Carbofuran 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.
Acknowledgements

The first draft of Carbofuran in Drinking-water, Background document for development of WHO Guidelines for Drinking-water Quality, was prepared by Dr P. Toft, Canada, to whom special thanks are due.

The work of the following working group coordinators was crucial in the development of this document and others in the third edition:

- Mr J.K. Fawell, United Kingdom (Organic and inorganic constituents)
- Dr E. Ohanian, Environmental Protection Agency, USA (Disinfectants and disinfection by-products)
- Ms M. Giddings, Health Canada (Disinfectants and disinfection by-products)
- Dr P. Toft, Canada (Pesticides)
- 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:

- Dr J. Bartram, Coordinator, Water Sanitation and Health Programme, WHO Headquarters, and formerly WHO European Centre for Environmental Health
- Mr P. Callan, Water Sanitation and Health Programme, WHO Headquarters
- Mr H. Hashizume, Water Sanitation and Health Programme, WHO Headquarters

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
EPA Environmental Protection Agency (USA)
FAO Food and Agriculture Organization of the United Nations
IUPAC International Union of Pure and Applied Chemistry
JMPR Joint FAO/WHO Meeting on Pesticide Residues
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.: 1563-66-2

Molecular formula: \( \text{C}_{12}\text{H}_{15}\text{NO}_{3} \)

The IUPAC name for carbofuran is 2,3-dihydro-2,2-dimethylbenzofuran-7-yl methylcarbamate.

1.2 Physicochemical properties

Carbofuran is a white crystalline solid. It is stable under neutral or acidic conditions but unstable in alkaline media (FAO/WHO, 1985; Health and Welfare Canada, 1991).

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vapour pressure</td>
<td>2.7 mPa at 33 °C</td>
</tr>
<tr>
<td>Melting point</td>
<td>150 °C</td>
</tr>
<tr>
<td>Log octanol–water partition coefficient</td>
<td>1.6–2.3</td>
</tr>
<tr>
<td>Water solubility</td>
<td>350 mg/litre at 25 °C</td>
</tr>
<tr>
<td>Specific gravity</td>
<td>1.18 g/cm(^3)</td>
</tr>
</tbody>
</table>

1.3 Major uses

Carbofuran is used worldwide for many crops. It is a broad-spectrum carbamate insecticide, acaricide and nematicide. The technical product contains a minimum of 95% carbofuran (FAO/WHO, 1977).

1.4 Environmental fate

Carbofuran is rapidly taken up by plants through the roots from soil and water and is translocated mainly into the leaves. The main metabolite in plants has been identified as 3-hydroxycarbofuran.

Carbofuran is degraded in soil by hydrolysis, microbial action and, to a lesser extent, photodecomposition. Its persistence is dependent upon pH, soil type, temperature, moisture content and the microbial population. Degradation products in soil include carbofuran phenol, 3-hydroxycarbofuran and 3-ketocarbofuran; field studies have indicated a half-life of 26–110 days in soil. Carbofuran may leach significantly, although leaching may not occur in highly organic soils.

Carbofuran is degraded in water by hydrolysis, microbial decomposition and photolysis. Hydrolysis half-lives in water at 25 °C of 690, 8.2 and 1.0 weeks have been reported at pH levels of 6.0, 7.0 and 8.0, respectively (Health and Welfare Canada, 1991).
2. ANALYTICAL METHODS

The concentration of carbofuran in water may be determined by separation by high-performance liquid chromatography, hydrolysis with sodium hydroxide, extraction of the resulting methylamine with o-phthalaldehyde and fluorescence detection of the derivative (detection limit 0.9 µg/litre). The concentration of carbofuran may also be quantified by acidification of the sample, extraction with dichloromethane and separation by gas chromatography with a nitrogen–phosphorus detector (detection limit 0.1 µg/litre) (Health and Welfare Canada, 1991).

3. ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE

3.1 Air

In a study designed to evaluate human exposure to carbofuran following aerial applications, it was estimated that maximum inhaled doses were in the range 0.7–2.0 mg/day (Draper et al., 1981).

3.2 Water

Carbofuran was detected only once (at 3.0 µg/litre) in 678 samples from surveys of Canadian municipal and private water supplies conducted from 1971 to 1986 (Health and Welfare Canada, 1991).

A maximum carbofuran concentration of 1 µg/litre was found in streams in the USA (Kimbrough & Litke, 1996). Levels found in groundwater in the USA ranged from 1 to 30 µg/litre (Cohen et al., 1984; Holden, 1986).

3.3 Food

Carbofuran does not bioaccumulate in food. Residues in treated crops are generally very low or not detectable (FAO/WHO, 1980; US EPA, 1987).

3.4 Estimated total exposure and relative contribution of drinking-water

Based upon the physical and chemical properties of carbofuran and the few data on occurrence, drinking-water from both groundwater and surface water sources has the potential of being the major route of exposure (US EPA, 1987).

4. KINETICS AND METABOLISM IN LABORATORY ANIMALS AND HUMANS

Carbofuran is rapidly absorbed, metabolized and eliminated, mainly in the urine, after oral administration to mice, rats, hens and goats. After oral administration of [14C]phenyl carbofuran to rats, 92% of the radiolabel was eliminated in the urine and

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1 This section has been summarized from FAO/WHO (1997).
CARBOFURAN IN DRINKING-WATER

3% in faeces. Most of the radiolabel was eliminated within 24 h after treatment. With a \[^{14}\text{C}\]carbonyl-labelled compound, 45% was eliminated as \(^{14}\text{CO}_2\). The metabolic pathway consists of hydroxylation, oxidation, hydrolysis and conjugation.

5. EFFECTS ON EXPERIMENTAL ANIMALS AND IN VITRO TEST SYSTEMS

5.1 Acute exposure

Carbofuran is highly toxic after acute oral administration. The oral LD\(_{50}\) values in cats, rabbits, guinea-pigs, rats, mice and dogs ranged from 3 to 19 mg/kg of body weight. Toxic signs observed were typical for cholinesterase inhibition; salivation, cramps, trembling and sedation were observed within minutes after administration and lasted for up to 3 days. WHO (2001) has classified carbofuran as “highly hazardous.”

5.2 Short-term exposure

In a 13-week study, carbofuran (purity 99.6%) was fed to groups of beagle dogs (four per sex per group) at dietary concentrations of 0, 10, 70 or 250 mg/kg of feed (equal to 0, 0.43, 3.1 and 10.6 mg/kg of body weight per day); the highest dose was reduced from 500 mg/kg of feed because of marked toxicity. Hyperaemia, increased salivation and inhibition of erythrocyte acetylcholinesterase activity were observed at the lowest dose. A NOAEL was not identified in this study.

In a subsequent 4-week study, groups of male beagle dogs (four per group) were fed carbofuran (purity 99.6%) at 0 or 5 mg/kg of feed (equal to 0 and 0.22 mg/kg of body weight per day). Clinical signs, mortality, body weight, food consumption and cholinesterase activity in plasma and erythrocytes were unaffected by treatment. The NOAEL in this study was 0.22 mg/kg of body weight per day, the only dose tested.

In a 1-year study, groups of beagle dogs (six per sex per group) were fed carbofuran (96.1% purity) at dietary concentrations of 0, 10, 20 or 500 mg/kg of feed (equal to 0, 0.3, 0.6 and 13 mg/kg of body weight per day). Plasma cholinesterase inhibition was observed in most males at 10 and 20 mg/kg of feed and markedly (77%) in all animals at 500 mg/kg of feed. Erythrocyte and brain acetylcholinesterase were not inhibited at 10 or 20 mg/kg of feed. Histopathological testicular changes were observed at 500 mg/kg of feed and in a single male at 20 mg/kg of feed. The plasma cholinesterase inhibition was considered non-significant, and attention was focused on the testicular changes. The NOAEL in this study was 10 mg/kg of feed, equal to 0.3 mg/kg of body weight per day.

The overall NOAEL in these short-term studies in dogs was 5 mg/kg of feed, equal to 0.22 mg/kg of body weight per day.

\(^2\) This section has been summarized from FAO/WHO (1997).
5.3 Long-term exposure

In a 2-year study, Charles River mice (100 per sex per group) were fed dietary carbofuran (purity 95.6%) concentrations of 0, 20, 125 or 500 mg/kg of feed (equal to 0, 2.8, 18 and 70 mg/kg of body weight per day). Mice receiving the highest dose showed a decrease in body weight gain. Cholinesterase activities were not measured in erythrocytes or plasma. At the two highest doses, a statistically significant depression of brain acetylcholinesterase activity was observed. The NOAEL was 20 mg/kg of feed, equal to 2.8 mg/kg of body weight per day.

Carbofuran (purity 95.6%) was fed to groups of Charles River rats (90 per sex per group) at concentrations of 0, 10, 20 or 100 mg/kg of feed for 2 years. Body weight gain and plasma, erythrocyte and brain acetylcholinesterase activities were reduced at 100 mg/kg of feed. The NOAEL was 20 mg/kg of feed, equivalent to 1 mg/kg of body weight per day.

5.4 Reproductive and developmental toxicity

In a three-generation reproductive toxicity study, Charles River rats were fed carbofuran (purity 95.6%) at concentrations of 0, 20 or 100 mg/kg of feed (equal to 0, 1.2 and 6 mg/kg of body weight per day for males and 0, 1.9 and 9.7 mg/kg of body weight per day for females). The NOAEL was 20 mg/kg of feed, equal to 1.2 mg/kg of body weight per day, on the basis of reductions in body weight gain in the parental generation and reductions in the growth and survival of pup generations at 100 mg/kg of feed.

In an early study of developmental toxicity, Charles River rats (24 per group) were given carbofuran (purity 95.6%) by gavage at doses of 0, 0.1, 0.3 or 1 mg/kg of body weight per day on days 6–15 of gestation. Dose-dependent, transient clinical signs (chewing motions) were observed at all dose levels for a short period after treatment. Overt signs of toxicity in animals at 0.3 mg/kg of body weight per day included rough coats and lethargy. At the highest dose, lacrimation, increased salivation, trembling and convulsions were also seen. A NOAEL was not identified in this study.

In a later study, carbofuran (purity 95.6%) was given orally by gavage to groups of Charles River rats (25 per group) at doses of 0, 0.25, 0.5 or 1.2 mg/kg of body weight per day from day 6 to day 15 of gestation. The NOAEL for maternal and fetal toxicity was 1.2 mg/kg of body weight per day, the highest dose tested.

In a further study of teratogenicity, groups of Charles River rats (40 females per group) were fed carbofuran (purity 95.6%) at dietary concentrations of 0, 20, 60 or 160 mg/kg of feed (equal to 0, 1.5, 4.4 and 11 mg/kg of body weight per day) on days 6–19 of gestation. The NOAEL for pup toxicity was 60 mg/kg of feed (equal to 4.4 mg/kg of body weight per day), based on reduced pup weight at 160 mg/kg of feed. The NOAEL for maternal toxicity was 20 mg/kg of feed (equal to 1.5 mg/kg of body weight per day), based on reduced body weight gain at the two highest doses. None of these studies showed teratogenic potential.
In an early teratogenicity study, New Zealand white rabbits (17 animals per group) were given carbofuran (purity 95.6%) by gavage at doses of 0, 0.2, 0.6 or 2 mg/kg of body weight per day on gestation days 6–18. Maternal toxicity was observed at 2 mg/kg of body weight per day and included trembling, salivation, sneezing, chewing motions and reduced food and water consumption. The NOAEL in this study was 0.6 mg/kg of body weight per day.

In a subsequent study, New Zealand white rabbits (20 animals per group) were given carbofuran (purity 95.6%) by gavage at doses of 0, 0.12, 0.5 or 2 mg/kg of body weight per day on days 6–18 of gestation. The NOAEL in this study was 0.5 mg/kg of body weight per day, on the basis of slightly reduced body weight gain in dams and a slightly increased incidence of skeletal variations in pups at 2 mg/kg of body weight per day. These studies provided no evidence of teratogenicity.

5.5 Neurotoxicity studies

In a 90-day study in Sprague-Dawley rats (10 per sex per group) at dietary carbofuran (purity 98.6%) concentrations of 0, 50, 500 or 1000 mg/kg of feed (equal to 0, 2.4, 27.3 and 55.3 mg/kg of body weight per day in males and 0, 3.1, 35.3 and 64.4 mg/kg of body weight per day in females), systemic toxicity (reduction in body weight gain) was observed at all doses. Clinical signs of neurotoxicity were observed at 500 and 1000 mg/kg of feed. No histopathological lesions were found in the nervous system. The NOAEL for neurotoxicity was thus 50 mg/kg of feed, equal to 2.4 mg/kg of body weight per day. There was no NOAEL for systemic toxicity.

In a study of developmental neurotoxicity, carbofuran (purity 98.1%) was administered in the diet of female Sprague-Dawley rats (24 per group) at concentrations of 0, 20, 75 or 300 mg/kg of feed (equal to 0, 1.7, 5 and 11 mg/kg of body weight per day) on gestation day 6 through lactation day 10. Reductions in the body weight gain of dams and pups and in pup survival and some evidence of delayed pup development were found at 75 and 300 mg/kg of feed. The NOAEL was 20 mg/kg of feed, equal to 1.7 mg/kg of body weight per day.

5.6 Mutagenicity and related end-points

Carbofuran has been tested for genotoxicity in a wide range of tests in vivo and in vitro. JMPR concluded that it was not genotoxic.

5.7 Carcinogenicity

No evidence of tumorigenicity was found in the 2-year dietary studies on mice and rats described above.
6. EFFECTS ON HUMANS

Carbofuran poisoning was reported in three female farm workers who were not wearing any protective clothing and were throwing carbofuran granules in a coffee plantation in Jamaica. Signs of poisoning included vomiting, lassitude, nausea and hypersalivation. Cholinesterase activity was not determined in these patients.

7. GUIDELINE VALUE

In the 1996 JMPR re-evaluation, an ADI of 0.002 mg/kg of body weight was determined based on a NOAEL of 0.22 mg/kg of body weight per day in a short-term (4-week) study of acute (reversible) effects in the dog, the most sensitive species, using an uncertainty factor of 100. This 4-week study was conducted as an adjunct to a 13-week study in which inhibition of erythrocyte acetylcholinesterase activity was observed at the lowest dose. Use of a 4-week study was considered appropriate because the NOAEL is based on a reversible acute effect. This NOAEL will also be protective for chronic effects (FAO/WHO, 1997).

On the basis of the JMPR ADI (2.2 µg/kg of body weight, if not rounded) and assuming a 60-kg body weight, drinking-water consumption of 2 litres/day and an allocation of 10% of the ADI to drinking-water, a guideline value of 7 µg/litre (rounded figure) can be calculated for carbofuran.

8. REFERENCES


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This section has been summarized from FAO/WHO (1997).


