Part II — Toxicological*. Geneva, World Health Organization, Joint FAO/WHO Meeting on Pesticide Residues (WHO/PCS/02.1; <http://www.inchem.org/documents/jmpr/jmpmono/2001pr04.htm>).

IPCS (1996) *Diflubenzuron*. Geneva, World Health Organization, International Programme on Chemical Safety (Environmental Health Criteria 184; <http://www.inchem.org/documents/ehc/ehc/ehc184.htm>).

Martinez-Galera M et al. (2001) Determination of benzoylureas in tomato by high-performance liquid chromatography using continuous on-line post-elution photoirradiation with fluorescence detection. *Journal of Chromatography A*, 918:79–85.

Mensah JK et al. (1997) Determination of diflubenzuron in apples by gas chromatography. *Journal of Chromatography A*, 765:85–90.

Miliadis GE, Tsiropoulos NG, Aplada-Sarlis PG (1999) High-performance liquid chromatographic determination of benzoylurea insecticides residues in grapes and wine using liquid and solid-phase extraction. *Journal of Chromatography A*, 835:113–120.

Molina C, Durand G, Barcelo D (1995) Trace determination of herbicides in estuarine water by liquid chromatography–high-flow pneumatically assisted electrospray mass spectrometry. *Journal of Chromatography A*, 712:113–122.

WHO (2006a) *Pesticides and their application for the control of vectors and pests of public health importance*, 6th ed. Geneva, World Health Organization, Department of Control of Neglected Tropical Diseases, Pesticides Evaluation Scheme (WHO/CDS/NTD/WHOPES/GCDPP/2006.1; http://whqlibdoc.who.int/hq/2006/WHO_CDS_NTD_WHOPES_GCDPP_2006.1_eng.pdf).

WHO (2006b) *Diflubenzuron: 1-(4-chlorophenyl)-3-(2,6-difluorobenzoyl)urea*. Geneva, World Health Organization (WHO Specifications and Evaluations for Public Health Pesticides; http://www.who.int/whopes/quality/diflubenzuron_eval_march_2006.pdf).

WHO/FAO (1996) *Diflubenzuron*. Geneva, World Health Organization; and Rome, Food and Agriculture Organization of the United Nations (WHO/FAO Datasheets on Pesticides No. 77; WHO/PCS/DS/96.77; http://www.inchem.org/documents/pds/pds/pest77_e.htm).