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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 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.

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GENERAL DESCRIPTION

Identity

CAS no.: 50-00-00
Molecular formula: CH_2O
The IUPAC name for formaldehyde is methanal.

Physicochemical properties (*1–4*) [Conversion factor in air: 1 ppm = 1.2 mg/m^3 at 25 °C]

Property	*Value*
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

Organoleptic properties

Formaldehyde has a pungent, suffocating, hay- or straw-like odour. Taste and odour thresholds are 50 and 25, respectively (*3,4*).

Major uses

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 (*1*).

ANALYTICAL METHODS

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 (*5*).

ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE

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 µg/m^3. Smokers are exposed to high levels of formaldehyde (*1,6,7*).

Water

Formaldehyde in drinking-water is formed mainly by the oxidation of natural organic (humic) matter during ozonation (*8*) and chlorination (*9*). It also enters drinking-water via industrial effluents and leaching from polyacetal plastic fittings. Concentrations of up to 30 µg/litre have been found in ozonated drinking-water (*10,11*).

Food

Concentrations of formaldehyde ranging from 3 to 23 mg/kg have been reported in a variety of foods (*6*).

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 (*1,7*). People are also exposed by ingesting contaminated drinking-water and food, and from the use of urea–formaldehyde foam in housing insulation, and of cosmetics containing formaldehyde.

KINETICS AND METABOLISM IN LABORATORY ANIMALS AND HUMANS

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 (*12*). It appears to be distributed mainly to muscle, lower levels being found in the intestines, liver, and other tissues (*13*).

Formaldehyde is rapidly oxidized to formic acid; the subsequent oxidation to carbon dioxide and water is slower in monkeys than in rats (*14*). Other metabolic products, such as *N*,*N*'-bis(hydroxymethyl)urea and *N*-(hydroxymethyl)urea, have been reported in rats (*15*). Metabolites are eliminated in the urine, faeces, and expired air, the relative amounts depending on the route of administration (*1,16,17*).

EFFECTS ON LABORATORY ANIMALS AND *IN VITRO* TEST SYSTEMS

Acute exposure

Oral LD_{50}s of 800 and 260 mg/kg of body weight have been reported for the rat and guinea-pig, respectively (*18*).

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 (*1,19*).

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 (*20*).

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. 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 NOAEL was 15 mg/kg of body weight per day (*21*).

In a similar study, Wistar rats were given formaldehyde in drinking-water at 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 (*1,22*).

Reproductive toxicity, embryotoxicity, and teratogenicity

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 (*23*). Growth and viability of neonates from mice given oral doses of 540 mg/kg of body weight per day on days 8–12 of gestation were unaffected (*24*). 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 (*25*). Sperm abnormalities were observed in male rats given single oral doses of 100–200 mg/kg of body weight (*26*). 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 (*27*).

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 (*28*). *In vivo*, formaldehyde increases both DNA synthesis in rats (*29*) and the number of micronuclei and nuclear anomalies in epithelial cells in rats (*30*).

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 (*21*). 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 (*31*).

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 (*32*). 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 (*29*). There is no evidence that formaldehyde acts as a carcinogen or promoter when applied to mouse skin (*33*).

There is some evidence that inhalation exposure to formaldehyde causes cancer in rats and mice by irritating the nasal epithelium. Rats exposed to 17 mg of formaldehyde per m^3, 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 (*34,35*).

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 (*36*). Its presence in some types of water filters has been associated with the occurrence of haemolytic anaemia in dialysis patients (*1,37*).

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 (*2,38*). An increase in the incidence of nasopharyngeal cancer was also noted but again did not appear to be related to formaldehyde (*39*).

GUIDELINE VALUE

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 (*34,35*). Ingestion of formaldehyde in drinking-water for 2 years caused stomach irritation in rats (*21,22*). Papillomas of the stomach associated with severe tissue irritation were observed in one study (*32*).

On the basis of studies in which humans and experimental animals were exposed to formaldehyde by inhalation, IARC has classified formaldehyde in Group 2A (*40*). The weight of evidence indicates that formaldehyde is not carcinogenic by the oral route. A guideline value has been derived, therefore, on the basis of a TDI. A TDI of 150 µg/kg of body weight was calculated based on the NOAEL of 15 mg/kg of body weight per day in a 2-year study in rats (*21*), incorporating an uncertainty factor of 100 (for intra- and interspecies variation). No account was taken of potential carcinogenicity from the inhalation of formaldehyde from various indoor water uses, such as showering. With an allocation of 20% of the TDI to drinking-water, the guideline value is 900 µg/litre.

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