

Formaldehyde 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 on selected chemicals in 1998 and on microbial aspects in 2002. The third edition of the GDWQ was published in 2004, and the first addendum to the third edition was published in 2005.

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 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 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 contributing to the first addendum to the third edition:

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The draft text was discussed at the Working Group Meeting for the first addendum to the third edition of the GDWQ, held on 17–21 May 2004. 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 coordinator was Dr J. Bartram, Coordinator, Water, Sanitation and Health Programme, WHO Headquarters. Ms C. Vickers provided a liaison with the International Programme on Chemical Safety, WHO Headquarters. Mr Robert Bos, Water, Sanitation and Health Programme, 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

CAS	Chemical Abstracts Service
DNA	deoxyribonucleic acid
EBCT	empty bed contact time
FAO	Food and Agriculture Organization of the United Nations
GAC	granular activated carbon
GDWQ	<i>Guidelines for Drinking-water Quality</i>
IUPAC	International Union of Pure and Applied Chemistry
LD ₅₀	median lethal dose
NOAEL	no-observed-adverse-effect level
NOEL	no-observed-effect level
ppm	part per million
RNA	ribonucleic acid
WHO	World Health Organization

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1. GENERAL DESCRIPTION

1.1 Identity

CAS No.: 50-00-00
Molecular formula: CH₂O

The IUPAC name for formaldehyde is methanal.

1.2 Physicochemical properties¹ (Bills et al., 1977; Verschueren, 1983; Acheson et al., 1984a; IPCS, 1989)

<i>Property</i>	<i>Value</i>
Physical state	Colourless gas
Boiling point	-19.2 °C
Melting point	-118 °C
Relative density	1.04 (air = 1)
Vapour pressure	52.6 kPa at -33 °C
Water solubility	Freely miscible at 25 °C
Log octanol–water partition coefficient	-1

1.3 Organoleptic properties

Formaldehyde has a pungent, suffocating, hay- or straw-like odour. Taste and odour thresholds are 50 and 25 mg/litre, respectively (Bills et al., 1977; Verschueren, 1983).

1.4 Major uses and sources in drinking-water

Formaldehyde in drinking-water arises mainly from the oxidation of natural organic (humic) matter during ozonation (Glaze et al., 1989) and chlorination (Becher et al., 1992). It also enters drinking-water via leaching from polyacetal plastic fittings in which the protective coating has been broken (IPCS, 2002).

Formaldehyde's main industrial use is in the production of urea–formaldehyde, phenolic, melamine, pentaerythritol, and polyacetal resins. Its second largest use is in the industrial synthesis of a number of organic compounds. It is also used in cosmetics, fungicides, textiles, and embalming fluids (IPCS, 1989).

2. ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE

2.1 Air

Formaldehyde is emitted into air from plastics and resin glues. Low levels in air may also result from the photo-oxidation of hydrocarbons derived from fossil fuel. Typical levels in air are a few micrograms per cubic metre. Smokers are exposed to high levels of formaldehyde (US NRC, 1980; IARC, 1982; IPCS, 1989).

¹ Conversion factor in air: 1 ppm = 1.2 mg/m³ at 25 °C.

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2.2 Water

In water, formaldehyde is hydrated and found largely in the form of methylene glycol and its oligomers (IPCS, 1989; OECD, 2002). Formaldehyde concentrations of up to 30 µg/litre have been found in ozonated drinking-water (Krasner et al., 1989; Tomkins et al., 1989). In a study in Taiwan, formaldehyde concentrations in bottled and packaged drinking-water were all below the detection limit of 129 µg/litre (Chia-Fen et al., 2003).

2.3 Food

Concentrations of formaldehyde ranging from 3 to 23 mg/kg have been reported in a variety of foods (IARC, 1982).

2.4 Estimated total exposure and relative contribution of drinking-water

The general population is exposed to formaldehyde mainly by inhalation, smokers receiving about 0.38 mg/day by this route (US NRC, 1980; IPCS, 1989). People are also exposed in food, from the use of urea–formaldehyde foam in housing insulation, and from the use of cosmetics containing formaldehyde.

Drinking-water treated with ozone is unlikely to contain formaldehyde at concentrations exceeding 50 µg/litre and so will be a minor source of exposure. It is uncertain whether boiling will have a significant impact on the concentration of formaldehyde in drinking-water. Formaldehyde is considered to be highly soluble in water, and its Henry's law constant (3×10^{-5} kPa·m³/mol) suggests that it will be very unlikely to volatilize from water. Exposure by inhalation during showering is therefore expected to be low. This view is supported by experimental data from Takahashi (1990).

3. KINETICS AND METABOLISM IN LABORATORY ANIMALS AND HUMANS

The kinetics and metabolism of formaldehyde have been reviewed by IPCS (1989, 2002). Ingested formaldehyde is readily absorbed by the gastrointestinal tract. In dermal studies, it was absorbed less readily in monkeys than in rats or guinea-pigs (Jeffcoat, 1983). It appears to be distributed mainly to muscle, lower levels being found in the intestines, liver, and other tissues (Bhatt et al., 1988).

Formaldehyde is rapidly oxidized to formic acid; the subsequent oxidation to carbon dioxide and water is slower in monkeys than in rats (McMartin et al., 1977). Other metabolic products, such as *N,N*-bis(hydroxymethyl)urea and *N*-(hydroxymethyl)urea, have been reported in rats (Mashford & Jones, 1982). Metabolites are eliminated in the urine, faeces, and expired air, the relative amounts depending on the route of administration (Galli et al., 1983; Upreti et al., 1987; IPCS, 1989).

4. EFFECTS ON LABORATORY ANIMALS AND IN VITRO TEST SYSTEMS

4.1 Acute exposure

Oral LD₅₀s of 800 and 260 mg/kg of body weight have been reported for the rat and guinea-pig, respectively (Smyth et al., 1941).

4.2 Short-term exposure

In a 4-week study, Wistar rats (10 per sex per dose) received formaldehyde in drinking-water at doses of 0, 5, 25, or 125 mg/kg of body weight per day. Rats receiving the highest dose showed lowered food and liquid intake, histopathological changes in the stomach (i.e., focal hyperkeratosis of the forestomach, moderate papillomatous hyperplasia), and, in males only, lowered total protein and albumin levels in plasma. The NOAEL was 25 mg/kg of body weight per day (Til et al., 1988; IPCS, 1989).

Oral doses of 0, 50, 100, or 150 mg/kg of body weight per day in rats and 0, 50, 75, or 100 mg/kg of body weight per day in dogs for 91 days had no effect on haematology, clinical chemistry, urinalysis, or gross microscopic pathology. Depression in body weight gain was observed in both species at the highest dose levels and in male rats given 100 mg/kg of body weight per day (Johannsen et al., 1986).

4.3 Long-term exposure

In a 2-year study, Wistar rats were exposed to formaldehyde in drinking-water at mean doses of 0, 1.2, 15, or 82 mg/kg of body weight per day for males and 0, 1.8, 21, or 109 mg/kg of body weight per day for females. The average concentrations of formaldehyde in the drinking-water were 0, 20, 260, and 1900 mg/litre in the control, low-, mid-, and high-dose groups, respectively. Adverse effects were observed only in animals receiving the highest dose and included lower food and liquid intake, lower body weights, and pathological changes in the stomach, characterized by thickening of the mucosal wall. Relative kidney weights were increased in high-dose females, and an increased incidence of renal papillary necrosis was found in both sexes. Exposure did not appear to affect survival, haematology, or clinical chemistry. The NOEL was 15 mg/kg of body weight per day, or 260 mg/litre (Til et al., 1989).

In a similar study, Wistar rats were given formaldehyde in drinking-water at 0, 10, 50, or 300 mg/kg of body weight per day. At the end of 12 months, rats of both sexes in the high-dose group were observed to have gastric erosions, ulcers, squamous cell hyperplasia, hyperkeratosis, and basal cell hyperplasia. Only one male and one female from the mid-dose group showed hyperkeratosis (IPCS, 1989; Tobe et al., 1989).

4.4 Reproductive and developmental toxicity

No teratogenic effects were reported in mice given formaldehyde at oral doses of 0, 74, 148, or 185 mg/kg of body weight per day on days 6–15 of gestation (Marks et al., 1980). Growth and viability of neonates from mice given oral formaldehyde doses of 540 mg/kg of body weight per day on days 8–12 of gestation were unaffected (Seidenberg et al., 1987). No effects on reproductive performance or on the health of offspring were observed in beagle dogs fed 0, 3.1, or 9.4 mg of formaldehyde per kg of body weight per day in their diet on days 4–56 after mating (Hurni & Ohder, 1977). Sperm abnormalities were observed in male rats given single oral formaldehyde doses of 100–200 mg/kg of body weight (Cassidy et al., 1983). Intraperitoneal injection of formaldehyde at 8 or 16 mg/kg of body weight per day for 10 days resulted in degeneration of testicular tissue, inhibition of spermatogenesis, and lowered male reproductive organ weights in rats (Shah et al., 1987).

4.5 Mutagenicity and related end-points

Formaldehyde has shown evidence of mutagenicity in prokaryotic and eukaryotic cells *in vitro*. It has also been shown to be genotoxic in *Drosophila melanogaster*. Formaldehyde binds readily to proteins, RNA, and single-stranded DNA to induce DNA–protein cross-links and breaks in single-stranded DNA. It reacts readily with macromolecules in cells, mainly at the point of exposure (Ma & Harris, 1988). *In vivo*, formaldehyde increases both DNA synthesis in rats (Overman, 1985) and the number of micronuclei and nuclear anomalies in epithelial cells in rats (Migliore et al., 1989).

4.6 Carcinogenicity

There is little evidence that formaldehyde is carcinogenic by the oral route. In a 2-year study in which Wistar rats were exposed to formaldehyde in drinking-water at mean doses of 0, 1.2, 15, or 82 mg/kg of body weight per day for males and 0, 1.8, 21, or 109 mg/kg of body weight per day for females, exposure did not appear to affect tumour incidence (Til et al., 1989). In a 2-year study in which Sprague-Dawley rats were exposed to formaldehyde in drinking-water at dose levels of 0, 1, 5, 10, 50, 100, or 150 mg/kg of body weight per day, a dose-dependent increase in the incidence of leukaemia (mainly lymphoblastic) and lymphosarcoma was reported at dose levels of 5 mg/kg of body weight per day or greater. The increase in the incidence of gastrointestinal neoplasms was not dose-related. Tumours of this type were rare in historical controls and not detected in concurrent controls (Soffritti et al., 1989).

In a carcinogenicity study, a group of 10 rats was given drinking-water containing 0.5% formalin (0.2% formaldehyde) for 32 weeks. Histopathological changes were observed in the stomach, as well as neoplastic changes in the forestomach and papillomas. In addition, the authors reported evidence that formaldehyde had tumour-promoting activity. However, because of the presence of high levels of methanol in formalin, the usefulness of this information is limited (Takahashi et al., 1986). In

another study, formaldehyde induced ornithine decarboxylase activity (an indication of tumour-promoting activity) in rats given a single oral formaldehyde dose of up to 100 mg/kg of body weight (Overman, 1985). There is no evidence that formaldehyde acts as a carcinogen or promoter when applied to mouse skin (Krivanek et al., 1983).

There is evidence that inhalation exposure to formaldehyde causes cancer in rats and mice by irritating the nasal epithelium. Rats exposed to formaldehyde at 17 mg/m³, 6 h per day, 5 days per week, for 2 years exhibited an increased incidence of squamous cell carcinoma of the nasal cavity. Tumours were also noted in mice at the same level of exposure, but this species was less sensitive than the rat (Swenberg et al., 1980; Kerns et al., 1983).

A number of other long-term studies by the oral route have been conducted, and these are reviewed in detail by Restani & Galli (1991) and IPCS (2002). The conclusion of these reviews was that formaldehyde is a normal mammalian metabolite and is not carcinogenic at low levels of exposure.

5. EFFECTS ON HUMANS

Irritation and allergic contact dermatitis have been associated with exposure of the skin to formaldehyde at levels higher than those encountered in drinking-water (Cosmetic, Toiletry and Fragrance Association, 1984).

There is some evidence that formaldehyde is a carcinogen in humans exposed by inhalation. Epidemiological investigations of the mortality of factory workers following prolonged occupational exposure to formaldehyde showed a slight excess of lung cancer that was not related to formaldehyde exposure (Acheson et al., 1984a,b). An increase in the incidence of nasopharyngeal cancer was also noted but again did not appear to be related to formaldehyde (Collins et al., 1988). Further studies of groups who have been occupationally exposed to formaldehyde by inhalation have largely supported this position but provide more evidence that formaldehyde may possibly pose a carcinogenic risk of lung or sino-nasal cancer, and possibly lymphoid leukaemia, in occupationally exposed groups (Coggon et al., 2003; Hauptmann et al., 2003, 2004; Pinkerton et al., 2004). However, all of the authors urged caution in interpreting their data.

6. PRACTICAL ASPECTS

6.1 Analytical methods and analytical achievability

Formaldehyde in drinking-water is generally determined by a high-performance liquid chromatographic method following derivatization with 2,4-dinitrophenylhydrazine and liquid–solid extraction. The detection limit is 6.2 µg/litre (US EPA, 1991).

6.2 Treatment and control methods and technical achievability

Concentrations of formaldehyde in water, which arise mainly from the oxidation of natural organic matter during ozonation and chlorination (see section 1.4), may be reduced by changes to disinfection practice or by GAC treatment to below 0.03 mg/litre.

Biological filtration, using dual media sand/GAC or sand/anthracite coal as media, has been evaluated for the removal of aldehydes, including formaldehyde. Pilot filters were operated at 14 m/h (EBCT 2.1 min), receiving raw water following pre-ozonation, coagulation, and sedimentation. Two types of virgin GAC (wood- and coal-based) were used. The influent concentration of formaldehyde to the filters (typically 7–12 mg/litre) was reduced by 50% after <32, <15, and 8 days for anthracite, coal-based GAC, and wood-based GAC, respectively. For the same media, 80% removal was achieved after 36, 18, and 15 days. GAC developed biological activity sooner than anthracite and was also a better bio-support medium (Krasner et al., 1993).

A study of full-scale treatment plants in France showed that formaldehyde concentrations increased to 2–4 times the raw water levels (1–25 µg/litre) following ozonation. Subsequent GAC filtration reduced formaldehyde concentrations to about the raw water levels (Jammes et al., 1995).

Anthracite/sand biological pilot filters (EBCT 7 min) gave approximately 85% removal of formaldehyde from a feed concentration of about 10 µg/litre. Backwashing using chlorinated water (1 mg of chlorine per litre) gave poorer removal than backwashing with non-chlorinated water (Miltner et al., 1995). In a study with sand filters operated with different contact times, formaldehyde levels were reduced by 60% after a 2-min EBCT, but no further removal occurred with EBCTs up to 7 min (influent concentration 7 µg/litre) (Wang & Summers, 1996).

7. CONCLUSIONS

Rats and mice exposed to formaldehyde by inhalation exhibited an increased incidence of carcinomas of the nasal cavity at doses that caused irritation of the nasal epithelium (Swenberg et al., 1980; Kerns et al., 1983). Ingestion of formaldehyde in drinking-water for 2 years caused stomach irritation in rats (Til et al., 1989; Tobe et al., 1989). Papillomas of the stomach associated with severe tissue irritation were observed in one study (Takahashi et al., 1986).

On the basis of studies in which humans and experimental animals were exposed to formaldehyde by inhalation, IARC (2004) has classified formaldehyde in Group 1 (carcinogenic to humans). The weight of evidence indicates that formaldehyde is not carcinogenic by the oral route.

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Owing to formaldehyde's high reactivity, effects in the tissue of first contact following ingestion are more likely to be related to the concentration of the formaldehyde consumed than to its total intake. IPCS (2002) has established a tolerable concentration of 2.6 mg/litre for ingested formaldehyde based on the NOEL of 260 mg/litre for histopathological effects in the oral and gastric mucosa of rats administered formaldehyde in their drinking-water for 2 years (Til et al., 1989) and using an uncertainty factor of 100 (for inter- and intraspecies variation). Although a health-based value could be derived on the basis of this tolerable concentration, it is not considered necessary to set a formal guideline value for formaldehyde in view of the significant difference between the expected concentrations of formaldehyde in drinking-water and the tolerable concentration.

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