Dichlorobenzenes 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.
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

<table>
<thead>
<tr>
<th>Compound</th>
<th>CAS no.</th>
<th>Molecular formula</th>
</tr>
</thead>
<tbody>
<tr>
<td>1,2-Dichlorobenzene (1,2-DCB)</td>
<td>95-50-1</td>
<td>C₆H₄Cl₂</td>
</tr>
<tr>
<td>1,3-Dichlorobenzene (1,3-DCB)</td>
<td>541-73-1</td>
<td>C₆H₄Cl₂</td>
</tr>
<tr>
<td>1,4-Dichlorobenzene (1,4-DCB)</td>
<td>106-46-7</td>
<td>C₆H₄Cl₂</td>
</tr>
</tbody>
</table>

Physicochemical properties (1–3) [Conversion factor in air: 1 ppm = 6.01 mg/m³]

<table>
<thead>
<tr>
<th>Property</th>
<th>1,2-DCB</th>
<th>1,3-DCB</th>
<th>1,4-DCB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melting point (°C)</td>
<td>-17.0</td>
<td>-24.7</td>
<td>53.1</td>
</tr>
<tr>
<td>Boiling point (°C)</td>
<td>180.5</td>
<td>173.0</td>
<td>174.0</td>
</tr>
<tr>
<td>Water solubility at 25 °C (mg/litre)</td>
<td>91</td>
<td>123</td>
<td>31</td>
</tr>
<tr>
<td>Vapour pressure at 25 °C (kPa)</td>
<td>0.2</td>
<td>0.31</td>
<td>0.226</td>
</tr>
<tr>
<td>Density at 20 °C (g/cm³)</td>
<td>1.305</td>
<td>1.288</td>
<td>1.247</td>
</tr>
<tr>
<td>Log octanol–water partition coefficient</td>
<td>3.38</td>
<td>3.48</td>
<td>3.38</td>
</tr>
</tbody>
</table>

Organoleptic properties

The organoleptic thresholds for all three isomers are low. Odour thresholds of 2–10, 20, and 0.3–30 µg/litre have been reported for 1,2-DCB, 1,3-DCB, and 1,4-DCB, respectively (4,5). Taste thresholds of 1 and 6 µg/litre have been reported for 1,2-DCB and 1,4-DCB, respectively (4,6).

Major uses

The DCBs are widely used in industry and in domestic products such as odour-masking agents, dyestuffs, and pesticides. 1,2-DCB and 1,4-DCB are the most widely used (7).

Environmental fate

The DCBs are expected to be adsorbed moderately to tightly onto soils of high organic content and are not expected to leach appreciably into groundwater. In soils, they are biodegraded slowly under aerobic conditions; volatilization may be important in surface soils. In water, the major DCB-removal processes are likely to be adsorption onto sediments and bioaccumulation in aquatic organisms. Evaporation from surface water may also be important, but not aquatic hydrolysis, oxidation, or direct photolysis. DCBs may biodegrade in aerobic water after microbial adaptation. However, they are not expected to biodegrade under the anaerobic conditions that may exist in lake sediments or various groundwaters (2).

ANALYTICAL METHODS

A standard method for chlorobenzenes involves extraction with hexane followed by capillary-column gas–liquid chromatography with electron-capture detection (detection limit in tapwater and river water approximately 0.01 µg/litre) (8).
ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE

Air

The DCBs have been detected in the atmosphere at extremely low levels. In the USA, mean 1,2-DCB concentrations of 1.2, 0.3 and 0.01 µg/m³ have been measured in industrial, urban, and rural locations, respectively; the overall mean concentration was 0.54 µg/m³. Similarly, mean 1,3-DCB concentrations of 0.9, 0.5 and 0.04 µg/m³ have been reported for the same three locations, respectively; the overall mean concentration was 0.57 µg/m³. Mean 1,2-DCB and 1,4-DCB concentrations of 0.06–0.18 µg/m³ and 0.24–0.42 µg/m³ were detected in the ambient air of three New Jersey (USA) cities in 1981 (2).

Water

DCBs have been detected in wastewater, raw water, surface water, and drinking-water (2). Although all have been detected in drinking-water, 1,4-DCB is generally present in the greatest concentration. DCBs have been found in potable water sources before treatment at levels as high as 10 µg/litre and in drinking-water at 0.01–3 µg/litre (7). In a survey of the water supplies of three Canadian cities, total mean DCB concentrations ranged from 1.0 to 13 ng/litre, most of which was 1,4-DCB (9). In a study in the USA on the contamination of 685 groundwaters, 1,2-DCB, 1,3-DCB, and 1,4-DCB were detected in 20, 19, and 19 samples at maximum concentrations of 6800, 236, and 996 µg/litre, respectively (2).

Food

DCBs tend to accumulate in biological materials rich in lipids, such as fatty tissue and milk. Mean levels of 1,2-DCB, 1,3-DCB, and 1,4-DCB of 2.6, 0.14, and 5.5 µg/kg, respectively, have been measured in milk (2,10). Fish have also been shown to be a major source of DCBs; mean levels were 1, 0.3–3, and 1–4 µg/kg for 1,2-DCB, 1,3-DCB, and 1,4-DCB, respectively (2).

Estimated total exposure and relative contribution of drinking-water

General population exposure may occur through the inhalation of contaminated air, especially in areas where DCBs are manufactured, and from the ingestion of contaminated drinking-water and food, particularly contaminated fish.

KINETICS AND METABOLISM IN LABORATORY ANIMALS AND HUMANS

DCBs are almost completely absorbed from the gastrointestinal tract. Once absorbed, they are rapidly distributed, primarily to fat or adipose tissue because of their lipophilicity and to kidney, liver, and lungs. They are metabolized mainly by oxidation in the liver to the respective dichlorophenols and their glucuronide and sulfate conjugates, although other minor metabolites have been detected. The metabolites are excreted mainly via the kidneys, and excretion is relatively slow. In rats, almost 100% of an oral dose of 1,4-DCB was excreted within 5 days, mostly in the urine (7).

EFFECTS ON LABORATORY ANIMALS AND IN VITRO TEST SYSTEMS

Acute exposure

The DCBs are of low acute oral toxicity in experimental animals. Oral LD₅₀/₈ in rodents range from 500 to 3863 mg/kg of body weight. The major target organs are the liver and kidneys (7).
Short-term exposure

F344/N rats and B6C3F1 mice were given 1,2-DCB in corn oil at 0, 30, 60, 125, 250, or 500 mg/kg of body weight per day by gavage 5 days per week for 13 weeks. Decreased survival in male and female mice and female rats was seen at the highest dose level. Liver necrosis, hepatocellular degeneration, and depletion of lymphocytes were seen in the thymus and spleen of both sexes of rats and mice. At 250 mg/kg of body weight, necrosis of individual hepatocytes was observed in both sexes of rats and in male mice. Minimal hepatocellular necrosis was observed in a few rats at 125 mg/kg of body weight, but no hepatic alterations were observed in mice at this dose. A NOAEL of 125 mg/kg of body weight per day was identified (7).

Long-term exposure

In a 2-year gavage study, B6C3F1 female and male mice were given 0, 60, or 120 mg of 1,2-DCB per kg of body weight per day by gavage in corn oil, 5 days per week. The only evidence of toxicity was a dose-related trend towards tubular regeneration of the kidney in male mice, the incidence of which increased at the highest dose level. Otherwise, there was no evidence of non-neoplastic toxicity. NOAELs of 60 and 120 mg/kg of body weight were identified for male and female mice, respectively (7).

1,4-DCB was administered by gavage for 2 years, 5 days per week, to male and female Fischer 344 rats at dose levels of 0, 150, or 300, and 0, 300, or 600 mg/kg of body weight in corn oil. In males, reduced survival and body weight gain were observed at 300 mg/kg of body weight. Increased severity of nephropathy and hyperplasia of the parathyroid were observed at 150 mg/kg of body weight in males. In females, there was a dose-related increase in nephropathy at or above 300 mg/kg of body weight. LOAELs of 150 and 300 mg/kg of body weight per day were identified for male and female rats, respectively (7).

Reproductive toxicity, embryotoxicity, and teratogenicity

All three isomers were reported to be non-teratogenic when Sprague-Dawley rats were given oral doses of 50, 100, or 200 mg/kg of body weight per day on days 6–15 of gestation (11). In another study, CD rats were given 1,4-DCB by gavage at doses of 0, 250, 500, 750, or 1000 mg/kg of body weight per day on days 6–15 of gestation. Reduction of fetal weight was seen at the highest dose, and an increase in skeletal variations was observed at or above 750 mg/kg of body weight per day. A dose-related increase in extra ribs was observed at doses at or above 500 mg/kg of body weight per day. A LOAEL and a NOAEL of 500 and 250 mg/kg of body weight per day were identified, respectively (7).

Mutagenicity and related end-points

All three isomers were non-mutagenic in Salmonella typhimurium strains TA98, TA100, TA1535, or TA1537, both in the presence and in the absence of metabolic activation. A number of other in vitro tests, such as those for the induction of chromosomal aberrations in Chinese hamster ovary cells, forward mutations in mouse lymphoma cells, and unscheduled DNA synthesis in human lymphocytes, have also given negative results for 1,4-DCB. In all but one study, 1,4-DCB has not produced chromosome damage in bone marrow of mice when administered in vivo. Negative results have also been obtained for this isomer in an assay of DNA damage in liver of mice following oral exposure. Low-level covalent binding of 1,4-DCB to the liver, kidneys, and lungs of mice has been reported (7).
Carcinogenicity

In the 2-year gavage study in which B6C3F₁ female and male mice were given 0, 60, or 120 mg of 1,2-DCB per kg of body weight in corn oil, 5 days per week, there was a dose-related trend in the incidence of malignant histiocytic lymphomas in both sexes; however, the authors concluded that there was no evidence for the carcinogenicity of 1,2-DCB in this study (7).

In the study in which 1,4-DCB was administered by gavage for 2 years, 5 days per week, to male and female Fischer 344 rats at dose levels of 0, 150, or 300, and 0, 300, or 600 mg/kg of body weight in corn oil, respectively, a dose-related increase in the incidence of tubular-cell adenocarcinomas of the kidney was observed in males only. A marginal increase in the incidence of mononuclear cell leukaemia was also noted in males when compared with the controls. It was concluded that the induction of kidney tumours in male rats was a species- and sex-specific response, probably a result of hyaline droplet formation. In the same study, 1,4-DCB increased the incidences of hepatocellular adenomas and carcinomas in mice dosed at 600 but not at 300 mg/kg of body weight (7).

EFFECTS ON HUMANS

Data on the health effects of exposure to DCBs are restricted to case reports of accidental exposure to or misuse of DCB products. Reported acute effects following short-term exposure (all of which are reversible) include acute haemolytic anaemia, respiratory irritation, glomerulonephritis, and allergic response of the skin. Prolonged exposure to 1,4-DCB has caused granulomatosis, anaemia, disturbances of the reticuloendothelial system, central nervous system effects, and liver damage. In workers exposed to 1,4-DCB, probably in combination with other chemicals, there have been case reports of haematological disorders, including anaemia, splenomegaly, and gastrointestinal and central nervous system effects. Two cases of acute myeloblastic anaemia were reported in females exposed mainly to 1,2-DCB over 1 year (7).

GUIDELINE VALUES

1,2-Dichlorobenzene

IARC has placed 1,2-DCB in Group 3 (12). This isomer is of low acute toxicity by the oral route of exposure. Oral exposure to high doses affects mainly the liver and kidneys. The balance of evidence suggests that 1,2-DCB is not genotoxic, and there is no evidence for its carcinogenicity in rodents. Using the NOAEL of 60 mg/kg of body weight per day for tubular degeneration of the kidney, identified in a 2-year mouse gavage study with administration 5 days per week (7), and applying an uncertainty factor of 100 (for inter- and intraspecies variation), a TDI of 429 µg/kg of body weight can be calculated. An allocation of 10% of the TDI to drinking-water gives a guideline value of 1000 µg/litre (rounded figure). This value far exceeds the lowest reported taste threshold in water of 1 µg/litre.

1,3-Dichlorobenzene

There are insufficient toxicological data on this compound to permit a guideline value to be proposed, but it should be noted that it is rarely found in drinking-water.

1,4-Dichlorobenzene

1,4-DCB is of low acute toxicity, but there is evidence that it increases the incidence of renal tumours in rats and hepatocellular adenomas and carcinomas in mice after long-term exposure. IARC has placed it in Group 2B (12).
1,4-DCB is not considered to be genotoxic, and the relevance for humans of the tumours observed in animals is doubtful. It is therefore valid to calculate a guideline value using the TDI approach. A TDI of 107 µg/kg of body weight has been calculated by applying an uncertainty factor of 1000 (100 for inter- and intraspecies variation and 10 for the use of a LOAEL instead of a NOAEL and because the toxic end-point is carcinogenicity) to a LOAEL of 150 mg/kg of body weight per day for kidney effects observed in a 2-year rat gavage study (administration 5 days per week) (7). A guideline value of 300 µg/litre (rounded figure) is proposed, based on an allocation of 10% of the TDI to drinking-water. This value far exceeds the lowest reported odour threshold in water of 0.3 µg/litre.

REFERENCES