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English only

Monochlorobenzene 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

Monochlorobenzene in Drinking-water, Background document for development of WHO *Guidelines for Drinking-water Quality*, is an update of the background document published in the second edition of the GDWQ.

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*)
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Prof. Y. Magara, Hokkaido University, Japan (*Analytical achievability*)
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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
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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

CAS	Chemical Abstracts Service
DNA	deoxyribonucleic acid
LD_{50}	median lethal dose
LOAEL	lowest-observed-adverse-effect level
MCB	monochlorobenzene
NOAEL	no-observed-adverse-effect level
TDI	tolerable daily intake
USA	United States of America

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1. GENERAL DESCRIPTION

1.1 Identity

CAS No.:	108-90-7
Molecular formula:	C_6H_5Cl

1.2 Physicochemical properties[1] *(1–3)*

Property	*Value*
Melting point	-45.6 °C
Boiling point	132.0 °C
Density	1.1058 g/cm^3 at 20 °C
Water solubility	500 mg/litre at 20 °C
Log octanol–water partition coefficient	2.84
Vapour pressure	1.18 kPa at 20 °C

1.3 Organoleptic properties

Taste and odour thresholds of 10–20 µg/litre (*4*) and odour thresholds of 50, 40–120 and 100 µg/litre (*2*,*5*,*6*) have been reported for monochlorobenzene (MCB).

1.4 Major uses

MCB is used mainly as a solvent in pesticide formulations, as a degreasing agent and as an intermediate in the synthesis of other halogenated organic compounds.

1.5 Environmental fate

The concentration of MCB released into water and onto land will decrease mainly because of volatilization into the atmosphere. In water, some biodegradation also occurs, proceeding more rapidly in fresh water than in estuarine and marine waters. The rate is also more rapid if there has been acclimatization of the degrading microorganisms. Some adsorption onto organic sediments occurs (*3*). MCB is relatively mobile in sandy soil and aquifer material and biodegrades slowly in these soils; it may therefore leach into groundwater (*3*). The octanol–water partition coefficient suggests that little or no bioconcentration of MCB will occur in aquatic species.

2. ANALYTICAL METHODS

A standard method for chlorobenzenes involves extraction with hexane followed by capillary column gas–liquid chromatography with electron capture detection. The method is capable of achieving detection limits in tap water and river water of about 0.1 µg/litre (*7*).

[1] Conversion factor in air: 1 ppm = 4.60 mg/m^3.

3. ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE

3.1 Air

Because MCB is volatile and is used extensively as a solvent, large quantities are released to air. However, atmospheric concentrations are usually very low, often much less than 4.6 µg/m^3 (*3*,*8*).

3.2 Water

MCB has been detected in wastewater, surface water, groundwater and drinking-water. In some Canadian potable water sources, mean concentrations were less than 1 µg/litre; the maximum value recorded was 5 µg/litre (*9*).

3.3 Food

Chlorobenzene has been found in edible freshwater and marine organisms, although levels are not significant. Human milk may be a source of exposure for infants; MCB was detected in five out of eight samples of human milk in a study in the USA (*10*).

3.4 Estimated total exposure and relative contribution of drinking-water

Despite the low levels of MCB in air, inhalation is probably the major route of environmental exposure.

4. KINETICS AND METABOLISM IN LABORATORY ANIMALS AND HUMANS

MCB appears to be readily absorbed via the oral and inhalation routes and accumulates mainly in fatty tissue (*11*,*12*). The major metabolites of MCB in mammals are *p*-chlorophenol mercapturic acid, 4-chlorocatechol and *p*-chlorophenol. In humans, the main metabolite is 4-chlorocatechol (*13*). The major route of MCB excretion is the urine; little is excreted in the faeces or retained in the body.

5. EFFECTS ON LABORATORY ANIMALS AND IN VITRO TEST SYSTEMS

5.1 Acute exposure

MCB is of low acute toxicity to experimental animals via the oral and inhalation routes. Oral LD_{50}s in the g/kg of body weight range have been reported for rodents. Major target organs of acute exposure are the liver and kidneys.

5.2 Short-term exposure

In a 13-week study, groups of 10 Fischer 344 rats and 10 B6C3F_1 hybrid mice of each sex received MCB in corn oil at 0, 60, 125, 250, 500 or 750 mg/kg of body weight by

gavage, for 5 days per week. Effects were seen mainly in the liver, kidney and haematopoietic system. A NOAEL of 125 mg/kg of body weight was identified in the study. The LOAEL was 250 mg/kg of body weight, which caused a slight decrease in spleen weight and lymphoid or myeloid depletion of the thymus, spleen or bone marrow (*14*,*15*).

5.3 Long-term exposure

In a 2-year study, groups of 50 Fischer 344 rats and 50 $B6C3F_1$ mice of each sex received MCB in corn oil by gavage, 5 days per week for 103 weeks. The doses administered were 0, 60 or 120 mg/kg of body weight for female mice and rats of both sexes and 0, 30 or 60 mg/kg of body weight for male mice. No evidence of MCB-related toxicity was reported. Although survival was reduced in male rats at 120 mg/kg of body weight and slightly reduced in male mice at 30 and 60 mg/kg of body weight, this was not thought to be compound-related, as body weight gains were unaffected and MCB-induced toxic lesions related to death were not observed. A NOAEL of 60 mg/kg of body weight was therefore identified for male mice and one of 120 mg/kg of body weight for female mice and male and female rats (*14*,*15*).

5.4 Reproductive and developmental toxicity

Exposure of Fischer 344 rats and New Zealand white rabbits to MCB at concentrations of 0, 345, 966 or 2714 mg/m^3 via inhalation for 6 h per day during the major period of organogenesis did not cause embryotoxicity or teratogenicity in the rats (*16*). Fetal effects in rats were limited to slight delays in skeletal development, which occurred only at concentrations causing maternal toxicity (2714 mg/m^3). In rabbits, fetuses exhibited a low incidence of visceral malformations, which were not dose-related. In a two-generation inhalation study, exposure concentrations of 230, 690 and 2070 mg/m^3 did not have any adverse effects on reproductive performance or fertility in male and female rats (*17*).

5.5 Mutagenicity and related end-points

MCB was not mutagenic in *Salmonella typhimurium* strains TA98, TA100, TA1535 or TA1537, with or without activation with rat or hamster liver S9 enzymes (*18*). In one study, the intraperitoneal injection of MCB in corn oil (up to 70% of the LD_{50}) to groups of five mice led to a dose-related increase in the formation of micronucleated polychromatic erythrocytes. The authors considered that the effects were due to the clastogenic activity of MCB (*19*). However, similar results have not been reported by other workers (*20*). MCB appears to bind covalently to DNA in liver, kidney and lung of rats and mice following intraperitoneal injection (*21*), but the level of binding was considered to be low (*20*).

5.6 Carcinogenicity

In the 2-year study in which groups of 50 Fischer 344 rats and 50 $B6C3F_1$ mice of each sex received MCB in corn oil by gavage, 5 days per week for 103 weeks, doses

of 60 or 120 mg/kg of body weight caused slight (statistically significant at 120 mg/kg of body weight) increases in the frequency of neoplastic nodules of the liver in male rats (*14,15*). Increased incidences of hepatocellular carcinomas were not observed in male or female rats. No increased tumour incidences were observed in female rats or in male or female mice. Rare tumours observed in three exposed animals were not statistically significant; they included one renal tubular cell adenocarcinoma in a high-dose (120 mg/kg of body weight) female rat and transitional cell papillomas of the bladder in two male rats, one in the low-dose group (60 mg/kg of body weight) and one in the high-dose group (120 mg/kg of body weight). The frequency of pituitary tumours was reduced in rats receiving MCB; the significance of this finding is not known. The study provided some not altogether convincing evidence of carcinogenicity in male Fischer 344 rats, but none in female Fischer 344 rats or in male or female B6C3F$_1$ mice (*14,15,20*).

6. EFFECTS ON HUMANS

MCB is toxic to humans; poisoning and occupational exposure caused central nervous system disturbances. In addition, subjects occupationally exposed to MCB for 2 years suffered from headaches, dizziness and sleepiness (*22*).

7. CONCLUSIONS

MCB is of low acute toxicity. Oral exposure to high doses of MCB affects mainly the liver, kidneys and haematopoietic system. There is limited evidence of carcinogenicity in male rats, with high doses increasing the occurrence of neoplastic nodules in the liver. The majority of evidence suggests that MCB is not mutagenic; although it binds to DNA *in vivo*, the level of binding is low.

A TDI of 85.7 µg/kg of body weight can be derived from a NOAEL of 60 mg/kg of body weight per day for neoplastic nodules identified in a 2-year rat study with dosing by gavage (*14,15*), applying an uncertainty factor of 500 (100 for inter- and intraspecies variation and 5 for the limited evidence of carcinogenicity) to the NOAEL and allowing for 5 days per week dosing. A health-based value of 300 µg/litre (rounded value) can be calculated for MCB from this TDI, based on an allocation of 10% of the TDI to drinking-water.

However, because MCB occurs at concentrations well below those at which toxic effects are observed, it is not considered necessary to derive a health-based guideline value. It should also be noted that the health-based value far exceeds the lowest reported taste and odour threshold for MCB in water.

8. REFERENCES

1. Weast RC, Astle MJ, Beyer WH, eds. (1986) *CRC handbook of chemistry and physics*, 67th ed. Boca Raton, FL, CRC Press.

2. Verschueren K (1983) *Handbook of environmental data on organic chemicals*, 2nd ed. New York, NY, Van Nostrand Reinhold Co.

3. Howard PH (1990) *Handbook of environmental fate and exposure data for organic chemicals*. Vol. 1. *Large production and priority pollutants*. Chelsea, MI, Lewis Publishers.

4. Varsavskaja SP (1968) [Comparative sanitary-toxicologic characteristics of chlorobenzene and dichlorobenzene (*ortho*- and *para*-isomers) from the viewpoint of the sanitary protection of water reservoirs.] *Gigiena i sanitarija*, 33(10):15–21 (in Russian) (*Chemical abstracts*, 1969, 70:22828y).

5. Alexander HC et al. (1982) Aqueous odour and taste values of industrial chemicals. *Journal of the American Water Works Association*, 74(11):595–599.

6. Zoeteman BCJ (1980) *Sensory assessment of water quality.* Oxford, Pergamon Press.

7. Department of the Environment (1985) *Methods for the examination of waters and associated materials — chlorobenzenes in water, organochlorine pesticides and PCBs in turbid waters, halogenated solvents and related compounds in sewage sludge and waters.* London, Her Majesty's Stationery Office.

8. US Environmental Protection Agency (1988) Monochlorobenzene. *Reviews of Environmental Contamination and Toxicology*, 106:37–50.

9. Otson R, Williams DT, Bothwell PD (1982) Volatile organic compounds in water at thirty Canadian potable water treatment facilities. *Journal of the Association of Official Analytical Chemists*, 65:1370–1374.

10. Pellizzari ED et al. (1982) Purgeable organic compounds in mother's milk. *Bulletin of Environmental Contamination and Toxicology*, 28:322–328.

11. Lindsay-Smith JR, Shaw BA, Foulkes DM (1972) Mechanism of mammalian hydroxylation: some novel metabolites of chlorobenzene. *Xenobiotica*, 2:215–226.

12. Sullivan TB, Born GS, Carlson GP (1983) The pharmacokinetics of inhaled chlorobenzene in the rat. *Toxicology and Applied Pharmacology*, 71:194–203.

13. Ogata M, Shimada Y (1983) Differences in urinary monochlorobenzene metabolites between rats and humans. *International Archives of Occupational and Environmental Health*, 51:51–57.

14. Kluwe WM et al. (1985) Toxic responses to acute, subchronic, and chronic oral administrations of monochlorobenzene to rodents. *Journal of Toxicology and Environmental Health*, 15:745–767.

15. NTP (1983) *Technical report on the carcinogenesis studies of chlorobenzene* (*CAS no. 108-90-7*) *in F344/N rats and B6C3F$_1$ mice* (*gavage studies*). Research Triangle Park, NC, US Department of Health and Human Services, National Toxicology Program, p. 192 (NTP TR 255).

16. John JA et al. (1984) Inhalation teratology study of monochlorobenzene in rats and rabbits. *Toxicology and Applied Pharmacology*, 76:365–373.

17. Nair RS, Barter JA, Schroeder RE (1987) A two-generation reproduction study with monochlorobenzene vapor in rats. *Fundamental and Applied Toxicology*, 9:678–686.

18. Haworth S et al. (1983) *Salmonella* mutagenicity test results for 250 chemicals. *Environmental Mutagenesis*, 5(Suppl. 1):3–142.

19. Mohtashamipur E et al. (1987) The bone marrow clastogenicity of eight halogenated benzenes in male NMRI mice. *Mutagenesis*, 2(2):111–113.

20. IPCS (1991) *Chlorobenzenes other than hexachlorobenzene*. Geneva, World Health Organization, International Programme on Chemical Safety (Environmental Health Criteria 128).

21. Grilli S et al. (1985) *In vivo* and *in vitro* covalent binding of chlorobenzene to nucleic acids. *Japanese Journal of Cancer Research*, 76:745–751.

22. Rozenbaum ND, Blekh RS, Kremneva SN (1947) [Use of chlorobenzene as a solvent from the standpoint of industrial hygiene.] *Gigiena i sanitarija*, 12:21–24 (in Russian).